

# Sulfur-Directed Ligand-Free C-H Borylation by Iridium Catalysis

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## **(5)** Supporting Information

**ABSTRACT:** An iridium-catalyzed *ortho* C–H borylation reaction directed by cyclic dithioacetal moiety is disclosed. A series of borylation products were obtained in moderate to good yields under mild conditions in exclusive mono- and *ortho*-regioselectivity. Thus, the 1,3-dithiane or 1,3-dithiolane group serves as a remarkable effective directing group for C–H borylation without any ligand assistance. The further transformations of the borylation products are also carried out to change boryl group to other functional groups.



rganoboron compounds are well-known as valuable synthetic scaffolds in preparation of drugs, agrochemicals and organic materials.<sup>1</sup> In comparison with the conventional methods based on functional group transformations, the direct C-H borylation, as a more atom-efficient approach for preparation of organoboron compounds, has gained tremendous attention in the past decades.<sup>2</sup> Among these, one of the important and effective strategies for regioselective borylation is ortho C-H borylation directed by a functional group within a substrate. Currently, effective directing groups have included esters, ethers, amines, imines, amides, carbamates, phosphines, and hydrosilanes.<sup>3</sup> These groups are mainly based on the coordinative oxygen, nitrogen, phosphine atoms, etc., which are essential to stabilize the metallacycle intermediate. In contrast, sulfur, generally regarded as a strongly coordinative atom with transition metals, has been far less explored in directed C-H activation. Thioether is widely present in many bioactive compounds and natural products. Moreover, its transformations to various functional groups are well investigated. Therefore, the utilization of thioether as a directing group for ortho C-H borylation should be of great potential in preparing transformative boron- and sulfur-containing building blocks.

However, only limited examples have recently been disclosed for ortho C-H borylation directed by thioethers. Braun and coworkers used an -SCF<sub>3</sub> group as a directing group to achieve Rh-catalyzed *ortho* C–H borylation reactions (Scheme 1, eq 1); monoborylation and 2,6-diborylation products could be obtained.<sup>4</sup> Kuninobu and Kanai also reported an ortho C-H borylation using aryl alkyl thioethers as the substrates.<sup>5</sup> A Lewis acidic boryl group that was incorporated into a bipyridine ligand was thought to be key for recognizing the thioether group through acid-base interaction and promoted the ortho selective C-H borylation (Scheme 1, eq 2). During the submission of this manuscript, iridium-catalyed ortho C-H borylation of phenol and aniline derivatives using a methylthiomethyl (MTM) protecting group has appeared.<sup>6</sup> In this work, we report an iridium-catalyzed ligand-free ortho C-H monoselective borylation reaction of various 2-aryl 1,3-

## Scheme 1. Transition-Metal-Catalyzed Ortho C–H Borylation of Thioethers

1) SCF<sub>3</sub> as a directing group (Braun, 2014)



2) Controlled by Lewis acid-base interaction (Kuninobu and Kanai, 2017)



3) This work: dithioacetal as the directing group



dithianes and 1,3-dithiolanes (Scheme 1, eq 3). Notably, the dithioacetal compounds can be readily prepared from aldehydes and have previously been widely used as protected carbonyls or umpolung synthons in organic synthesis.<sup>7,8</sup>

As shown in Table 1, the reaction conditions were investigated with 2-phenyl-1,3-dithiane as a model substrate, which was readily prepared in one step from benzaldehyde. Several transition-metal catalysts were initially tested. Pd- $(OAc)_2$  is totally ineffective for the reaction (Table 1, entry 1). Ruthenium and rhodium catalysts promoted the reaction to furnish *ortho* monoborylation product **2a** exclusively, although

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 Table 1. Optimization of Sulfur-Directed Ortho C-H

 Borylation<sup>a</sup>

		B2pin2 1.2 equiv [M] 2 mol % solvent, 80 °C, 20 h	S Bpin 2a	n
entry	[M]	ligand	$\operatorname{conv}^{\boldsymbol{b}}(\%)$	yield <sup>b</sup> (%)
1	$Pd(OAc)_2$		0	0
2	Ru(PPh <sub>3</sub> ) <sub>3</sub> Cl <sub>2</sub>		15	12
3	$[RhCl(cod)]_2$		20	17
4	$[Ir(OMe)(cod)]_2$		28	86
5	$[IrCl(cod)]_2$		91	87
6	$[IrCl(cod)]_2$	$PPh_3$	10	8
7	$[IrCl(cod)]_2$	PCy <sub>3</sub>	17	15
8	$[IrCl(cod)]_2$	dtbpy	55	53
9	$[IrCl(cod)]_2$		80	77
10	$[IrCl(cod)]_2$		43	42
11	$[IrCl(cod)]_2$		53	51
12	$[IrCl(cod)]_2$		10	6
13	$[IrCl(cod)]_2$		58	55
14	$[IrCl(cod)]_2$		60	56

