Boron-mediated directed aromatic C–H hydroxylation

Transition metal-catalysed C–H hydroxylation is one of the most notable advances in synthetic chemistry during the past few decades and it has been widely employed in the preparation of alcohols and phenols. The site-selective hydroxylation of aromatic C–H bonds under mild conditions, especially in the context of substituted (hetero)arenes with diverse functional groups, remains a challenge. Here, we report a general and mild chelation-assisted C–H hydroxylation of (hetero)arenes mediated by boron species without the use of any transition metals. Diverse (hetero)arenes bearing amide directing groups can be utilized for ortho C–H hydroxylation under mild reaction conditions and with broad functional group compatibility. Additionally, this transition metal-free strategy can be extended to synthesize C7 and C4-hydroxylated indoles. By utilizing the present method, the formal synthesis of several phenol intermediates to bioactive molecules is demonstrated.
Phenols are structural constituents of pharmaceuticals, agrochemicals, polymers, and naturally occurring compounds and serve as versatile synthetic intermediates\(^1\)\(^-\)\(^3\). Bioactive molecules of particular interest are (hetero)arenes such as amides, indolines, and indoles-containing hydroxyl groups (Fig. 1a)\(^5\)\(^-\)\(^11\). The site-selective introduction of a hydroxyl group to a (hetero)arene is an important task in both chemical industry and organic synthesis. Traditional methods used for phenol preparation include nucleophilic aromatic substitution of activated aryl halides\(^1\)\(^2\) and Sandmeyer-type hydroxylation\(^1\)^, as well as the transition-metal-catalysed hydroxylation of (hetero)aryl halides with hydroxide salts (e.g., KOH and NaOH)\(^1\)\(^4\)\^-\(^1\)\(^8\). All of which require the presence of a (pseudo)halide in the (hetero)arenes. During the past decade, C–H functionalization and harsh reaction conditions. Substrates bearing a chelating functional group can coordinate with the metal catalyst and undergo further C–H functionalization\(^3\)\(^2\)\^-\(^3\)\(^4\). In this context, several groups have explored transition-metal-catalysed directed C–H functionalization reactions\(^2\)\(^9\)\^-\(^3\)\(^0\). As early as 1990, Fujiwara et al. explored the hydroxylation of benzene using O\(_2\) as the oxidant enabled by Pd catalysis\(^3\)\(^1\). However, this pioneering work had several limitations, such as a low efficiency, poor selectivity, and harsh reaction conditions. Substrates bearing a chelating functional group can coordinate with the metal catalyst and undergo further C–H functionalization\(^3\)\(^2\)\^-\(^3\)\(^4\). In this context, several groups have explored transition-metal-catalysed directed aromatic C–H hydroxylation using organic oxidants, hydrogen peroxide or molecular oxygen (Fig. 1b)\(^3\)\(^5\)\^-\(^4\)\(^6\). While synthetically very attractive, most of these protocols still suffer from the use of expensive noble metals, such as Pd, Rh, Ru, and Ir, as catalysts. This requirement may be a significant limitation, especially for applications needing large-scale synthesis methods and for the removal of toxic trace metals from pharmaceutical products. From a synthetic perspective, the ability to prepare synthetically relevant scaffolds via regio-controlled C–H hydroxylation under mild conditions by using cheap oxidants and avoiding the use of transition metals would be of great importance.

The transition-metal-catalysed C–H borylation reaction has emerged as an effective method for the construction of arylboronic acids and their derivatives\(^4\)\^-\(^6\)\^-\(^9\). Recently, our group\(^4\)\(^0\) and the Ingleson group\(^3\)\(^1\) reported a general strategy for the mild directed C–H borylation of (hetero)arenes using BBr\(_3\) as both the reagent and catalyst under metal-free conditions\(^4\)\(^2\)\^-\(^4\)\(^5\). BBr\(_3\) is an attractive borylation agent because it is a commercially available and the Ingleson group\(^3\)\(^1\) reported a general strategy for the mild directed C–H borylation of (hetero)arenes using BBr\(_3\) as both the reagent and catalyst under metal-free conditions\(^4\)\(^2\)\^-\(^4\)\(^5\). In this context, several groups have explored transition-metal-catalysed directed aromatic C–H hydroxylation. a Phenol-based bioactive molecules. b Transition-metal-catalysed directed aromatic C–H hydroxylation. c Our approach for directed aromatic C–H hydroxylation under transition-metal-free conditions.

