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Catalytic C-H Borylation Using Iron Complexes Bearing 4,5,6,7-Tetrahydroisoindol-2-ide-Based PNP-Type Pincer Ligand

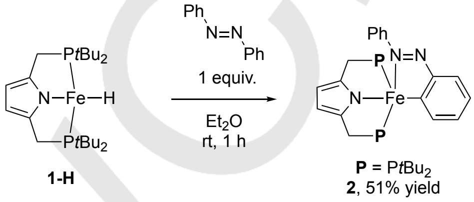
Takeru Kato,[a] Shogo Kuriyama,[a] Kazunari Nakajima,*[b] and Yoshiaki Nishibayashi*[a]

Abstract: We have newly designed the iron-catalyzed C-H borylation using iron complexes bearing a 4,5,6,7-tetrahydroisoindol-2-ide-based PNP pincer ligand, based on results of stoichiometric reactions of the iron complexes. As a result, we can apply a variety of arenes, not only benzene derivatives but also 5-membered heteroarenes such as pyrrole derivatives, to the C-H borylation. We have also found the first successful example of the iron-catalyzed sp^3 C-H borylation in the reaction of 4-methylanisole.

Carbon-hydrogen (C-H) bond is the most fundamental and plentiful chemical bond in organic chemistry. Direct functionalization of C-H bonds based on metal-catalyzed C-H activation has attracted broad interest in the last decades.[1] Although various metal species have been used in a variety of C-H activation reactions to date, iron species have provided outstanding utility because iron is the most abundant and cheapest transition metal on earth.[2]

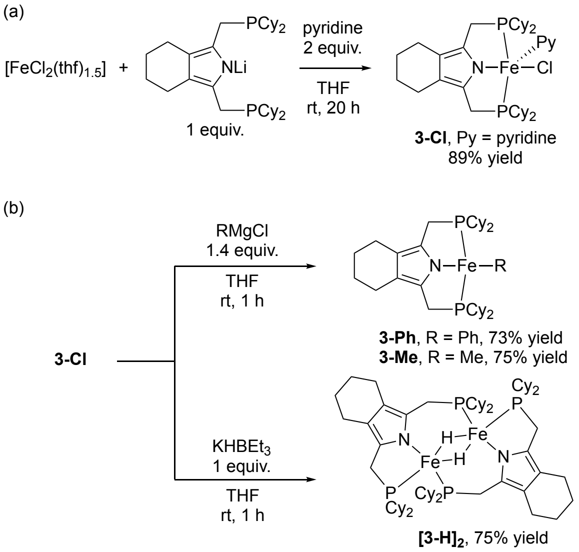
To control reactivity of metal complexes, introduction of well-defined supporting ligands plays a critical role. In the last decades, pyridine-based PNP ligands (2,6-bis(dialkylphosphinomethyl)pyridines) have been typically utilized in various transition metal complexes to achieve novel reactivities.[3] On the other hand, pyrrolide-based PNP pincer ligands (2,5-bis(dialkylphosphinomethyl)pyrrolide) have been recently studied as a new candidate.[4,5] However, applications of pyrrolide-based PNP pincer-iron complexes as catalysts for molecular transformations have been limited.[6] Quite recently, our group has developed iron-catalyzed conversion of dinitrogen into ammonia and hydrazine, where pyrrolide-based PNP-iron complexes have been used as catalysts.[7] We have also developed iron-catalyzed hydroboration of alkynes with the use of similar PNP-iron complexes as catalysts.[8] To explore further utility of these iron complexes in organic synthesis, we have newly designed the iron-catalyzed C-H borylation using iron complexes bearing a 4,5,6,7-tetrahydroisoindol-2-ide-based PNP pincer ligand.

