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Bismuth Acetate as a Catalyst for the Sequential Protodeboronation of Di- and Triborylated Indoles

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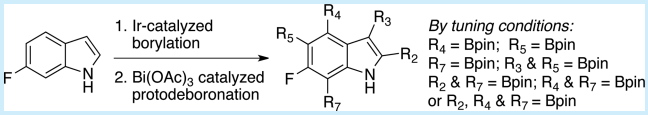
Supporting Information

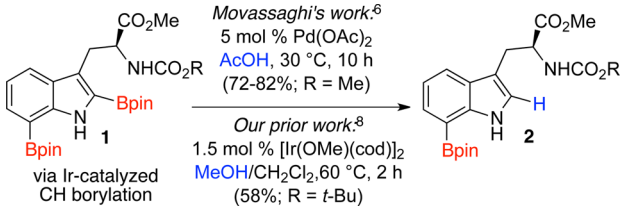
ABSTRACT: Bismuth(III) acetate is a safe, inexpensive, and selective facilitator of sequential protodeboronations, which when used in conjunction with Ir-catalyzed borylations allows access to a diversity of borylated indoles. The versatility of combining Ir-catalyzed borylations with Bi(III)-catalyzed protodeboronation is demonstrated by selectively converting 6-fluoroindole into products with Bpin groups at the 4-, 5-, 7-, 2,7-, 4,7-, 3,5-, and 2,4,7-positions and the late-stage functionalization of sumatriptan.



Arylboronates are versatile synthetic building blocks.[1,2] Iridium catalyzed C−H activation/borylation reactions are a powerful way of making such compounds as they can obviate the need for prior functionalization (e.g., halogenation), pyrophoric reagents, cryogenic conditions, etc.[3] While the regioselectivity of aromatic C−H borylations is mainly driven by steric effects, C−H acidity is a secondary driver.[4] For example, Ir-catalyzed borylation of unprotected indoles first installs a Bpin group at C2 and then upon further reaction at C7.[5]

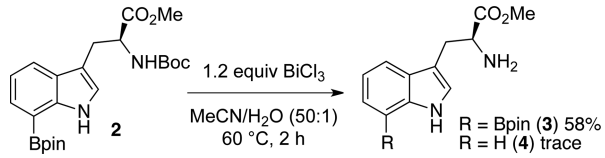
Recently, Movassaghi and co-workers[6] showed that the 2,7-diborylation of tryptophans, tryptamines, and 3-alkylindoles could be followed by in situ palladium-catalyzed C2-protodeboronation to selectively afford the C7 products (Scheme 1). While this tactic may not seem atom economical, from a strategic perspective such a borylation/protodeboronation sequence enables a streamlined approach to 7-borylated indoles that are otherwise difficult to access without additional steps and/or prefunctionalization[7] We too had observed selective deborylations of a number of diborylated heterocycles, including several 2,7-diborylated indoles (Scheme 1).[8] Our protodeboronations were Ir-catalyzed and for some systems could be exposing a crude Ir-catalyzed borylation mixture to protic material. Perhaps most usefully, we noted that for diborylated indoles, azaindoles, thiophenes, and benzthiophenes the first Bpin group to be installed during the Ir-catalyzed borylation was also the first Bpin to be removed in the Ir-catalyzed protodeboronation.

Scheme 1. Prior Art



During a total synthesis project, we prepared 7-borylated **2** as shown in Scheme 1. The next step in the synthesis called for $BiCl_3$-promoted removal of the Boc group[9] (Scheme 2). Close examination of this deprotection revealed that **3** formed along with trace amounts of byproduct **4** where the C7-BPin was missing. This small amount of deborylated byproduct led us to consider whether bismuth salts could facilitate selective protodeboronation in a way similar to the previously described Ir- and Pd-catalyzed protodeboronations. Such a method would be quite attractive because bismuth salts are earth abundant, harmless, and orders of magnitude less expensive than the corresponding precious metal salts.[10]

Scheme 2. Discovery of Bicatalyzed Protodeboronations



After screening $BiCl_3$, $Bi(OTf)_3$ and numerous other metal salts and other additives,[11] $Bi(OAc)_3$ emerged as the catalyst of choice. Subjecting purified **1** to 20 mol % $Bi(OAc)_3$ in MeOH (127 equiv) and THF at 80 °C (sealed tube) for 7 h afforded 7-borylated **2** in 90% yield (Scheme 3).

