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Boryl-Directed, Ir-Catalyzed C(sp^3)−H Borylation of Alkylboronic Acids Leading to Site-Selective Synthesis of Polyborylalkanes

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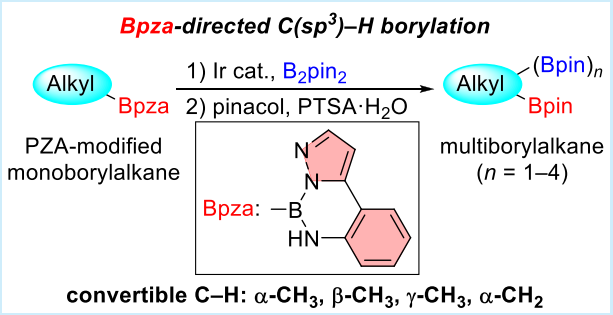
Supporting Information

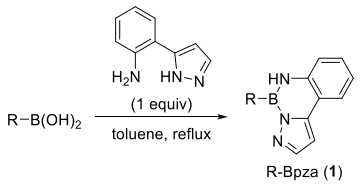
ABSTRACT: Pyrazolylaniline serves as a temporary directing group attached to the boron atom of alkylboronic acids in Ir-catalyzed C(sp^3)−H borylation. The reaction takes place at α-, β-, and γ-C−H bonds, giving polyborylated products including di-, tri-, tetra-, and even pentaborylalkanes. α-C−H borylation was generally found to be the preferred reaction of primary alkylboronic acid derivatives, whereas β- or γ-borylation also occurred if β- or γ-C−H bonds were located on the methyl group.



Polyborylated organic compounds are gaining increasing attention in organic synthesis because they allow stepwise conversion of boryl groups into various functional groups, leading to the selective synthesis of highly functionalized organic molecules.[1] Along with constant demands for polyborylated aromatic and heteroaromatic compounds, emerging interest has focused on polyborylalkanes in which boryl groups are attached to the sp^3-carbon centers. Particular attention is focused on synthetic applications of 1,1-diborylalkanes[2] because they show unique reactivities[3−6] resulting from the higher reactivity of one of the two boryl groups in synthetic transformations in addition to their utilization as reagents for the boron−Wittig reaction.[6] 1,1-Diborylalkanes have been accessible by several methods[7−11] such as borylation of 1,1-dihalides[7] and hydroboration of 1-borylalkenes and terminal alkynes.[8] Although transition-metal-catalyzed directed[12] or nondirected[13] C(sp^3)−H borylation would provide the most efficient routes,[11] difficulties lie in the site-selective introduction of multiple boryl groups into the alkane molecule. It should be noted that the boryl group accelerates the nondirected C−H borylation at the boron-bound carbon atom to allow geminally polyborylated products including 1,1,1-triborylalkane, although the substrate scope is still limited.[13j] It would be most attractive if a boryl group that is introduced initially in the molecule can serve as a directing group in C−H borylation to help the introduction of the second and even the third boryl groups in a site-selective manner.

We have developed pyrazorylaniline (PZA)[14] and anthranilamide (AAM)[15] as easily attachable and detachable *ortho*-directing boron modifiers in C(sp^2)−H functionalization of arylboronic acids such as Ru-catalyzed silylation,[14a,15] Ir-catalyzed borylation,[14c] and Rh-catalyzed alkenylation.[14d] PZA also works as a directing group in Ru-catalyzed C(sp^3)−H silylation of methyl and ethylboronic acids.[14b] In this communication, we disclose the optimized reaction conditions for the boryl-directed C(sp^3)−H borylation and its site selectivity depending upon the structure of the substrates (Scheme 1).

Scheme 1. Preparation of PZA-Modified Alkylboronic Acid



PZA-modified 1-octylboronic acid **1a**, which was easily accessible by heating octylboronic acid with PZA in toluene under reflux, was subjected to Ir-catalyzed C−H borylation (Table 1). In the presence of 2.5 mol % of [Ir(OMe)(cod)]$_2$ (**A**) and 1.2 equiv of B_2pin_2, borylation of **1a** proceeded at 50 °C. After treatment of the reaction mixture with pinacol for detection and quantification of the borylation product in the form of pinacol ester,[17] monoborylation product 1,1-diboryloctane **2a** was obtained in 59% yield (entry 1). α,α-Diborylated 1,1,1-triboryloctane **3a** was also obtained in 14% yield. It should be noted that only a trace amount of other borylated products was detected in the reaction mixture. Use of 3.0 equiv of B_2pin_2 increased the yield of **2a** to 66% (entry 2). Formation of double-borylation product **3a** became predominant when a larger amount (5 mol %) of [Ir(OMe)(cod)]$_2$ was employed (entry 3). Use of other solvents such as dimethoxyethane, dichloroethane, toluene, and cyclohexane decreased the