In the course of our previous study,[7,8] we found that an iron-hydride complex bearing 2,5-bis(di-*tert*-butylphosphinomethyl)pyrrolide ligand (**1-H**) reacted with azobenzene via directing group-assisted C-H activation of the benzene ring (Scheme 1). Treatment of **1-H** with azobenzene in diethyl ether at room temperature for 1 h afforded the corresponding penta-coordinate aryl-iron complex (**2**) in 51% yield. The successful activation of the aromatic C-H bond prompted us to investigate further transformation of **2** with various reagents. However, **2** was inert toward various reagents and further functionalization of the azobenzene was not successful.



Scheme 1. C-H activation of azobenzene with iron-hydride complex **1**.

To explore a novel reactivity of iron complexes bearing PNP-type pincer ligand toward aromatic C-H functionalization, we have modified the pyrrolide-based PNP ligand. We have designed and prepared 1,3-bis(dicyclohexylphosphinomethyl)-4,5,6,7-tetrahydroisoindol-2-ide ligand as a novel anionic PNP-type pincer ligand. We first prepared an iron-chloride complex (**3-Cl**) from the reaction of $[FeCl_2(thf)_{1.5}]$ with lithium 1,3-bis(dicyclohexylphosphinomethyl)-4,5,6,7-tetrahydroisoindol-2-ide in the presence of 2 equiv of pyridine (Scheme 2a). Treatment of **3-Cl** with 1.4 equiv of PhMgCl and MeMgCl gave the corresponding phenyl- and methyl complexes (**3-Ph** and **3-Me**) in 73% and 75% yields, respectively (Scheme 2b). The reaction of **3-Cl** with 1 equiv of $KHBEt_3$ gave the corresponding hydride-bridged diiron complex (**[3-H]₂**) in 75% yield (Scheme 2b). A similar hydride-bridged diiron complex bearing PNP pincer ligands was reported by Tonzetich and co-workers.[4a] Detailed molecular structures of **3-Ph**, **3-Me**, and **$[3\text{-}H]_2$** were confirmed by X-ray analysis. ORTEP drawings of **3-Ph**, **3-Me**, and **$[3\text{-}H]_2$** are shown in Figure 1.



Scheme 2. Preparation of PNP-iron complexes.

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[a] T. Kato, Dr. S. Kuriyama, Prof. Dr. Y. Nishibayashi
Department of Systems Innovation
School of Engineering
The University of Tokyo
Bunkyo-ku, Tokyo, 113-8656 (Japan)
E-mail: ynishiba@sys.t.u-tokyo.ac.jp
[b] Dr. K. Nakajima
Frontier Research Center for Energy and Resources
School of Engineering
The University of Tokyo
Bunkyo-ku, Tokyo, 113-8656 (Japan)
E-mail: nakajima@sys.t.u-tokyo.ac.jp

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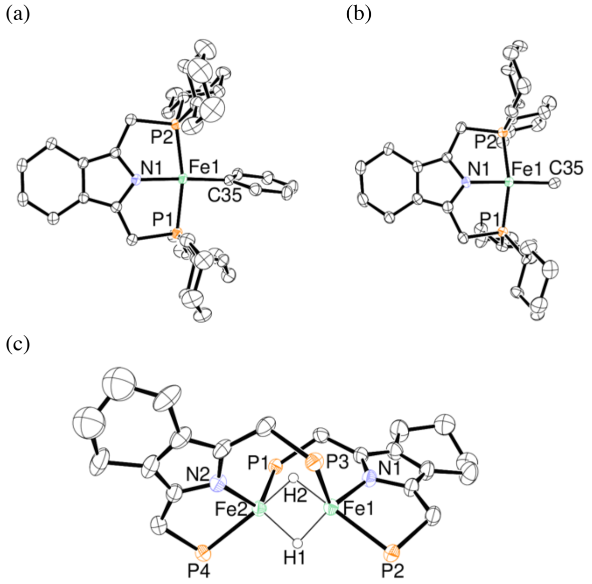
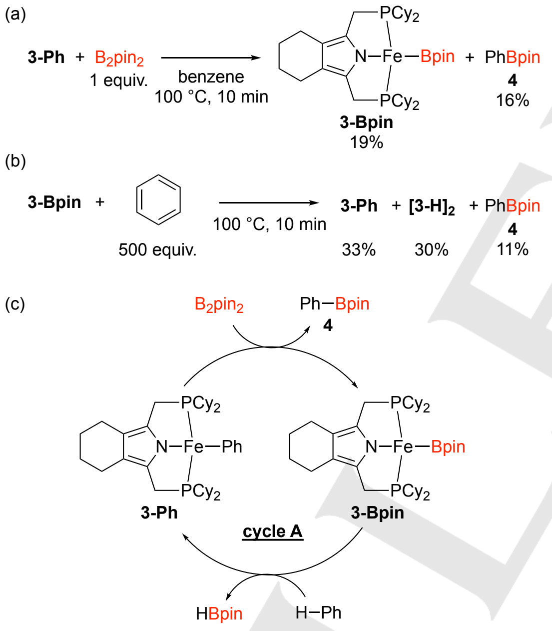


