論文の内容の要旨

論文題目 Development of *ortho*-Selective C-H Borylation Reaction of Aromatic Compounds
(芳香族化合物オルト位選択的 C–H 結合ホウ素化反応の開発)

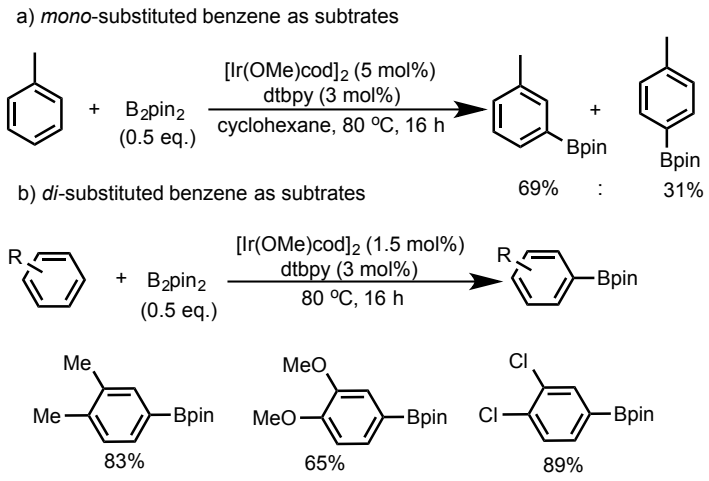
氏　　名　李　紅亮

Research background

Since its discovery in 1950s, C-H activation reactions has become a powerful method to direct functionalization of alkyl, alkenyl, and aryl C-H bonds over the past few decades. Among of them, iridium catalyzed transformation of aryl C-H bonds to C-B bonds[1] is one of the most useful methods because the borylated compounds can be converted to more complex molecules by further transformations, such as cross-coupling reactions. However, a central challenge in these reactions is controlling their site selectivity, especially for *ortho*-selectivity, because steric effects often dominate the regioselectivity of C-H borylation[2].

As shown in **Figure 1**, using *mono*-substituted benzene as substrates, a mixture of *meta*- and *para*- borylated products was formed in a 2 : 1 ratio [3]. The *ortho*-isomer was not formed due to the steric repulsion between the catalytic complex and the substituent of the substrates. In addition, borylation always proceeded at the position of less steric hindrance in the case of disubstituted aryl substrates. Therefore, developing a method which could overcome the repulsion is highly desirable to achieve *ortho*-selective C-H borylation.