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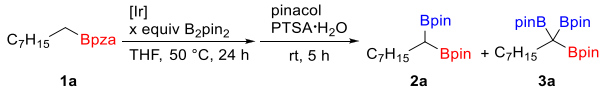
Table 1. C(sp^3)−H Borylation of PZA-Modified Octylboronic Acid 1a[a]



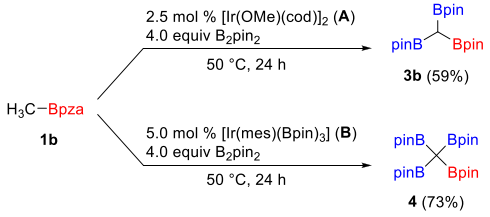
entry	Ir cat. (mol %)	B_2pin_2 (equiv)	yield[b] (%) 2a	3a
1	$[Ir(OMe)(cod)]_2$ (**A**) (2.5)	1.2	59	14
2	$[Ir(OMe)(cod)]_2$ (**A**) (2.5)	3.0	66	14
3	$[Ir(OMe)(cod)]_2$ (**A**) (5.0)	3.0	12	64
4	$[IrCl(cod)]_2$ (5.0)	3.0	35	0
5	$[Ir(mes)(Bpin)_3]$ (**B**) (5.0)	3.0	3	77

[a]Reaction conditions: **1a** (0.10 mmol), Ir catalyst, and B_2pin_2 were heated in THF (0.5 mL). To the mixture were added pinacol and *p*-toluenesulfonic acid monohydrate at room temperature, and the mixture was stirred for 5 h. [b]GC yield.

yield of **3a** (see the Supporting Information (SI)). The necessity of the pza group was confirmed by a reaction of pinacol-modified octylboronic acid (*n*-octylBpin) under similar reaction conditions, which gave no C−H borylation product (see the SI). Whereas $[IrCl(cod)]_2$ showed low catalytic activity (entry 4), trisborylcomplex $[Ir(mes)(Bpin)_3]$ (**B**)[16] exhibited high catalytic activity, giving α,α-diborylated product **3a** in 77% yield (entry 5).

By using 2.5 mol % of $[Ir(OMe)(cod)]_2$ (**A**) and 4.0 equiv of B_2pin_2 at 50 °C, PZA-modified methylboronic acid **1b** afforded triborylmethane **3b** through α,α-diborylation in 59% isolated yield (Scheme 2). Use of $[Ir(mes)(Bpin)_3]$ (**B**) as a catalyst led

Scheme 2. Polyborylation of PZA-Modified Methylboronic Acid



to the formation of tetraborylmethane **4** through α,α,α-triborylation in 73% yield. To our knowledge, this is the first catalytic synthesis of tetraborylmethane.[18]

The time course of the conversion of **1b** in the presence of catalyst **A** or **B** was separately monitored by GC analysis (Figure 1). In both reactions, a diborylation product, namely, triborylmethane, was quickly formed with consumption of the starting MeBpza (**1b**). It is notable that the initial monoborylation product was rapidly converted into the triborylmethane. With highly active catalyst $[Ir(mes)(Bpin)_3]$, thus formed triborylmethane was gradually converted into tetraborylmethane. These results suggest that the boryl group accelerates the C−H borylation electronically but decelerates it sterically.

Various alkylboronic acid derivatives were subjected to the Bpza-direced C−H borylation in the presence of $[Ir(OMe)(cod)]_2$ (**A**) or $[Ir(mes)(Bpin)_3]$ (**B**) as a catalyst (Table 2). In the reactions of *n*-octylBpza (**1a**), 1,1-diboryloctane **2a** was selectively formed and isolated in 54% yield using **A** as a catalyst, whereas 1,1,1-trisboryloctane **3a** was obtained selectively in the presence of **B**. β-Branched as well as γ-branched primary