Figure 1. ORTEP drawings of PNP-iron complexes: (a) **3-Ph**, (b) **3-Me**, and (c) **$[3\text{-}H]_2$**. Hydrogen atoms except for H1 and H2 in (c) and cyclohexyl groups on phosphorous atoms in (c) are omitted for clarity.



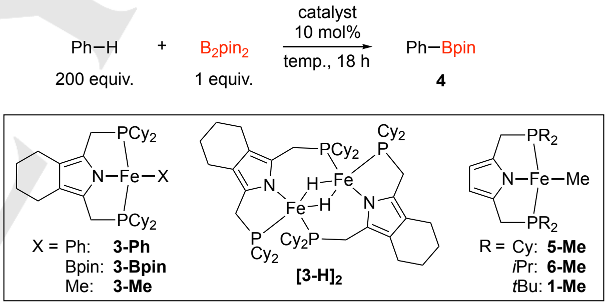
Scheme 3. Reactivity of iron-phenyl and iron-boryl complexes (**3-Ph** and **3-Bpin**).

Next, we carried out a stoichiometric reaction of **3-Ph** with 1 equiv of bis(pinacolato)diboron (B_2pin_2) in benzene at 100 °C for a short reaction time such as 10 min to afford the corresponding iron-boryl complex (**3-Bpin**) and 2-phenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (PhBpin: **4**) in 19% and 16% yields, respectively, together with unreacted **3-Ph** in 66% recovery (Scheme 3a). On the other hand, **3-Bpin** was heated in benzene at 100 °C for 10 min to give **3-Ph** in 33% yield together with **$[3\text{-}H]_2$** and PhBpin **4** in 30% and 11% yields, respectively (Scheme 3b). This result indicates that **3-Ph** and HBpin were formed from the reaction of **3-Bpin** with benzene. The iron-hydride complex **$[3\text{-}H]_2$** was formed by the reaction of some iron species with HBpin generated *in situ* from the reaction of **3-Bpin** with benzene. Similarly, PhBpin **4** was formed by the reaction of **3-Ph** with HBpin. As a result, only **4** (11%) was identified as a boron compound.

Based on the interconversion between **3-Ph** and **3-Bpin** shown in Schemes 3a and 3b, we have envisaged a proposed catalytic cycle for the iron-catalyzed C-H borylation[9-13] of benzene with B_2pin_2. A plausible reaction pathway is shown in Scheme 3c (**Cycle A**). The reaction of **3-Ph** with B_2pin_2 affords **3-Bpin** and borylation product PhBpin **4**. Then, the reaction of **3-Bpin** with benzene proceeds to regenerate **3-Ph** along with the presumable formation of pinacolborane (HBpin). The generated HBpin may react with some iron species to form **$[3\text{-}H]_2$** as a side product as observed in Scheme 3b. Separately, we confirmed the regeneration of **3-Bpin** through the reaction of **$[3\text{-}H]_2$** with B_2pin_2 (see Supporting Information for details).

