

Benzoic Acid-Promoted C2–H Borylation of Indoles with Pinacolborane

Youliang Zou, Binfeng Zhang, Li Wang, and Hua Zhang*



Indole, a "privileged" structural core motif, exists in a wide variety of biologically active compounds such as pharmaceuticals, agrochemicals, and natural products.¹ During the past several decades, transition-metal-catalyzed C-H functionalization has emerged as a powerful tool for the late-stage modification of indoles.² For example, growing efforts have been devoted to the development of C-H borylation for indoles, due to the significant opportunity of using organoboron compounds in organic synthesis.³ Various transitionmetal catalysts have been developed for C-H borylation of indoles and exhibit high efficiency.⁴ Although transition-metal catalysis dominates aromatic C-H borylation, the metal-free approach has emerged as a promising alternative strategy.⁵ In recent years, metal-free C-H borylation of indoles has been achieved utilizing borenium cations,⁶ N-heterocyclic carbene boranes,⁷ bis(pinacolato)diborane,⁸ boron trihalides,⁹ and aryl boronic esters¹⁰ as boron sources.

As commonly used boron sources in transition-metalcatalyzed C-H borylation, commercially available and mild boranes such as pinacolborane (HBpin) and catecholborane (HBcat) are also good choices in metal-free C-H borylation. Very recently, various catalytic electrophilic C-H borylations of indoles with HBpin or HBcat were achieved in the presence of frustrated Lewis pair (FLP) catalysts,¹¹ boron-based Lewis acid catalysts,¹² and a tethered ruthenium(II) thiolate complex¹³ (Scheme 1A). However, despite the great advances made in this area, several challenges remain to be addressed. On one hand, the catalysts employed in the previous reports were either commercially unavailable or very expensive. On the other hand, due to the intrinsic nature of the indole substrate, C3-H borylation of indoles was dominantly favored while C2-H borylation of indoles remains challenging. Therefore, a C2-selective C-H borylation of indoles enabled by simple, easy-handling, commercially available, and inexpensive catalysts is highly desired. We report herein a benzoic acidpromoted C2-H borylation of indoles with pinacolborane (Scheme 1B).

Scheme 1. Catalytic Electrophilic C–H Borylation of Indoles



We began our study by examining various commercially available and cheap promoters in the reaction of 1methylindole (1a) and HBpin. During the investigation, we are thrilled to find that the addition of benzoic acid (PhCO₂H) provided C2–H borylation product **2a** predominately in considerable yield. After extensive screening, we determined that the reaction of **1a** with HBpin in the presence of PhCO₂H

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(10 mol %) in 'hexane at 180 °C for 16 h afforded C2borylated product 2a, C3-borylated product 3a, and C2,C3diborylated product 4a in 62%, 8%, and 15% NMR yields, respectively.¹⁴ As C3 protodeboronation of 4a afforded 2aquantitatively under acidic conditions, a 74% NMR yield of 2awas obtained by treating the reaction residue with an aqueous hydrochloride solution.

As shown in Table 1, several examples of variations from the "standard conditions" are illustrated. In addition to benzoic

Table 1. Effects of Reaction Parameters^{a,b} on the Benzoic Acid-Promoted C2–H Borylation of 1a with Pinacolborane



^aStandard reaction conditions: **1a** (0.4 mmol), HBpin (2.4 mmol), PhCO₂H (0.04 mmol), 'hexane (1.0 mL), 180 °C, 16 h. ^{b1}H NMR yield. ^cThe reaction residue was treated with HCl (1.0 mL, 6.0 M) for 0.5 h. ^dFor 48 h.

acid, acetic acid (CH₃CO₂H) was also found to be a suitable promoter (Table 1, entry 2). The use of BnOBpin as a promoter afforded 2a and 4a in 40% and 9% yields, respectively (Table 1, entry 3).¹⁵ Remarkably, a 19% yield of 2a and a 6% yield of 4a were obtained in the absence of benzoic acid, which revealed that the borylation could occur without the addition of exogenous promoters (Table 1, entry 4). Increasing the reaction time led to a 37% yield of 2a and an 11% yield of 4a (Table 1, entry 5). Less HBpin resulted in a lower conversion of 1a and lower yields of desired products (Table 1, entries 6-8). When B_2pin_2 was employed as a boron source, no products were obtained (Table 1, entry 9). The use of "octane as a solvent showed an efficiency lower than that of 'hexane, while 2a was obtained in 22% yield under neat conditions (Table 1, entries 10 and 11, respectively). Decreasing the temperature or the reaction time led to decreased yields (Table 1, entries 12-14).