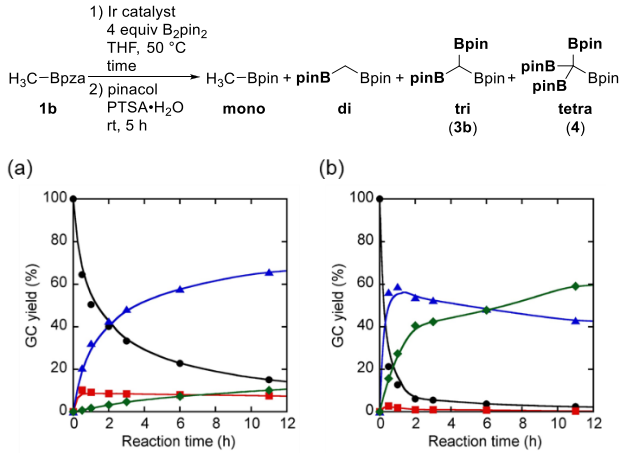
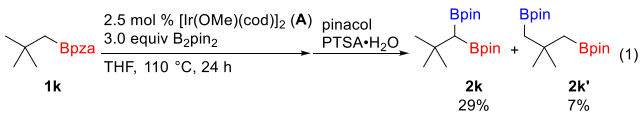
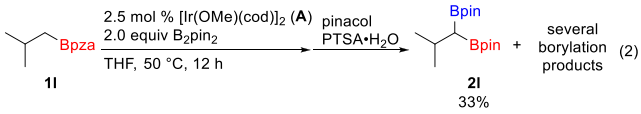


Figure 1. Time course for polyborylation of PZA-modified methylboronic acid with (a) 2.5 mol % of $[Ir(OMe)(cod)]_2$ and (b) 2.5 mol % of $[Ir(mes)(Bpin)_3]$. GC yields of mono- (●), di- (■), tri- (▲), and tetraborylmethane (◆) were plotted against the reaction time.

alkylboronic acid derivatives **1c−e** afforded the corresponding α-monoborylated products in good yields (entries 3−5). Alkylboronates **1f−h**, having phenyl groups at the β-positions, also afforded α-monoborylated products in good yields (entries 6−8). Selective C(sp^3)−H borylation over C(sp^2)−H borylation was also observed in the reactions of benzylic boronates **1i** and **1j**, even though the aromatic hydrogen atoms are located at the γ-positions (entries 9 and 10).

In the course of our examinations of the Bpza-directed C−H borylation of alkylboronates, we encountered low-yield formation of expected α-borylation products. For instance, neopentylBpza **1k** underwent the C−H borylation only sluggishly to form α-monoborylation product **2k** in low yield along with γ-monoborylation product **2k′**, with the formation of trace amounts of double-borylation products (eq 1). This result





suggests that γ-borylation can be compatible with α-borylation and that, by incorporation of the first boryl groups at either the α- or γ-position, the other C−H bond may become more sterically congested, suppressing the second C−H borylation. The reaction of isobutylboronate **1l**, a β-branched alkylboronate, with 2 equiv of B_2pin_2 afforded α-C−H borylation product **2l** in only 33% isolated yield (eq 2). Careful inspection of the reaction mixture suggested the formation of several other C−H borylation products including those containing three boryl groups, although structural identification of each product was challenging.

We then subjected **1l** to the reaction with 3 equiv of B_2pin_2 under the same reaction conditions. We found the predominant formation of triboryl product **5**, which was derived through C−H borylation at both the α- and γ-positions (Table 3, entry 1).

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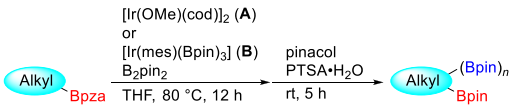
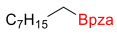
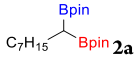
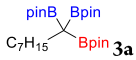
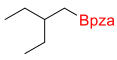
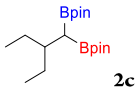
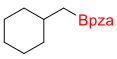
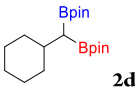
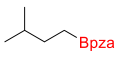
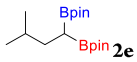
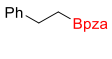
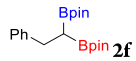
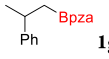
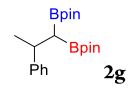
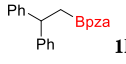
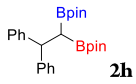
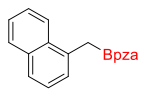
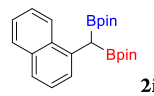
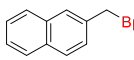
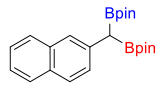
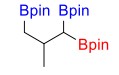
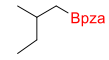
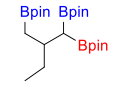
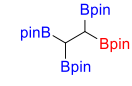
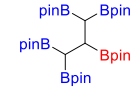
Table 2. α-C−H Borylation of PZA-Modified Primary Alkylboronic Acids[a]