Figure 1 Borylation reaction of mono- and di-substituted arenes

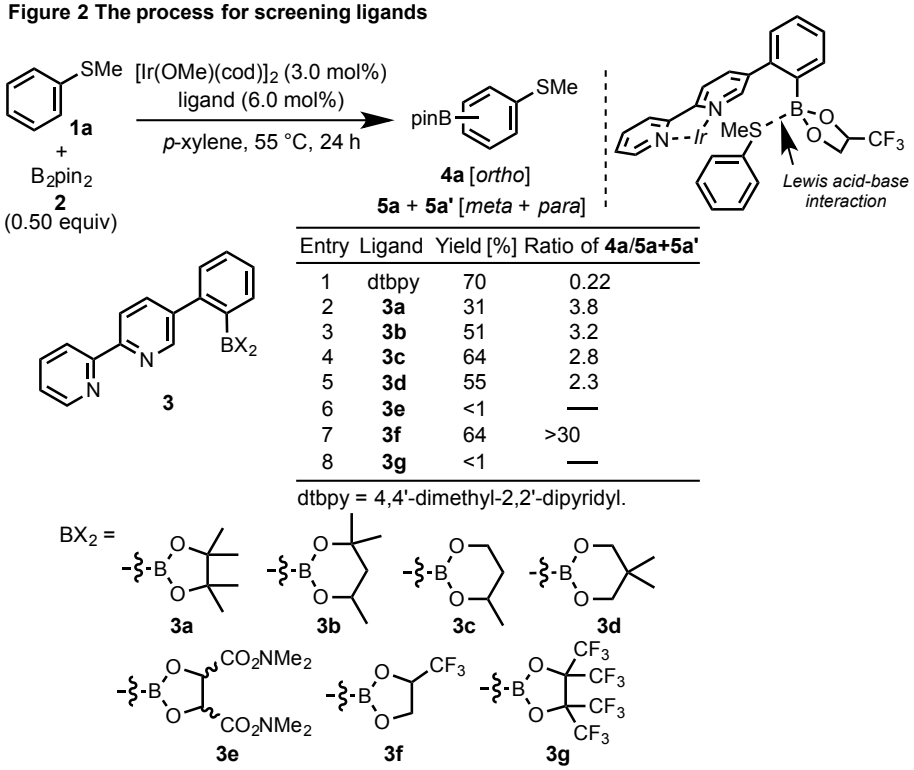


(1) Lewis acid-base controlled *ortho*-selective C-H borylation of aryl sulfides

In 2015, our group successfully achieved *meta*-selective C-H borylation of aromatic compounds controlled by hydrogen bonding between a ligand and substrates[4]. Based on this method, I developed an *ortho*-selective C-H borylation of aryl sulfides controlled by Lewis acid-base interaction between a designed-ligand and substrates. Initially, I hypothesized that ligands with a Lewis acidic boryl group attached at the *ortho* position of a bipyridine moiety would be suitable for recognizing the functional group of substrates and promoting *ortho*-selective C-H borylation (**Figure 2**). Thus, I initiated this study by investigated several bipyridine-type ligands with a boryl group as a Lewis acid center. Treatment of thioanisole (**1a**) with bis(pinacolato)diboron (**2**) in the presence of an iridium catalyst $[Ir(OMe)(cod)]_2$ and dtbpy (4,4'-dimethyl-2,2'-dipyridyl) at 55 °C gave a mixture of *ortho*-, *meta*-, and *para*-borylated thioanisoles **4a** and **5a** + **5a′** in 70% yield, and the [*ortho*/(*meta* + *para*)] ratio

was only 0.22. However, in the case of ligand **3a** with a pinacolboryl group, the [*ortho*/(*meta* + *para*)] ratio improved to 3.8. I thought that the pinacolboryl group was too bulky for the ligand-substrate interaction. Then, I investigated several ligands with a sterically less hindered boryl group. The ratio of the products, however, was not increased further using ligands **3b**, **3c**, or **3d** (entries 3–5). One possiblity to account for this result is that the moderate ratios should be due to the low Lewis acidity of the boryl group in **3a**-**3d**. Therefore, I turned my attention on increasing the Lewis acidity of ligands. Ligand **3f** with a *mono*-trifluoromethyl group gave the best result with a [*ortho*/(*meta* + *para*)] ratio over than 30[5]. The *ortho*-selective borylation did not proceed using ligand **3g** bearing four trifluoromethyl groups in the 1,3,2-dioxaborolanyl group. Besides its poor solubility, the excessively strong interaction between the boryl group of **3g** and a sulfur atom of substrate **1a** is another reason.

Figure 2 The process for screening ligands

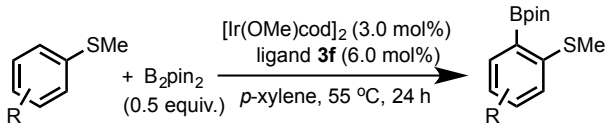


Entry	Ligand	Yield [%]	Ratio of **4a**/**5a+5a'**
1	dtbpy	70	0.22
2	**3a**	31	3.8
3	**3b**	51	3.2
4	**3c**	64	2.8
5	**3d**	55	2.3
6	**3e**	<1	—
7	**3f**	64	>30
8	**3g**	<1	—

dtbpy = 4,4'-dimethyl-2,2'-dipyridyl.

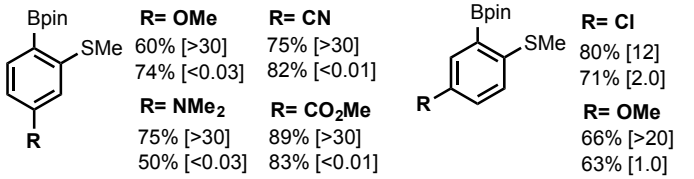
Next, I began to explore substrates scope under the best conditions. Borylation reaction proceeded in good to excellent yield with high *ortho*-regioselectivity by introducing EDG or EWG on the benzene ring. These functional groups show good tolerance during the reaction. This is the first example of regioselective C-H borylation controlled by Lewis acid-base interaction between ligand and substrates.

Figure 3 Substrates Scope



Ligand [*ortho*/*meta*+*para*]

dtbpy [*ortho*/*meta*+*para*]



(2) Iridium catalyzed *ortho*-selective C-H borylation of phenol and aniline derivatives

I also developed an *ortho*-selective C-H borylation reaction of phenol and aniline derivatives. Introducing a methylthiolmethyl group on the oxygen or nitrogen atom of the substrates, the borylation reaction proceeded in high *ortho*-regioselectivity using a

bipyridine-type ligand with an electron-withdrawing group at *para* position. First, I investigated a series of ligands with different electronic properties (**Figure 4**). In the case of dtbpy, the [*ortho*/(*meta* + *para*)] ratio of borylated product **3a** was 0.83 in yield of 88%. I found that electron-poor ligands (**L2**, **L3**, **L6**) are beneficial to increase the [*ortho*/(*meta* + *para*)] ratio. Ligand **L6** with a trifluoromethyl group at a *para* position gave the best result with a [*ortho*/(*meta* + *para*)] ratio over 30 in 90% yield. Under the best conditions, I explored the substrates scope. Using phenol and aniline derivatives as substrates gave high yield of the *ortho*-borylated products in wide substrate scope and good functional group tolerance.