Given this favorable result, a series of indoles were subjected to multiple borylations (Table 1). Several of these Ir-catalyzed borylations are worthy of comment. Following C7 borylation, the next site for C−H borylation proved to be C4. In this way,

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Scheme 3. $Bi(OAc)_3$ Catalyzed Protodeboronation of 1

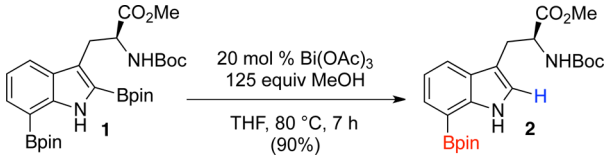
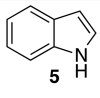
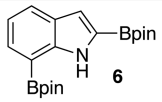
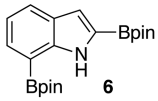
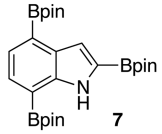
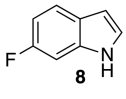
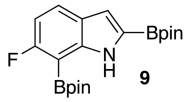
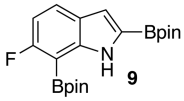
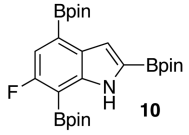
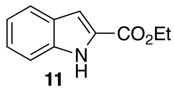
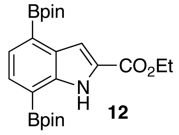
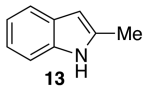
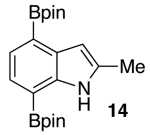
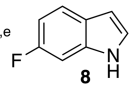
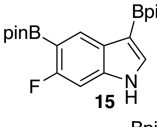
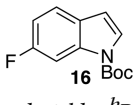
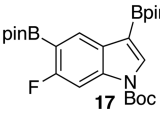
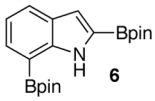
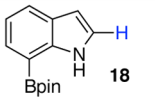
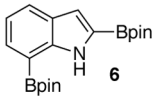
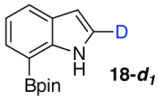
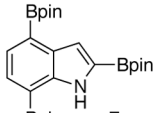
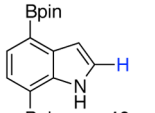
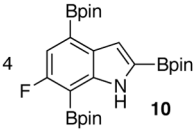
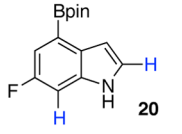
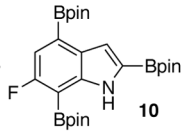
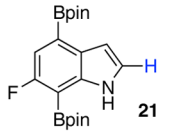
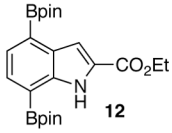
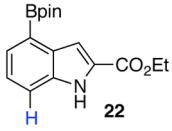
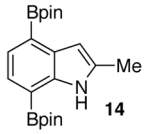
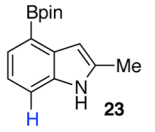
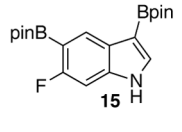
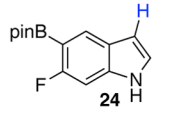
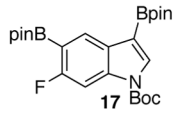
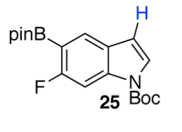


Table 1. Ir-Catalyzed Borylation of Indoles

entry	starting indole	product	time (h)	yield (%)[a]
1[b]	 5	 6	48	77
2[c]	 6	 7	12	96
3[b]	 8	 9	24	82
4[c]	 9	 10	12	92
5[b]	 11	 12	12	84
6[b]	 13	 14	24	71
7[d,e]	 8	 15	5	90
8[e]	 16	 17	3	80

[a]Isolated yields. [b]Borylations ran with 2.0 equiv B_2pin_2, 2.8 mol % HBpin, 0.5 mol % $[Ir(OMe)COD]_2$, 1 mol % d^tbpy, at 80 °C. [c]Borylations ran as described above, but with 1.0 equiv B_2pin_2. [d]Substrate stirred in neat HBpin (4 equiv) at rt for 1 h before being subjected to the borylation conditions. [e]Borylation ran with 2.0 equiv B_2pin_2, 3 mol % $[Ir(OMe)COD]_2$, 6 mol % d^tbpy, at 80 °C.