entry	substrate	catalyst	equiv of B_2Pin_2	product	yield (%)[b]
1[c]	 **1a**	**A** 2.5 mol %	1.2	 **2a**	54
2[c,d]	**1a**	**B** 5 mol %	3	 **3a**	60
3	 **1c**	**A** 2.5 mol %	2	 **2c**	78
4[c]	 **1d**	**B** 2 mol %	1.2	 **2d**	80
5	 **1e**	**A** 2.5 mol %	2	 **2e**	67
6	 **1f**	**A** 2.5 mol %	1.2	 **2f**	50
7	 **1g**	**A** 2.5 mol %	2	 **2g**	70
8	 **1h**	**A** 2.5 mol %	2	 **2h**	69
9	 **1i**	**A** 2.5 mol %	2	 **2i**	98
10	 **1j**	**A** 2.5 mol %	2	 **2j**	76

[a]Reaction conditions: **1** (0.30 mmol), Ir catalyst, and B_2pin_2 were heated in THF (1.5 mL). To the mixture was added pinacol and *p*-toluenesulfonic acid monohydrate at room temperature and stirred for 5 h. [b]Isolated yield. [c]50 °C. [d]24 h.

Table 3. β- and γ-C−H Borylation of PZA-Modified Alkylboronic Acids[a]

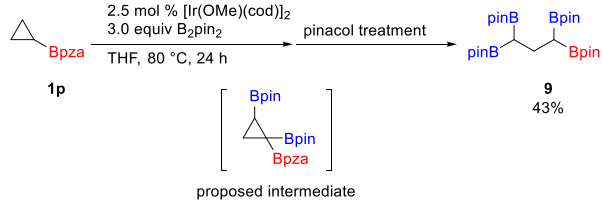
entry	substrate	catalyst	equiv of B_2Pin_2	temp (°C)	time (h)	product	yield (%)[b]
1	**1l**	**A** 2.5 mol %	3	50	12	 **5**	62
2	 **1m**	**B** 10 mol %	5	80	24	 **6**	74
3	 **1n**	**A** 5 mol %	4	50	24	 **7**	55
4	 **1o**	**B** 6 mol %	5	80	24	 **8**	60

[a]See footnote a in Table 2. [b]Isolated yield.

The same trend was observed in the reaction of 2-methylbutylboronic acid derivative **1m**; in this case, α,γ-diborylated product **6** was obtained in 74% yields with 5 equiv of B_2pin_2 at 80 °C (entry 2), whereas α-monoborylated product **2m** was obtained in only 25% yield with 2 equiv of B_2pin_2 at 50 °C. These results are interesting when compared with the reaction of β-branched **1c** and **1d** shown above, which resulted in the predominant formation of the α-C−H borylation products (Table 2, entries 3 and 4). It is suggested that the presence of the less sterically hindered γ-C−H bond on the methyl group allowed γ-borylation to compete with α-borylation. The reaction of ethylBpza **1n** also suffered from the formation of a mixture of polyborylation products under the standard reaction conditions using 2 equiv of B_2pin_2. The use of 4 equiv of B_2pin_2 allowed us to isolate tetraboryl product **7**, which was derived through α,β,β-triple C−H borylation (entry 3). In the reaction of isopropylBpza **1o**, we observed no α-borylation but found the selective formation of pentaboryl product **8**, a quadruple β-borylation product, which was isolated in 60% yield (entry 4). CyclohexylBpza showed no reaction under identical reaction conditions.

CyclopropylBpza **1p** was subjected to the reaction with B_2pin_2 using $[Ir(OMe)(cod)]_2$ (**A**) as a catalyst (Scheme 3). We isolated 1,1,3,3-tetrakisborylpropane **9** in 43% yield through cleavage of the C−C bond in the cyclopropane ring.[19] Analysis of the crude mixture obtained by the reaction using 1.2 equiv of B_2pin_2 at 50 °C for 12 h suggested the formation of 1,1,2-trisborylcyclopropane before the C−C bond cleavage (see the SI).

Scheme 3. Borylation of PZA-Modified Cyclopropylboronic Acids



The synthetic utility of these polyborylated molecules has been demonstrated by a cross-coupling reaction[3b] and boron-Wittig reaction[6] according to previous reports (Scheme 4). 1,1-Diborylalkane **2c**, which was prepared on a gram-scale reaction under modified reaction conditions (1.5 mol % of catalyst **A**, see the SI for the details), underwent cross-coupling with *m*-bromotoluene at one of the two boryl groups, giving secondary organoboronate **10** in good yield. α-Lithiated **2c** reacted with 3-phenylpropanal and gave alkenylboronate **11** through a boron-