Figure 4 Ligand screening process

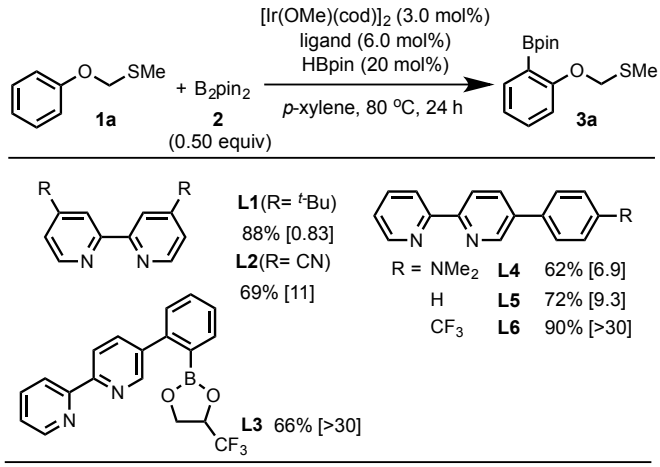
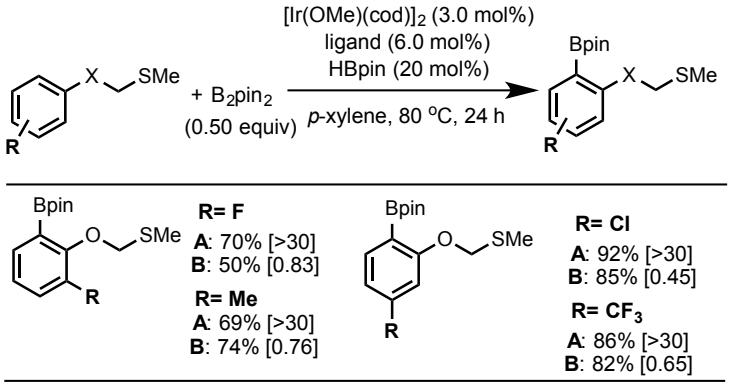


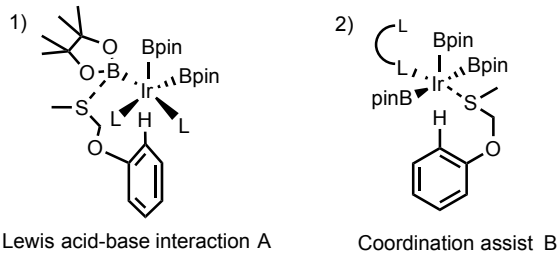
Figure 5 Substrate scope



I propose two possible mechanisms for this reaction: (1) via outer-sphere Lewis acid-base interaction between a boryl ligand of an iridium center and a sulfur atom of a substrate (**Figure 6**, 1)); (2) via coordination of a sulfur atom of a substrate to an iridium center as a directing group (**Figure 6**, 2)). The results of ligand screening support both pathways: an electron-withdrawing group on the phenyl ring of Ar-bipyridine ligands could enhance *ortho*-regioselectivity.

In summary, I successfully developed two methods of iridium catalyzed *ortho*-selective C-H borylation of aromatic compounds. The two reactions could proceed in good to excellent yield with wide substrates scope and have good functional group tolerance. The study for mechanism of *ortho*-selective C-H borylation of phenol and aniline derivatives is currently in progress.

Figure 6 Two possible mechanism for this reaction



Reference

[1] (a) Hartwig J. F. *Chem. Soc. Rev.* **2011**, *40*, 1992. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. [2] Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J.-F. *J. Am. Chem. Soc.* **2002**, *124*, 390. [3] Cho, J.-Y.; Tse, M.-K.; Holmes, D.; Smith III, M. R. *Science* **2002**, *295*, 305. [4] Kuninobu, Y.; Ida, H.; Nishi, M.; Kanai, M. *Nature Chem*. **2015**, *7*, 712. [5] Li, H. L.; Kuninobu, Y.; Kanai, M. *Angew. Chem. Int. Ed.* **2017**, *56*, 1495.