Table 2. $Bi(OAc)_3$ Catalyzed Protodeboronations

entry	starting indole	product	conditions and yield[a]
1	 6	 18	20 mol % $Bi(OAc)_3$, 125 equiv MeOH, THF, 80 °C, 17 h, 82%
2	 6	 18-d_1	20 mol % $Bi(OAc)_3$, 40 equiv CD_3OD, THF, 80 °C, 2.5 h, 83%
3	 7	 19	20 mol % $Bi(OAc)_3$, 125 equiv MeOH, THF, 80 °C, 17 h, 75%
4	 10	 20	20 mol % $Bi(OAc)_3$, 250 equiv MeOH, THF, 80 °C, 15 h, 80%
5	 10	 21	20 mol % $Bi(OAc)_3$, 60 equiv MeOH, THF, 80 °C, 5 h, 67%
6	 12	 22	40 mol % $Bi(OAc)_3$, 375 equiv MeOH, THF, 80 °C, 16 h, (54:9:41 **22**:**11**:**12**)[b] Ref 8 Ir-catalysis (33:67 **22**:**11**)[b] Modified[d] Ir-catalysis[c] 54% **22**, 13% **11**
7	 14	 23	40 mol % $Bi(OAc)_3$, 500 equiv MeOH, THF, 80 °C, 16 h, (52:5:43 **23**:**13**:**14**)[b] Ref 8 Ir-catalysis[c] 74% (91:9 **23**:**14**)[b]
8	 15	 24	20 mol % $Bi(OAc)_3$, 50 equiv MeOH, THF, 80 °C, 3 h, 88% Ref 8 Ir-catalysis[c] 66% (87:13 **24**:**8**)[b]
9	 17	 25	40 mol % $Bi(OAc)_3$, 500 equiv MeOH, THF, 80 °C, 16 h, (no reaction)[b] Ref 8 Ir-catalysis[c] 47% (60:40 **25**:**16**)[b]

[a]Isolated yields. [b]Ratio determined by ^{1}H NMR of the crude reaction mixture. [c]See Supporting Information for details. [d]3 mol % $[Ir(OMe)COD]_2$, 40 equiv MeOH, THF at rt.

2,4,7-triborylated indoles **7** and **10** (entries 2 and 4)[12,13] and 4,7-diborylated **12** and **14** (entries 5 and 6) were generated. We previously showed that placing a Boc[14] or Bpin[15] on the indole nitrogen directs borylation to the C3-position. Herein we report for the first time that, provided the C6 position is blocked, borylation of in situ N-borylated (entry 7) or N-Boc protected (entry 8) indoles occurs at the C3 and then the C5-positions, affording **15** and **17** respectively.[16−18]

With the borylated indoles in hand, we explored their $Bi(OAc)_3$ mediated protodeboronations (Table 2). Examining first 2,7-diborylated indole (**6**), we found that heating this compound with 20 mol % $Bi(OAc)_3$ and 125 equiv of ACS grade MeOH in THF afforded the 7-borylated indole (**17**) in 82% yield after 17 h (entry 1). Curiously, when we looked to deuterate **6**, the reaction was complete (83% isolated yield, 87% deuterium incorporation[19,20]) after stirring with 60 equiv of 99.8% CD_3OD for 12 h at room temperature (entry 2). A closer look into these differences revealed that, as we had observed with some of the Ir-catalyzed deboronations,[8] the grade of MeOH could significantly impact the reaction rate. For example, protodeboronation of **6** was complete in less than 3 h when anhydrous MeOH that came in sealed bottles was

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employed. Notably, reactions with either grade of methanol were reproducible. To highlight the method's relative robustness and economy, we chose to continue our study with the lower grade methanol.[21]