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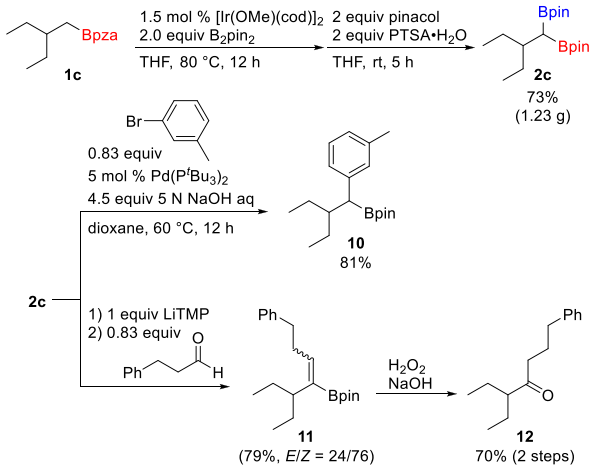
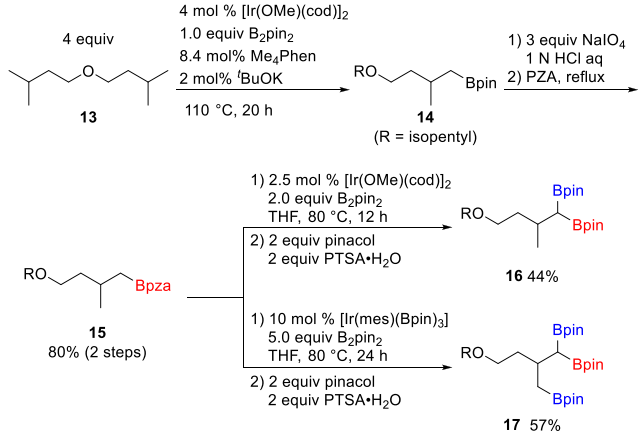
Scheme 4. Transformation of 1,1-Diborylalkane 2c



Wittig reaction, which was subsequently converted into ketone **12**.

The present Bpza-directed borylation allows synthesis of polyborylated organic compounds from unfunctionalized starting materials in combination with nondirected C−H borylation (Scheme 5). Monoboryl ether **14** was prepared by

Scheme 5. Synthesis of Polyborylated Ester from Diisopentyl Ether



Ir-catalyzed nondirected C−H borylation of diisopentyl ether (**13**) in the presence of a catalytic amount of potassium *tert*-butoxide.[13g] Hydrolysis of boronic acid pinacol ester followed by condensation with PZA gave PZA-modified monoboryl ether **15** in 80% yield. In the presence of 2.0 mol % of $[Ir(OMe)(cod)]_2$ and 2.0 equiv of B_2pin_2, borylation of **15** proceeded at the α-C−H bond preferentially, giving 1,1-diboryl ether **16** in 44% yield. In addition, by using 10 mol % of **B** and 5.0 equiv of B_2pin_2 at 80 °C for 24 h, 1,1,3-triboryl ether **17** was obtained in 57% yield.

In conclusion, we established Ir-catalyzed C(sp^3)−H borylation of alkylboronic acids by attaching PZA as a removable directing group on the boron atom. Although the directed C−H borylation can proceed at the α-, β-, and γ-C−H bonds, the selectivity largely depends upon the structure of the alkyl group (Figure 2). In general, α-borylation is the preferred reaction pathway in the reactions of primary alkylboronic acid derivatives. However, if there is a methyl C−H bond at either the β- or γ-position, these C−H bonds undergo C−H borylation

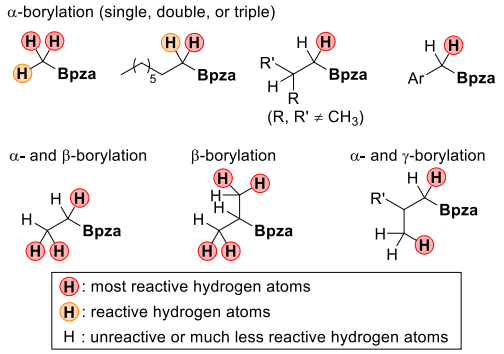


Figure 2. Classification of site selectivity of Bpza-directed C−H borylation by substrate structures.

at rates comparable to that of α-C−H borylation, leading to multiple C−H borylations. Although no α-C−H borylation takes place with secondary alkyl derivatives, borylation can proceed at other methyl C−H bonds as exemplified by the reaction of isopropylBpza, which undergoes quadruple β-C−H borylation. The present boryl-directed C−H borylation enables the efficient synthesis of polyborylated organic molecules from unfunctionalized starting materials by employing nondirected C−H borylation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02112.

Detailed experimental procedures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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