![Fig. 1 Towards a transition-metal-free process for directed aromatic C–H hydroxylation. a Phenol-based bioactive molecules. b Transition-metal-catalysed directed aromatic C–H hydroxylation. c Our approach for directed aromatic C–H hydroxylation under transition-metal-free conditions.](https://doi.org/10.1038/s41467-020-15207-x)
Table 1 Optimization of the reaction conditions.\textsuperscript{a}

| Entry | Variation from the “standard conditions” | Yield of 1c (%)\textsuperscript{b} |
|-------|------------------------------------------|----------------------------------|
| 1     | None                                     | 92                               |
| 2     | BF\textsubscript{3} instead of BBr\textsubscript{3} | 0                                |
| 3     | BCl\textsubscript{3} instead of BBr\textsubscript{3} | 5                                |
| 4     | ClBcat instead of BBr\textsubscript{3} | 0                                |
| 5     | 9-BBN instead of BBr\textsubscript{3} | 0                                |
| 6     | 1a (DG = Me) instead of 1a | 0\textsuperscript{c}            |
| 7     | Oxone instead of NaBO\textsubscript{3}·4H\textsubscript{2}O | 55                              |
| 8     | H\textsubscript{2}O\textsubscript{2} instead of NaBO\textsubscript{3}·4H\textsubscript{2}O | 73                              |

\textsuperscript{a}Standard conditions: 1a (0.20 mmol), BBr\textsubscript{3} (0.22 mmol) in 1.0 mL of DCM at room temperature, 1 h, under Ar; then, 1.0 mL of THF/H\textsubscript{2}O (1/1) and NaBO\textsubscript{3}·4H\textsubscript{2}O (0.6 mmol) were added to the mixture at room temperature, 1 h, under Ar.

\textsuperscript{b}Isolated yield.

\textsuperscript{c}The corresponding ortho C–H borylation product.