Within these parameters, 2,4,7-triborylated indole (**7**) was monoprotodeboronated to afford 4,7-diborylated indole (**19**) in 75% yield under similar conditions (entry 3). Attempts at the selective C2/C7 diprotodeboronation of **7** were disappointing. While 4-borylated indole (**20**) was formed as the major product, NMR analysis of the crude reaction mixture revealed a 50/45/5 mixture of **20**/**19**/indole.[22] In contrast, 2,4,7-triborylated-6-fluoroindole (**10**) underwent clean diprotodeboronation to afford **20** in 80% yield (entry 4) when the amount of MeOH was increased. A qualitative feature of deborylating **10** is that upon completion the reaction mixture takes on a slight pink color. Monoprotodeboronation of **10** (entry 5) provided further indication that these reactions are in part substrate dependent, as relative to **7**, trisboylated **10** required less time and equivalents of methanol to achieve the selective deborylation of the Bpin at C2 in similar yields.

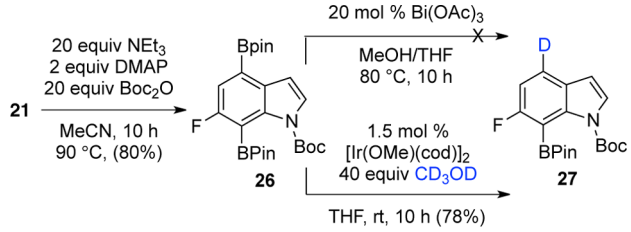
The protodeboronation of 4,7-diborylated-2-carboethoxyindole **12** (entry 6) was instructive for comparing the synthetic efficiency of Bi vs Ir-catalyzed deboronations. After 24 h at 80 °C, indole **12** and 40 mol % $Bi(OAc)_3$ in MeOH/THF gave monoprotodeboronated **22** as the major product along with fully protodeboronated **11** and unreacted **12** in a 54/9/41 ratio per NMR analysis of the crude reaction product. Our recently published Ir-mediated conditions of 2 h at 1.5 mol % $[Ir(OMe)COD]_2$ in 2:1 MeOH/CH_2Cl_2 at 60 °C[8] performed worse, giving the fully protodeboronated **11** and **22** in a ratio of 67:33. However, Ir catalysis in MeOH/THF (~1:6) at rt reacted best, affording **22** in 54% isolated yield along with 13% **11**. 4,7-Diborylated-2-methyindole **14** under the $Bi(OAc)_3$ conditions also afforded a 52/5/43 mixture of monoprotodeboronated **23** to **13** to **14**, respectively. Indole **14** was another substrate where Ir-mediated protodeboronation proved superior, giving a 91/9 mixture of **23** and starting material **14** with **23** being isolated in 74% yield (entry 7).

The 3,5-diborylated indoles (**15** and **17**) were informative substrates in their own right. **15** was exclusively monoprotodeboronated at C3 by 20 mol % $Bi(OAc)_3$ in MeOH/THF after 3 h at 80 °C, affording **24** in 88% yield (entry 8). Deboronation of **15** under our published Ir-catalyzed protodeboronation conditions proved less selective. With Ir, the crude reaction product contained 13% of fully deboronated 6-fluoroindole (**8**) and **24** was isolated in 66% yield. Attempts to optimize Ir-catalyzed deboronation of **15** never met with the selectivity observed with $Bi(OAc)_3$ unless the reaction was stopped prior to complete consumption of starting material.[22]

In contrast to **15**, Boc-protected **17** failed to undergo any deboronation by the action of $Bi(OAc)_3$ (entry 9). Indole **17** was susceptible to Ir-catalyzed deboronation, but again those conditions proved too harsh, giving the N-Boc protected 6-fluoroindole as the major product (21/79 **25**/**16** in the crude reaction mixture). The ratio of **25**/**16** improved to 60/40 (47% isolated yield of **25**) when the protodeboronation was run with 3 mol % Ir in MeOH/THF at room temperature for 10 h.

The reactivity difference between unprotected and *N*-Boc-indoles was probed further. 4,7-Diborylated-6-fluoroindole **21** was converted to its Boc derivative (**26**) and then subjected to both the Bi and Ir deboronation conditions (Scheme 4). Again, there was no reaction by $Bi(OAc)_3$. However, under the Ir-catalyzed protodeboronation conditions, using CD_3OD as the

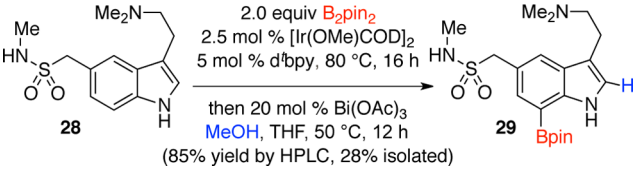
Scheme 4. Changing the Sequence of Protodeboronation



protic material, afforded the C4 deuterated product **27** in 78% yield. This result demonstrates that the general order of the first boron "on" being the first boron "off" in Ir-catalyzed deborations can be altered subsequent to borylation by introducing nearby functionality that is sterically demanding.

