

Synthesis of 1-Borylisoindoles via Palladium-Catalyzed Dehydrogenation/C–H Borylation of Isoindolines

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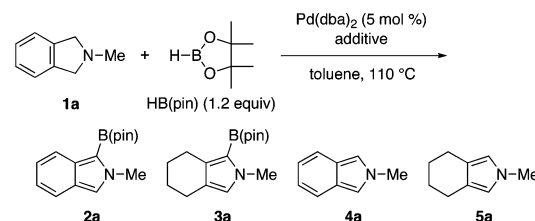
Boryl-substituted heterocyclic compounds are receiving increasing attention because they can serve as versatile intermediates in the syntheses of functionalized heterocyclic compounds.¹ Much effort has been devoted to the development of efficient syntheses of borylated heterocycles, including transition metal-catalyzed conversion of C–X (X = halogen or OTf) and C–H bonds in heteroaromatic compounds into C–B bonds.^{2–4} These methods have enabled chemo- and regioselective synthesis of borylated pyridines, pyrroles, indoles, furans, and thiophenes. To expand the scope of the strategy based on transformation of borylated heterocycles, further enlargement of the substrate library is highly desirable.

Isoindole is a constitutional isomer of indole and has attracted much interest in organic chemistry and materials sciences.^{5,6} Isoindoles are relatively unstable because of the *o*-quinoid structure; therefore, direct functionalization of isoindoles has been limited only to electrophilic aromatic substitution reactions.^{5b,7} Thus, efficient conversion of stable starting materials to isoindoles accompanied by C–B bond formation is highly desirable. Herein, we describe a palladium-catalyzed reaction of isoindolines (i.e., dihydroisoindoles) with pinacolborane [HB(pin)] that affords borylated isoindoles via dehydrogenation followed by C–H borylation.⁸ 1-Boryl- and 1,3-diborylisoindoles are obtained selectively, depending on the reaction conditions.

A toluene solution of 2-methylisoindoline (**1a**) and HB(pin) (1.2 equiv) was stirred at 110 °C in the presence of 5 mol % Pd(dba)₂ (Table 1, entry 1). After 1 h, 98% of **1a** was consumed, and a mixture of several products was obtained. We found that 1-borylisoindole **2a** and 1-boryl-4,5,6,7-tetrahydroisoindole **3a** were formed in 50 and 6% yields, respectively. In addition to these borylated products, a small amount (4%) of 2-methylisoindole (**4a**) and a significant amount (38%) of 4,5,6,7-tetrahydro-2-methylisoindole (**5a**) were detected in the mixture. The product distribution changed when the reaction was carried out for 15 h under otherwise identical conditions, showing a higher yield of **3a** (49%) with formation of less **2a** (11%) (entry 2). It should be noted that the formation of **3a** was completely suppressed when the reaction was carried out with 1 mol % Me₂S (entries 3 and 4). Under these conditions, borylation of **1a** was complete within 1 h, giving **2a** in high yield (entry 3). The borylation was not sensitive to the amount of Me₂S (entries 3, 5, and 6). In sharp contrast, addition of tertiary phosphines such as PPh₃ (entry 7), PMe₃, and DPPE made the catalyst inactive. Borylation of **1a** did not take place when B₂(pin)₂ was used instead of HB(pin) (entry 8). Several palladium salts and complexes, such as Pd(OAc)₂, Pd(acac)₂, [(η³-C₃H₅)PdCl]₂, CpPd(η³-C₃H₅), and even Pd black, showed catalytic activity for the borylation, although with lower conversion and product selectivity than the Pd(dba)₂/Me₂S catalyst.