Our delight, other common oxidants, such as oxone and H\textsubscript{2}O\textsubscript{2}, were also effective for this hydroxylation. To achieve this transformation, considering the importance of the directing bonds, to our system resulted in the selective formation of the difunctionalization products directing para and meta positions underwent facile hydroxylation and afforded the corresponding products 3–13c in good to excellent yields. The amides bearing electron-withdrawing groups such as CF\textsubscript{3} (14–15a), COOMe (16a), and CN (17a) are particular noteworthy; these substrates produced ortho-hydroxylated products 14–17c with 66–80% yields. Electron-donating groups such as OTBS (18c) and SMe (19c) at the para position of the amides are tolerated. Substrate 20a bearing a methoxy group can undergo ortho C–H hydroxylation and O-demethylation to generate the corresponding product 20c with a 81% yield. Notably, the phenyldiazenyl substituent in substrate 21a, which is also susceptible to C–H borylation, remained intact during the reaction. Other N-pivaloyl amides, including N-methylaniline (22c), tetrahydroquinoline (23c), and indoline (24c), are also tolerated for C–H hydroxylation. This protocol is compatible with heterocyclic motifs such as thiophene 25c. Polyaromatic substrates 26–28c were also shown to be highly reactive. As a prominent structural motif, N-arylpyrrolidinones have been used in Ru(II)-catalysed C–H hydroxylation\textsuperscript{36,37}. We found that the boron-mediated directed C–H hydroxylation of N-phenylpyrrolidinone (29a) in the presence of BBr\textsubscript{3} could provide the desired product 29c with a 79% yield. The system was compatible with the different para- and meta-substitution patterns in the phenyl ring of the N-arylpyrrolidinone backbone (30–36c). In addition, this C–H hydroxylation method is not limited to N-arylpyrrolidinones. Lactams such as 37–38a, oxazolidin-2-ones 39a, and thiophene 40a could also undergo C–H hydroxylation at the ortho position, affording good yields of products 37–40c. Subjecting N-pivaloyl amides 41–45a, which are substrates bearing two N-pivaloyl directing bonds, to our system resulted in the selective formation of the difunctionalization products 41–45c in 60–89% yields. These bisphenols could be utilized as precursors for construction of polymers\textsuperscript{38}.
Fig. 2 Boron-mediated directed ortho C-H hydroxylation of amides. Reaction conditions: substrates 1a–28a (0.20 mmol), BBr₃ (0.22 mmol) in 0.5 mL DCM at room temperature, 1 h, under Ar; NaBO₃·4H₂O (0.60 mmol) in 0.5 mL THF and 0.5 mL H₂O, at room temperature, 1 h. 29a–40a (0.20 mmol), BBr₃ (0.60 mmol) in 0.5 mL DCM at 60 °C, 24 h; NaBO₃·4H₂O (0.60 mmol) in 0.5 mL THF and 0.5 mL K₂CO₃ (aq), at room temperature, 1 h. 41a–45a (0.20 mmol), BBr₃ (0.40 mmol) in 0.5 mL DCM at room temperature, 1 h, under Ar; NaBO₃·4H₂O (1.50 mmol) in 0.5 mL THF and 0.5 mL H₂O, at room temperature, 1 h. aUsing BBr₃ (2.0 mmol) in 0.1 mL of DCM. bN-(4-methoxyphenyl)pivalamide (0.20 mmol), BBr₃ (0.5 mmol).
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Fig. 3 Boron-mediated directed C–H hydroxylation of indoles. a Directed C–H hydroxylation of indoles at the C7 position. b Directed C–H hydroxylation of indoles at the C4 position. Reaction conditions: substrates 46–57a (0.20 mmol), BBr3 (0.22 mmol) in 0.5 mL DCM at room temperature, 1 h, under Ar; NaBO3·4H2O (0.60 mmol) in 0.5 mL THF and 0.5 mL K2CO3 (aq), at room temperature, 1 h; 58–69a (0.20 mmol), BBr3 (0.60 mmol) in 0.5 mL DCM at 60 °C, 10 h, under Ar; NaBO3·4H2O (1.50 mmol) in 0.5 mL THF and 0.5 mL H2O, at 60 °C, 6 h; 61–69a (0.20 mmol), BBr3 (0.22 mmol) in 0.5 mL DCM at room temperature, 9 h, under Ar; NaBO3·4H2O (1.0 mmol) in 0.5 mL THF and 0.5 mL H2O, at room temperature, 2 h.

We next investigated the scope of the C7 selective C–H borylation/oxidation/DG removal protocol, in which the N-Piv group can be removed automatically during work-up with K2CO3. Indoles bearing methyl (47–49a) substituents at the 4–6 positions underwent facile hydroxylation and afforded the corresponding products in 74–85% yields. Again, halogen-containing motifs (F, Cl, and Br, 50–56a) work very well in the C7 selective borylation process. In addition, substrate 57a contains a phenyl substituent also delivering coupled product 57c with a 70% yield. We further examined the scope of using C3-pivaloyl indoles as coupling partners with BBr3; these compounds reacted with a high regioselectivity to produce C4-hydroxylated indoles (Fig. 3b)59. We first evaluated the influence of the N–H protection groups on the indoles. Notably, the free indole 58a could provide the desired product 58c with a 59% yield. The treatment of the indoles 59–60a bearing N-Me and N-Bn groups in the system provided a 71% and 54% isolated yields of the corresponding C4-hydroxylation products 59–60c. Indole 61a bearing an N-Ts protection group can promote the reactivity of this transformation, affording the product 61c with a 85% yield. Regarding the scope of the indole framework, diverse substituents, including methyl (62c), F (63a), Cl (64–65c), Br (66–67c), I (68c), and phenyl (69c) are tolerated.