To demonstrate this chemistry in late-stage functionalization, we applied the one-pot diborylation/deboronation sequence to 5-HT receptor agonist sumatriptan (**28**) (Scheme 5). Thus,

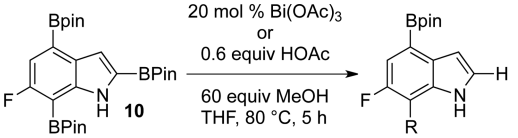
Scheme 5. Functionalization of Sumatriptan



indole **28** was thus converted to the 2,7-diborylated product. Selective $Bi(OAc)_3$ catalyzed deboronation of the crude product was then achieved in 85% yield by quantitative HPLC. However, the highly polar nature of **29** coupled with the hydrolytic instability of the Bpin ester made purification a challenge and the isolated yield of **29** was only 28%.

Questions on the mechanism of these deboronations remain. Analysis of the crude reaction material showed a mixture of boronates but no evidence of MeOBpin. The above examples do point to an interaction with the indole nitrogen as being important to achieving selectivity and gaining reactivity. Given Movassaghi and co-workers' Pd-catalyzed C2 protodeboronation of indoles with HOAc as the proton source,[6] we questioned if HOAc, either residual in the $Bi(OAc)_3$ or in situ generated, was playing a part in our bismuth-catalyzed protodeboronations. Toward this end, we examined the reactivity of diborylated **10** with 0.6 equiv of HOAc, which would correspond to the theoretical amount of acetic acid available from 20 mol % of $Bi(OAc)_3$ (Scheme 6). Under these conditions no protodebornation was observed. Increasing the amount of HOAc to 40 equiv had no affect as again only starting **10** was observed after 5 h at 80 °C. The next set of experiments was performed with $Bi(OAc)_3$ that had been washed with CCl_4 until the washings showed no HOAc by

Scheme 6. Exploring the Potential Role of HOAc



$Bi(OAc)_3$ "free" of HOAc: 90% 3:1 R = Bpin (**21**) / R= H (**20**)
$Bi(OAc)_3$ used "as is": 67% R = Bpin (**21**)
HOAc used in place of $Bi(OAc)_3$: no reaction

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NMR. Somewhat surprisingly, HOAc free $Bi(OAc)_3$ exhibited enhanced reactivity, as washed $Bi(OAc)_3$ afforded a 3:1 mixture of **21** and **20** while the same reaction with unwashed $Bi(OAc)_3$ gave no **20**. While not quantified, it appears that adventitious HOAc lowers the relative reactivity of the unwashed $Bi(OAc)_3$, perhaps by interfering with a putative Bi/indole nitrogen interaction.

In conclusion, bismuth(III) acetate is a safe, shelf stable, inexpensive, and operationally simple alternative to Ir and Pd for the catalytic protodeboronations of indoles. Where as the conditions for deboronations with Ir[8] and Pd[6] call for an inert atmosphere, Bi(III)-catalyzed deboronations can be run under air. Furthermore, while reaction times are dependent on the grade of methanol employed, solvents need not be distilled or degassed. In general, sequential deboronations with $Bi(OAc)_3$ occur in the same order in which the Bpin groups are installed via Ir-catalyzed borylation. Relative to related methods, $Bi(OAc)_3$ tends to offer greater selectivity in protodeboronations of di- and triborylated indoles. Thus, by tuning the C−H borylation and deboronation conditions, one can access a variety of boron substitution patterns from a single starting indole.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00356.

Experimental details and product characterization data (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors approved the final version of this manuscript.

Notes

The authors declare the following competing financial interest(s): MRS and REM acknowledge financial interest in BoroPharm, Inc..

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(20) The percent deuterium incorporation was determined by integration of the ^1H NMR spectrum.
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