With the optimized reaction conditions in hand, the substrate scope of this benzoic acid-promoted C2–H borylation was investigated (Scheme 2). Similar to 1a, the borylation of 1-butyl indole (1b) occurred smoothly to afford desired product 2b in good yield. A methyl substituent at different positions of the phenyl ring was well-tolerated in this

Scheme 2. Benzoic Acid-Promoted C2–H Borylation of Indoles with Pinacolborane a,b



^{*a*}Reaction conditions: 1 (0.4 mmol), HBpin (2.4 mmol), PhCO₂H (0.04 mmol), ^chexane (1.0 mL), 180 °C, 16 h. ^{*b*}Isolated yield. ^{*c*}The reaction residue was treated with HCl (1.0 mL, 6.0 M) for 0.5 h. ^{*d*}1 (1.0 mmol). ^{*c*}CH₃CO₂H (0.04 mmol). ^{*f*}¹H NMR yield (C2 and C3 isomers were obtained as a mixture).

C2-H borylation (2c-2g). 1-Methylindoles bearing both electron-donating and electron-withdrawing substituents such as methoxy, 1-piperidyl, phenyl, and trifluoromethyl groups reacted well to produce the corresponding C2-borylated products in good yields (2h-2k). Halo substituents, such as F, Cl, and Br, and boron substituent Bpin were all welltolerated, providing the possibility for further functionalization (21-20). Remarkably, NH indole (1p) also reacted with pinacolborane to afford desired C2-H borylation product 2p in satisfying yield in the presence of acetic acid. In a similar manner, other heteroarenes like 7-aza indole (1q) and 1-benzyl pyrrole (1r) were also suitable substrates giving the corresponding products in 66% and 42% yields, respectively. Low yields of C2-borylated products 2s and 2t were obtained employing benzo[b]thiophene (1s) and thiophene (1t) as substates. N-Methyl carbazole (1u) gave only a trace amount of the product under the reaction conditions presented here.

The synthetic versatility of 2-boryl indoles obtained by this C-H borylation was demonstrated (Scheme 3). Various



transformations, including oxidation (5), Suzuki coupling (6), cyanation (7), and C–S bond formation (8), of 2-boryl indoles were performed, in which different important C2-functionalized indoles were obtained in moderate to good yields.

To gain brief insights into the mechanism of this C–H borylation, several control experiments were conducted. Considering the present reaction conditions and the relevant literature reports, ^{16–18} we speculate that the active catalyst in this C–H borylation might be BH₃-related borane species formed by the decomposition of HBpin with the aid of promoters. Various borane complexes such as BH₃·DMS, BH₃·THF, BH₃·Py, and BH₃·TMA were tested as promoters in this C–H borylation (Scheme 4a). Moderate to good yields of **2a** and **4a** were obtained in the presence of these borane complexes. Thomas and co-workers reported that simple nucleophiles such as LiAlH₄, LiO⁴Bu, NaO⁴Bu, and KO⁴Bu can readily mediate the formation of BH₃ from HBpin,¹⁸ and the