<sup>*a*</sup>Reaction conditions: **1a** (0.5 mmol), B<sub>2</sub>pin<sub>2</sub> (0.6 mmol), [M] 2 mol % in 1.0 mL of solvent, 80 °C, 20 h. <sup>*b*</sup>Conversion, yields were based on <sup>1</sup>H NMR analysis of the crude products with **1a** as the limiting reagent.

in quite low yields (Table 1, entries 2 and 3). To our delight, the reaction proceeded in high conversion using 1 mol % of  $[IrOMe(cod)]_2$  or  $[IrCl(cod)]_2$ , giving the desired product in 86% and 87% yield, respectively (Table 1, entries 4 and 5). Attempts at addition of P- or N-based ligands were unsuccessful; all of the reactions were dramatically inhibited (Table 1, entries 6–8). At last, various solvents were also screened (Table 1, entries 9–14), and the results showed that nonpolar solvent *n*-hexane was the best and gave highest conversion to 2a.

With the optimized reaction conditions in hand, we explored the substrate scope by varying both the substituents on the aryl group and the size of the dithioacetal ring. (Scheme 2). In general, the sterically less encumbered five-membered 1,3dithiolane substrates (2c, 2e, 2j, 2l, 2n) were also effective for this reaction system, although the reaction temperature had to be raised to 100 °C. Both electron-withdrawing and electrondonating groups at the para or meta position were found to be compatible in the present ortho-borylation reaction, giving the desired products in moderate to good yields (2b-p). Reactive halogen groups such as -Br and -I atoms were retained (2i, 2j, 20, 2p). Interestingly, the substrates bearing potentially competitive directing groups such as an ester group  $(1d, 1e)^3$ or an -SMe group  $(1g)^5$  exclusively yielded the monoborylation products at the ortho position of 1,3-dithiane. These results make the current method complementary to the previous works in controlling site selectivity of the borylation of multisubstituted arenes. Ortho-substituted 2-aryl 1,3dithianes, however, were much less reactive under the present conditions. While 2-(o-tolyl)-1,3-dithiane (1q) gave monoborylation product 2q in 70% yield accompanied by benzylic C-H borylation product (2q', not shown) in 20% yield, substrates such as 1r and 1s were totally unreactive. These results were consistent with the fact that no 2,6-diborylation products have been detected in all cases. The ortho-substituent might inhibit the reaction by sterically or electronically forcing

[IrCl(cod)]<sub>2</sub> 1 mol % n (آ B<sub>2</sub>pin<sub>2</sub> 1.2 equiv *n*-hexane, 80 °C, 20 h Bpin **1** n = 0, 1 2 S ή)<sub>n</sub> MeC Bpin Bnin F<sub>2</sub>C Bnin 2a, 80% **2b,** n = 1, 85% 2d, n = 1, 90% (76% in 1.5 mmol scale) **2e**, n = 0, 70%<sup>b</sup> **2c.** n = 0. 87%<sup>b</sup> Bpin MeC Bpin E Bpin MeS **2f**, 80% 2g, 85% 2h, 83% ) n MeC Bpin Bnin Bpin **2m,** n = 1, 87% 2i, n = 1, 81% 2k, n = 1, 81% **2j**, n = 0, 91%<sup>b</sup> **2I**, n = 0, 81%<sup>b</sup> **2n**, n = 0, 72%<sup>b</sup> Bpin Bpin Bpin **2q,** 70%<sup>c,d</sup> 20, 89% **2p**, 60% QМе S Bpin Bpin Bpin 2t, n = 1, 87% **2r**, 0%<sup>c</sup> **2s**, 0%<sup>c</sup> **2u,** n = 0, 82%<sup>b</sup> Bpin Bpin Bpin 2v, 56% 2w. 60% **2x**, 70%

<sup>*a*</sup>Reaction conditions: 1 (0.5 mmol),  $B_2pin_2$  (0.6 mmol),  $[IrCl(cod)]_2$  (0.005 mmol) in 1.0 mL of *n*-hexane, 80 °C, 20 h, yields were based on isolated spectroscopically pure materials. <sup>*b*</sup>Reaction temperature: 100 °C. <sup>*c*</sup>Reaction temperature: 90 °C. <sup>*d*</sup>Monoborylation of methyl group (2q') was observed in 20% yield.

improper conformation of the dithioacetal group, which is necessary for successful directed borylation. Furthermore, 2naphthaldehyde-derived 1,3-dithiane and 1,3-dithiolane could be selectively borylated at the 3-position (2t, 2u). Fivemembered heteroaryl 1,3-dithianes also yielded 2v and 2w in moderate yields. In the case of ferrocene-containing substrate, excellent regioselectivity was observed in this reaction system (2x). Finally, a 1.5 mmol scale reaction of 1a under the standard conditions provided 2a in 76% isolated yield.