The optimized reaction conditions were applied to dehydrogenative C–H borylation of various isoindolines (Table 2). The reactions of 2-ethyl- and 2-isopropylisoindolines **1b** and **1c** gave the corresponding products **2b** and **2c**, although the reactions were slower than that of **1a** (entries 1 and 2). Conversion of **1d** to **2d** was successfully achieved

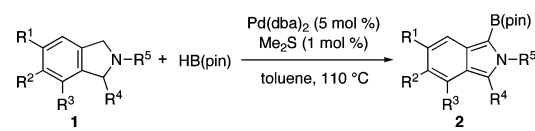
Table 1. Screening of Reaction Conditions^a



entry	additive (mol %)	time (h)	% yield ^b			
			2a	3a	4a	5a
1	—	1	50	6	4	38
2	—	15	11	49	3	26
3	Me ₂ S (1)	1	93 (71) ^c	1	1	3
4	Me ₂ S (1)	24	84	3	6	1
5	Me ₂ S (0.4)	1	75	3	<1	14
6	Me ₂ S (10)	1	90	<1	4	1
7	PPh ₃ (10)	1	0	0	9	0
8 ^d	Me ₂ S (1)	1	0	0	65	2

^a **1a** (0.20 mmol), HB(pin) (0.24 mmol), Pd(dba)₂ (5 mol %), and additive were stirred in toluene at 110 °C. ^b GC yield. ^c Isolated yield in 0.5 mmol scale reaction. ^d B₂(pin)₂ (0.6 equiv) was used instead of HB(pin).

Table 2. Pd-Catalyzed Dehydrogenation/C–H Borylation of **1**^a



entry	R ¹	R ²	R ³	R ⁴	R ⁵	time (h)	% yield ^b	
1	H	H	H	H	Et	1b	2	56 (2b)
2	H	H	H	H	<i>i</i> -Pr	1c	6	67 (2c)
3 ^{c,d}	H	H	H	H	(CH ₂) ₂ Ph	1d	4	73 ^e (2d)
4	Me	H	H	H	Me	1e	2	69 ^f (2e , 2e')
5	Me	Me	H	H	Me	1f	1	72 (2f)
6	H	H	Me	H	Me	1g	3	61 (2g)
7	H	H	H	Me	Me	1h	2	81 ^g (61) ^h (2h)

^a **1** (0.50 mmol), HB(pin) (0.60 mmol), Pd(dba)₂ (5 mol %), and Me₂S (1 mol %) were stirred in toluene at 110 °C. ^b Isolated yield. ^c **6** (10 mol %) was added. ^d **1** (0.30 mmol) and HB(pin) (0.36 mmol) were used. ^e The ¹H NMR yield was 82%. ^f Mixture of the 3-boryl (**2e**) and 1-boryl (**2e'**) isomers (54:46). ^g ¹H NMR yield. ^h Isolated yield after conversion to 1,2-dimethyl-3-phenylisoindole.

when the reaction was carried out with 10 mol % P(*t*-Bu)₂(2'-methylbiphenyl-2-yl) (**6**) together with Pd(dba)₂ (5 mol %) and Me₂S (1 mol %) (entry 3).⁹ No borylation of the aryl C–H and benzylic C–H bonds in **1d** took place under the same conditions. 2-Methylisoindoline derivatives **1e–h** were then subjected to dehydrogenation/C–H borylation (entries 4–7). Methyl groups on the benzene ring did not affect the reactivity, giving **2e–g** in good yields (entries 4–6). It should be noted that the 4-methyl derivative afforded **2g** exclusively,

with no formation of a 3-boryl derivative (entry 6). The reaction of 1,2-dimethylisoindoline (**1h**) gave the corresponding product **2h** in good yield (entry 7). On the other hand, none of the desired products were obtained in the reaction of isoindolines having H, Bn, Ph, and Ts on the nitrogen atom.¹⁰

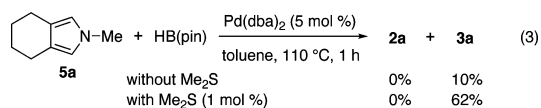
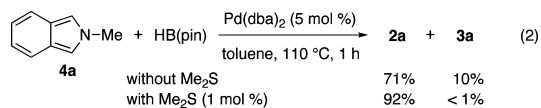
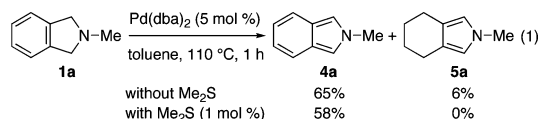
The second borylation of **2a** proceeded slowly under these conditions. Reactions of **1a** and **1b** with 3.0 equiv of HB(pin) gave 1,3-diborylisoindoles **7a** and **7b** in 83 and 88% yields, respectively, after 90 h (Table 3, entries 1 and 2). The use of phosphine ligand **6** (10 mol %) was effective in making these substrates undergo double borylation. Reaction of 5-methyl- and 5-methoxy-substituted **1e** and **1i** gave the corresponding products **7e** and **7i** in the presence of the Pd(dba)₂/Me₂S catalyst (entries 3 and 4).