Scheme 4. Control Experiments

a) BH ₃ •L as promoters in C2–H borylation of 1a					
1a + HBpin	BH3●F	(10 mol%)	2a	+	4a
	^c hexane,	180 °C, 16 h			
	E	3H₃∙DMS	50%		20%
	I	BH₃∙THF	40%		15%
		BH₃∙Py	42%		11%
	E	BH₃∙TMA	36%		13%
 b) Various simple nucleophiles as promoters 					
1a + HBpin	nucleoph	ile (10 mol%)	2a	+	4a
	^c hexane,	180 °C, 16 h			
nucleophile 2a	4a	nucleophile	2a	4	a
LiAIH ₄ 30 ⁴	% 59%	NaO ^t Bu	42%	3%	6
LiO ^t Bu 48°	% 11%	KO ^t Bu	46%	14	%
c) Inhibition of C–H borylation of 1a by TMEDA					
te UPnin	PhCO ₂ H	PhCO ₂ H (10 mol%) TMEDA		т	40
та + порт	T			т	4a
	Chovano				
	nexane,	180 ºC, 16 h			
	TMEDA	180 °C, 16 h (10 mol%)	36%		16%
	TMEDA TMEDA TMEDA	180 °C, 16 h (10 mol%) (30 mol%) (100 mol%)	36% 17% 3%		16% 7% 0%
d) Stoichiometric rea	TMEDA TMEDA TMEDA TMEDA	180 °C, 16 h (10 mol%) (30 mol%) (100 mol%) with BH ₂ •DMS	36% 17% 3%		16% 7% 0%
d) Stoichiometric rea	TMEDA TMEDA TMEDA TMEDA ction of 1a v	180 °C, 16 h (10 mol%) (30 mol%) (100 mol%) vith BH ₃ •DMS IBpin (1 2 equ	36% 17% 3%		16% 7% 0%
d) Stoichiometric rea 1a BH ₃ •DMS (TMEDA TMEDA TMEDA TMEDA Stion of 1a v 3.0 equiv) H	180 °C, 16 h (10 mol%) (30 mol%) (100 mol%) vith BH ₃ •DMS IBpin (1.2 equ	36% 17% 3% ∺	+	16% 7% 0% 4a
d) Stoichiometric rea 1a ^{BH} 3•DMS (^C hexane, 18	TMEDA TMEDA TMEDA TMEDA Ction of 1a v 3.0 equiv) <u>H</u> 0 °C, 16 h	180 °C, 16 h (10 mol%) (30 mol%) (100 mol%) vith BH ₃ •DMS IBpin (1.2 equ r.t., 16 h	36% 17% 3% iv) → 2a 13%	+	16% 7% 0% 4a 2%
d) Stoichiometric rea 1a ^{BH} 3•DMS (^c hexane, 18 e) The stability of 3a	TMEDA TMEDA TMEDA ction of 1a v 3.0 equiv) <u>H</u> 0 °C, 16 h n reaction s	180 °C, 16 h (10 mol%) (30 mol%) (100 mol%) vith BH ₃ •DMS IBpin (1.2 equ r.t., 16 h	36% 17% 3% iiv) 2a 13%	+	16% 7% 0% 4a 2%
d) Stoichiometric rea 1a ^{BH} 3•DMS (^c hexane, 18 e) The stability of 3a	TMEDA TMEDA TMEDA Stion of 1a v 3.0 equiv) H 0 °C, 16 h n reaction s	180 °C, 16 h (10 mol%) (30 mol%) (100 mol%) with BH ₃ •DMS Bpin (1.2 equ r.t., 16 h system PhCO ₂ H (10 mol%)	36% 17% 3% 5 iv) → 2a 13%	+	16% 7% 0% 4a 2%
d) Stoichiometric rea 1a ^{BH} 3∙DMS (^C hexane, 18 e) The stability of 3a 1a + HBpin +	TMEDA TMEDA TMEDA totion of 1a v 3.0 equiv) H 0 °C, 16 h n reaction s 3a	180 °C, 16 h (10 mol%) (30 mol%) (100 mol%) with BH ₃ •DMS Bpin (1.2 equ r.t., 16 h system PhCO ₂ H (10 mol%)	36% 17% 3% iiv) → 2a 13% 2a +	+ 6 3a	16% 7% 0% 4a 2% + 4a