We then tested if this catalytic system could be applicable to substrates bearing flexible acyclic thioethers (Scheme 3). Treatment of benzyl(methyl)sulfane (3a) under the standard conditions resulted in the formation of *ortho*-monoborylation (4a) and 2,6-diborylation product (5a) in 50% and 46% yield, respectively. Similarly, benzyl(phenyl)sulfane (3b) gave the monoborylation compound 4b in 52% yield and the diborylation product 5b in 47% yield. The fact that the sum

Scheme 2. Scope of Iridium-Catalyzed Ortho C(sp<sup>2</sup>)-H Borylation of 2-Aryl-1,3-dithianes and 1,3-Dithiolanes<sup>*a*</sup>



<sup>*a*</sup>Reaction conditions: substrate **3** (0.5 mmol),  $B_2pin_2$  (0.6 mmol), [IrCl(cod)]<sub>2</sub> (0.005 mmol) in 1.0 mL of *n*-hexane, 80 °C, 20 h. <sup>*b*</sup>Isolated yield.

of the yields of the monoborylation and the diborylation products was over 100% indicated that HBpin also took part in this reaction.

Based on the observation where 1q afforded 20% of  $C(sp^3)$ – H borylation product 2q' (Scheme 2), we also explored this method in benzylic  $C(sp^3)$ –H borylation (Scheme 4), which



[IrCl(cod)]<sub>2</sub> (0.005 mmol) in 1.0 mL of *n*-hexane, 90 °C, 20 h. <sup>b</sup>Isolated yield. NA: not applicable.

has yet been revealed using a sulfur-directing group in the past.<sup>9</sup> Thus, under the typical conditions, thioanisole (6a) gave *ortho*borylation products (9a) in 24% yield, and *ortho*-methylphenyl methyl thioether 6b yielded a mixture of benzylic monoborylation (7b), benzylic diborylation (8b), and *ortho*borylation (9b) products. When 6c was subjected to this reaction, the corresponding benzylic monoborylation (7c) and diborylation (8c) products were formed in good overall yield (75%).

In considering the possible mechanism of this ligand-free iridium-catalyzed borylation, we were inspired by a phosphinedirected ligand-free C-H borylation disclosed by Clark and coworkers.<sup>3k</sup> Thus, a thioether moiety might serve as both a directing group and a supporting ligand in the current borylation reaction (Scheme 5). Reaction of [IrCl(cod)]2 with the dithioacetal substrate and  $B_2 pin_2$  might form Ir(III) intermediate A via ligand exchange and oxidative addition. A plausible intramolecular C-H activation of A then might generate iridacycle B featuring a C,S-bidentate ligand that might serve as a supporting ligand for the formally ligand-free catalysis. Intramolecular C-H oxidative addition might generate Ir(V) intermediate C which then could undergo reductive elimination to form D. Ligand exchange of D with the substrate 1a could produce the borylation product 2a and Ir(III) hydride E, which finally could undergo  $\sigma$ -bond metathesis with  $B_2 pin_2$  to regenerate **B**. Compared to the flexible benzyldiphenylphosphines<sup>4</sup> where ortho-diborylation products were often formed together with monoborylation products, the more rigid cyclic dithioacetal substrates should be more sensitive to ortho-substituents and therefore solely

Scheme 5. Proposed Mechanism of Ortho-Borylation of 1a



afforded monoborylation products. More comprehensive study of the mechanism is ongoing to understand the reaction.

Further transformations of the boryl group in 2a were conducted to demonstrate the potential synthetic usefulness of the borylation product as shown in Scheme 6. Consequently,





copper-catalyzed or mediated reactions of **2a** with NaN<sub>3</sub>, CuCl<sub>2</sub>, diphenyl disulfide, diphenyl diselenide, and diphenyl ditelluride under operationally simple conditions smoothly afforded 2-(2-azidophenyl)-1,3-dithiane (**10**), 2-(2-(phenylthio)phenyl)-1,3-dithiane (**11**), 2-(2-chlorophenyl)-1,3-dithiane (**12**), 2-(2-(phenylselanyl)phenyl)-1,3-dithiane (**13**), and 2-(2-(phenyltellanyl)phenyl)-1,3-dithiane (**14**) in moderate to good yields. The cleavage of the 1,3-dithiane was

achieved after a Suzuki–Miyaura coupling reaction, giving the corresponding product **15** in excellent yield.

In summary, we have developed a sulfur-directed, particularly a cyclic dithioacetal group-directed, ligand-free C–H borylation reaction using commercially available iridium catalyst. This highly *ortho-* and monoselective borylation under operationally simple conditions provides a new, practical, and complementary approach for the rapidly developing regioselective C–H borylation chemistry.

## ASSOCIATED CONTENT

#### **Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.7b03008.

Detailed experimental procedures; spectral data of products (PDF)

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#### Notes

The authors declare no competing financial interest.

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