

## Ir-Catalyzed Functionalization of 2-Substituted Indoles at the 7-Position: Nitrogen-Directed Aromatic Borylation

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Indoles have important biological functions. Traditionally, substituted indole syntheses fall into two classes:<sup>1</sup> (i) construction of the indole ring system from other substrates,<sup>1a</sup> and (ii) direct functionalizations of an existing indole.<sup>1b</sup> The Fischer indole synthesis is an example of the former class, while electrophilic addition is an example of the latter. In this regard, metal-mediated C–H functionalizations of indoles are particularly attractive because elaborations of unprotected indoles are possible.<sup>2</sup>

7-Functionalized indoles exist in some intriguing natural products,<sup>3</sup> such as asperazine,<sup>3a</sup> chloropectin I,<sup>3b</sup> diazomamide A,<sup>3c</sup> dragmacidin D,<sup>3d</sup> and TMC-95A and B.<sup>3e</sup> Because most of these have aryl or alkyl substituents at C7, cross-coupling reactions have been linchpins in synthetic approaches, as indicated in Scheme 1. Since C7 of indole is difficult to functionalize selectively, construction of the requisite coupling partners can be a nontrivial synthetic bottleneck.

For N-protected, 2-substituted indoles, reactions that selectively functionalize C7 are extremely rare.<sup>4,5</sup> Snieckus and co-workers have developed the most general method for functionalizing 2-substituted indoles. Theirs is a directed metalation approach that requires N-protection/deprotection.<sup>6</sup> Certainly, direct functionalization of *unprotected* 2-substituted indoles at C7 would have appeal. In this communication, we offer Ir-catalyzed borylation as one means toward this end.

In our studies on borylations of heterocycles,<sup>7</sup> we noted that small quantities of a single diborylated product arose when indole borylation was carried out with pinacolborane (HBPIn) at elevated temperatures. This product could be obtained in good yield by adjusting the HBPIn stoichiometry. A series of NMR experiments conclusively identified C7 as the site of the second borylation.

To assess the reaction scope, various substrates and conditions were examined. Bipyridine-ligated catalysts disclosed by Ishiyama, Miyaura, and Hartwig performed best.<sup>8</sup> The conversion of reactants to products was clean, as judged by <sup>1</sup>H and <sup>11</sup>B NMR, and intermediates were not detected. Of note, moderately elevated temperatures shortened reaction times *and* improved isolated yields. As shown in Table 1, borylation yields and functional group tolerance are good. Because substrates unsubstituted at C2 gave diborylated products (entries 13 and 14), most of the indoles in Table 1 are 2-substituted. Entry 11 is noteworthy as selective removal of the SiMe<sub>3</sub> allows access to the 7-borylated indole.<sup>9</sup> Entry 12 indicates that, for 2-phenylindole, borylation is favored at the indole 7-position over the phenyl sites. Significant N-borylation likely accounts for the low yield in entry 10.

Borylations at positions flanking the indole N hint at its participation in the reaction. Three possibilities that we envision are depicted in Scheme 2. In the first pathway, initial N–H scission affords an Ir–N intermediate. Subsequent Ir insertion into the C–H bond at C7 (not shown) would precede product formation. In the second pathway, hydrogen bonding between the hydrogen on the indole nitro-

### Scheme 1. Approaches to C7-Arylated Indole Natural Products

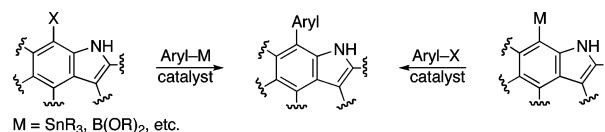


Table 1. Ir-Catalyzed Synthesis of 7-Borylated Indoles<sup>a</sup>

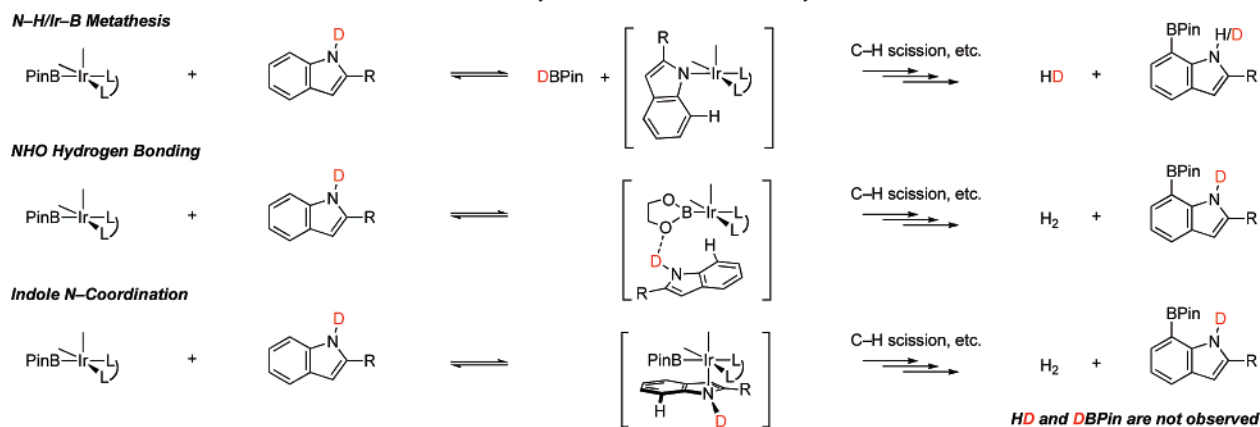
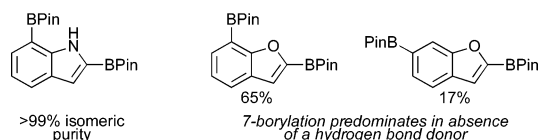
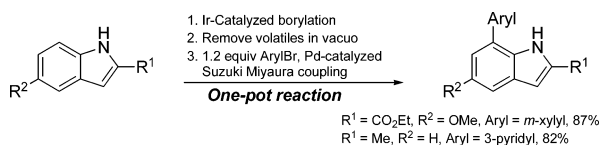
entry	product	time, yield	entry	product	time, yield
1		4 h, 78%	8		8 h, 79%
2 <sup>b</sup>		20 h, 91%	9 <sup>d</sup>		2.5 h, 90%
3		4 h, 88%	10 <sup>c</sup>		36 h, 45%
4		1 h, 87%	11 <sup>c</sup>		1 h, 76%
5 <sup>c</sup>		6 h, 83%	12		3 h, 69%
6 <sup>c</sup>		3 h, 82%	13 <sup>e</sup>		4 h, 90%
7 <sup>d</sup>		18 h, 64%	14 <sup>f</sup>		10 h, 92%