Table 3. Synthesis of Doubly Borylated Isoindoles^a

		Pd(dba) ₂ (5 mol %) Me ₂ S (3 mol %)							
		toluene							
		110 °C, 90 h							
entry	R ¹	R ⁵	1	% yield ^b	entry	R ¹	R ⁵	1	% yield ^b
1 ^c	H	Me	1a	83 (7a)	3	Me	Me	1e	55 (7e)
2 ^c	H	Et	1b	88 (7b)	4	MeO	Me	1i	66 ^d (7i)

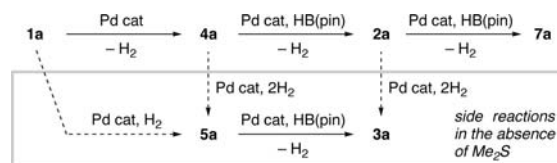
^a **1** (0.30 mmol), HB(pin) (0.90 mmol), Pd(dba)₂ (5 mol %), and Me₂S (3 mol %) were stirred in toluene at 110 °C for 90 h. ^b Isolated yield. ^c Carried out with **6** (10 mol %). ^d ¹H NMR yield.

To obtain insight into the mechanism, the reaction pathway was studied (eqs 1–3). Pd(dba)₂ converted **1a** to **4a** and **5a** in the absence of HB(pin),¹¹ although the reaction was slower than the original borylation (eq 1). In this reaction, addition of 1 mol % Me₂S suppressed the formation of **5a**. The borylations of **4a** and **5a** were then examined independently (eqs 2 and 3). The reaction of **4a** with HB(pin) in the absence of Me₂S gave a mixture of **2a** and **3a**, whereas **2a** was selectively formed in high yield when the reaction was carried out with 1 mol % Me₂S (eq 2). The reaction of **5a** with HB(pin) afforded only **3a**, in which the borylation was accelerated by addition of Me₂S (eq 3). These results suggest that the reaction pathway for the present dehydrogenation/borylation of isoindoline proceeds as shown in Scheme 1. Dehydrogenation of **1a** gives **4a**,^{11c} which is converted into **2a** by C–H borylation. The second borylation proceeds slowly to afford **7a**. When the reaction is carried out in the absence of Me₂S, hydrogenation of the six-membered ring in **1a**, **4a**, and **2a** may proceed to give **5a** and **3a**. The hydrogenation is probably catalyzed by a small amount of a different Pd species that is formed during the reaction. Addition of Me₂S may suppress the hydrogenation pathways by poisoning the catalyst.¹²

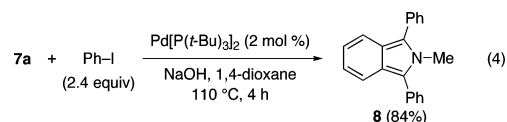


Synthetic application of the borylated isoindoles was demonstrated (eq 4). Suzuki–Miyaura coupling of **7a** with iodobenzene (2.4 equiv)

Scheme 1. Reaction Pathway (Solid Arrows Show Dehydrogenative Reactions; Dashed Arrows Show Hydrogenations)



under the conditions using Pd[P(*t*-Bu)₃]₂ catalyst with NaOH gave 1,3-diphenylisoindole **8** in 84% yield.



In conclusion, we have established an efficient access to borylated isoindoles via palladium-catalyzed dehydrogenation/C–H borylation of isoindolines.

Supporting Information Available: Experimental details and characterization data for the products. This material is available free of charge via Internet at <http://pubs.acs.org>.

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