employment of these compounds as promoters was also examined in which significant desired products were obtained (Scheme 4b). N,N,N',N'-Tetramethylethylenediamine (TMEDA) could form mono- and bisadducts with BH₃ and serve as a BH₃ indicator.^{18,19} The addition of TMEDA significantly inhabited the C–H borylation of 1a (Scheme 4c). Furthermore, small amounts of borylated products were observed by the stoichiometric reaction between 1a and BH₃·DMS followed by the addition of HBpin at room temperature (Scheme 4d). These results indicated BH₃-related borane species are the probable catalyst in this reaction. The ¹¹B NMR analysis of the reaction system was conducted; however, unfortunately no BH₃-related borane species was observed, which might be due to the very low concentration of active species (for details, see the Supporting Information).

In contrast to the C3 regioselectivity observed in previous catalytic electrophilic C–H borylation of indoles, a unique C2 regioselectivity was obtained in this transformation. One possible reason to explain this phenomenon is that the facile protodeboronation of the C3 isomers results in the accumulation of thermodynamically more stable C2 isomers.⁷ However, the model reaction with the addition of a stoichiometric amount of **3a** afforded a 106% yield of **3a**. The result obtained revealed the stability of **3a** under the conditions presented here, and thus, the speculation presented above was ruled out (Scheme 4e).

In addition, we monitored the C2–H borylation of 1a by ¹H NMR analysis. As shown in Figure 1, the yield of 2a increased



Figure 1. Monitoring of the borylation of 1a with HBpin. The yields were determined by ¹H NMR analysis.

with longer reaction times while the yields of **3a** and **4a** increased at a rate much lower than that of **2a** during the whole reaction process. This result confirmed the constant C2 regioselectivity in the whole process.

On the basis of the results presented above and previous reports, $^{16-18}$ a mechanism is proposed for this C–H borylation (Scheme 5). Initially, BH₃-related borane species 9 is formed by the decomposition of HBpin mediated by either promoters or 1a. The reaction of 1a with 9 affords C2-borylated indole intermediate 10, which subsequently undergoes transborylation with HBpin to produce 2a, and regenerate the borane species.

Scheme 5. Proposed Mechanism



In summary, we have demonstrated a benzoic acidpromoted C2–H borylation of indoles with pinacolborane. A broad substrate scope and good functional group tolerance are obtained. The mechanistic insights reveal that the BH_3 -related borane species involves the probable catalyst in this C–H borylation. By employing this protocol, the prompt synthesis of C2-functionalzied indoles could be achieved.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00809.

Experimental details and NMR spectra (PDF)

AUTHOR INFORMATION

Corresponding Author

Hua Zhang – Key Laboratory of Catalysis and Energy Materials Chemistry of Ministry of Education and Hubei Key Laboratory of Catalysis and Materials Science, School of Chemistry and Materials Science, South-Central University for Nationalities, Wuhan 430074, China; College of Chemistry, Nanchang University, Nanchang 330031, China;
orcid.org/0000-0002-4960-0838; Email: huazhang@ scuec.edu.cn

Authors

- Youliang Zou Key Laboratory of Catalysis and Energy Materials Chemistry of Ministry of Education and Hubei Key Laboratory of Catalysis and Materials Science, School of Chemistry and Materials Science, South-Central University for Nationalities, Wuhan 430074, China; College of Chemistry, Nanchang University, Nanchang 330031, China
- Binfeng Zhang Key Laboratory of Catalysis and Energy Materials Chemistry of Ministry of Education and Hubei Key Laboratory of Catalysis and Materials Science, School of Chemistry and Materials Science, South-Central University for Nationalities, Wuhan 430074, China; College of Chemistry, Nanchang University, Nanchang 330031, China
- Li Wang Key Laboratory of Catalysis and Energy Materials Chemistry of Ministry of Education and Hubei Key Laboratory of Catalysis and Materials Science, School of Chemistry and Materials Science, South-Central University for Nationalities, Wuhan 430074, China; College of Chemistry, Nanchang University, Nanchang 330031, China

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c00809

Notes

The authors declare no competing financial interest.

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