<sup>a</sup> Typically, a solution containing the indole, 1.5 equiv of HBPIn, and 3 mol % of pregenerated Ir catalyst<sup>8b</sup> was heated at 60 °C until the indole was consumed. Yields are for isolated products. See Supporting Information for details. <sup>b</sup> Reaction at room temperature. <sup>c</sup> 2.0 equiv of HBPIn used. <sup>d</sup> B<sub>2</sub>Pin<sub>2</sub> (1.0 equiv) was the borylating reagent. <sup>e</sup> 2.2 equiv of HBPIn used. <sup>f</sup> 2.5 equiv of HBPIn used.

gen and a pinacolate oxygen directs C–H insertion. In the third mechanism, coordination of the indole N to Ir directs C–H insertion.<sup>10</sup>

To test the first mechanism in Scheme 2, catalytic borylation of *N*-*d*<sub>1</sub>-5-chloro-2-methylindole using HBPIn was examined. At 50% conversion, deuterium incorporation in HBPIn or H<sub>2</sub> could not be detected by <sup>1</sup>H and <sup>11</sup>B NMR. Hence, the N–H activation mechanism can be excluded.

Diborylation of *N*-methyl indole was initially examined to exclude the second mechanism in Scheme 2. Like indole, initial borylation at C2 predominated, but 58 and 22% of the second borylation occurred at C6 and C5, respectively.<sup>11</sup> This outcome could be construed as support for H bonding, but a N coordination pathway could also be sterically sensitive to methylation.

**Scheme 2.** Potential N-Directed Mechanisms for Indole Borylation. Positions Affected by N-Deuteration are Indicated in Red**Chart 1.** Regiochemistry for Diborylation of Benzofuran and Indole**Scheme 3.** One-Pot, 7-Arylation of 2-Substituted Indoles

Because benzofuran is an isosteric analogue of indole absent the heteroatom-attached proton, its reactivity can address whether hydrogen bonding is a prerequisite for borylation at C7. As shown in Chart 1, the 2,7- and 2,6-isomers comprise 65 and 17% of the diborylated isomers of benzofuran. Even though the respective *meta* and *para* directing effects of OMe and BPin suggest that the second borylation should be favored at C6,<sup>12</sup> the 7-borylated isomer dominates, as was the case for indole.<sup>13</sup> Thus, hydrogen bonding to an acidic substrate proton is not absolutely required for the observed regioselectivity. On the basis of these observations, we presently favor the last mechanism in Scheme 2, where N-chelation to Ir (or B) directs borylation.<sup>14</sup>

A recent study raises concerns that the products in Table 1 might perform poorly in Suzuki–Miyaura cross-couplings.<sup>15</sup> Thus, two one-pot transformations were attempted, where the crude product from Ir-catalyzed borylation was subjected to Pd-catalyzed cross-coupling with two aryl bromides (Scheme 3). On the basis of the starting indoles, the arylated products were isolated in 87 and 82% yield, bolstering the prospects for synthetic utility.

In conclusion, Ir-catalyzed borylation provides the first general approach to functionalizing unprotected indoles at C7. Efforts toward further validating the mechanism, expanding the substrate scope, and elaborating the resulting boronate esters are ongoing.

**Acknowledgment.** We thank Professors Aaron Odom and Babak Borhan for helpful discussions, BASF, Inc. and Frontier Scientific, Inc. for generous gifts of HBPIn and B<sub>2</sub>Pin<sub>2</sub>, and the Michigan Economic Development Corp., NSF REU (R.C.R.), NIH (GM63188 to M.R.S.), and the Astellas USA Foundation for generous financial support.

**Supporting Information Available:** Spectral data for all new compounds, as well as general experimental procedures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (9) TBAF cleaves the SiMe<sub>3</sub> group, affording the 7-borylated indole in 88% yield. See Supporting Information for details.
- (10) An intriguing alternative to this latter mechanism, involving coordination of the indole N to B in one of the boryl ligands, is not shown.
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JA0631652