Synthetic applications. To further demonstrate the potential synthetic applications of this method, we showed three examples to compare existing strategies with our developed C–H hydroxylation method. Previously, using N-acetylindoline 70 as a model substrate for the total synthesis of the potent caspase-8 inhibitor (+)-haplocidine and its N1-amide congener (+)-haplocine, the precursor acetoxy-indoline 71′ was generated with a 84% yield by the palladium-catalysed C7 hydroxylation of indoline60. Based on the boron-mediated strategy, we prepared product 71 from substrate 70 with a 71% yield, in which N-acetyl can be used as a directing group (Fig. 4a). Trauner and co-workers61 reported the evolution of the total synthesis of exiguamines,
where nitrovinylindole 74 was a key intermediate. To simplify this synthesis process, we provided an alternative route to 74 using the developed C–H hydroxylation protocol. The indole substrate 72 was regio-selectively hydroxylated at the C7 position and further deprotected and then protected as a benzyl ether to yield 7-hydroxy-6-bromoindole derivative 73 with a 63% yield. Then, indole 73 was formylated and condensed with nitromethane to yield nitrovinylindole 74 with a 89% yield (Fig. 4b).

The Renata group recently identify a concise synthetic route to access tambromycin. During the study, they were drawn to a thallium-mediated C–H hydroxylation of indoles at the C4 position, suffering from highly variable yields and a lack of scalability. Inspired by this result, we finally focused our attention on the boron-mediated strategy to synthesize indole 78. Using N-methyl indole 75 as a substrate, C4-hydroxylation was identified as a viable approach to access the desired indole fragment 76 after etherification with Me. To our delight, the removal of a pivaloyl group from 76 was readily accomplished by a reverse Friedel-Crafts reaction in the presence of TsOH and glycol, providing a good yield of 77. Further C3 formylation and oxidation could provide a good yield of the key building block 78, which was facile to convert to tambromycin (Fig. 4c).

**Discussion**

In summary, we have developed an efficient boron-mediated system that is capable of mimicking the chelation-assisted metallic system to achieve directed C–H hydroxylation. The use of this method for the preparation of substituted phenols and downstream-functionalized products showcases the strategic opportunity to use this strategy for the synthesis of biologically active compounds. The reaction provides a simple new bond disconnection protocol for constructing these motifs with...
different regioselectivities and broader functional group compatibilities than existing methods.

**Methods**

**General procedure for the synthesis of phenol 1c.** A flame-dried 25 mL Schlenk tube was charged with aryl and N-pivaloyl amide 1a (0.2 mmol, 1.0 equiv) and dry DCM (0.5 mL, 0.4 M) were sequentially added to the reaction mixture and stirred at room temperature for another 1 h (monitored by TLC). After that, the excess water was removed with MgSO4 and then washed with EtOAc (10.0 mL × 3). The filtrate was collected, and the crude mixture was directly subjected to column chromatography on a silica gel, using petrol ether/EtOAc (10/1) as the eluent to give the desired product 1c as a white solid (41.5 mg, 92%).

**Data availability**

The authors declare that the data supporting the findings of this study are available within the article and Supplementary Information file or from the corresponding author upon reasonable request. The X-ray crystallographic coordinates for the structures reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC) under deposition numbers CCDC 1910134. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Author contributions
Z.S. conceived the concept, directed the project, and wrote the paper. J.L. and B.Z. performed the experiments. Y.Y. and Y.H. discussed the results.

Competing interests
The authors declare no competing interests.

Additional information

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