With the assumption, we investigated the catalytic C-H borylation (Table 1). Treatment of B_2pin_2 in the presence of 10 mol% of **3-Ph** in benzene (200 equiv) at 100 °C for 18 h gave PhBpin **4** in 80% yield based on the mole of B_2pin_2 (Table 1, entry 1). The use of other iron complexes **3-Bpin** and **$[3\text{-}H]_2$** as catalysts gave PhBpin **4** in slightly lower yields (Table 1, entries 2 and 3). When iron-methyl complex **3-Me** was used as a catalyst, a similar catalytic activity to **3-Ph** was observed (Table 1, entry 4). Separately, we confirmed that the reaction of **3-Me** with B_2pin_2 afforded the corresponding iron-boryl complex **3-Bpin** in quantitative yield (see Supporting Information for details). This result indicates that **3-Me** is also a candidate of catalyst precursors.

Table 1. Catalytic C-H borylation reactions of benzene with B_2pin_2.[a]



entry	catalyst	temp. [C°]	yield [%][b]
1	**3-Ph**	100	80
2	**3-Bpin**	100	72
3[c]	**$[3\text{-}H]_2$**	100	64
4	**3-Me**	100	79 (76[d])
5	**5-Me**	100	48
6	**6-Me**	100	42
7	**1-Me**	100	0
8[e]	**3-Me**	100	10
9	**3-Me**	80	23

[a] Reactions of 20 mmol of benzene with 0.10 mmol of B_2pin_2 in the presence of iron catalyst (0.01 mmol, 10 mol%) were carried out. The yields were determined based on the mole of B_2pin_2. [b] NMR yield. [c] 5 mol% of **$[3\text{-}H_2]$**. [d] Isolated yield. [e] HBpin (0.10 mmol) was used instead of B_2pin_2.

To examine the effect of substituents on the phosphorous atom in the PNP ligand, we investigated the catalytic borylation with benzene using iron-methyl complexes bearing (2,5-bis(dicyclohexylphosphinomethyl)pyrrolide), (2,5-bis(diisopropyl

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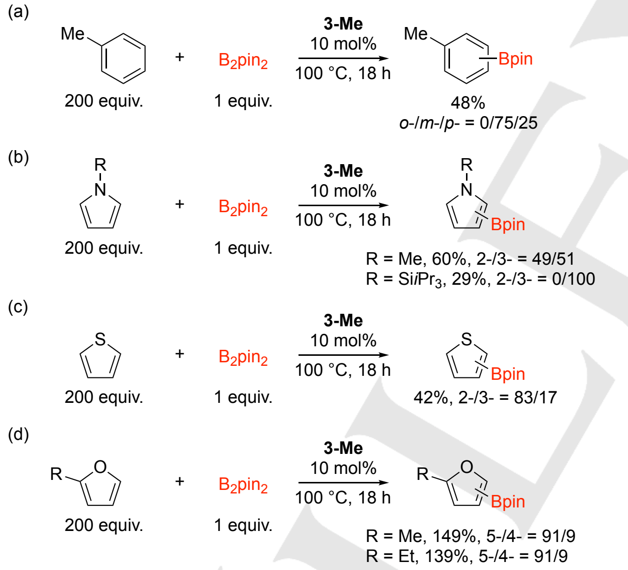
phosphinomethyl)pyrrolide), and (2,5-bis(di-*tert*-butyl phosphinomethyl)pyrrolide) as PNP-type pincer ligands (**5-Me**, **6-Me**, and **1-Me**, respectively). Lower yields of **4** were obtained in the cases using **5-Me** and **6-Me** as catalysts (Table 1, entries 5 and 6). However, no catalytic activity was observed when **1-Me** was used as a catalyst (Table 1, entry 7).

When we used HBpin as a boron source instead of B_2pin_2, PhBpin **4** was obtained only in 10% yield (Table 1, entry 8). This result indicates only B_2pin_2 is applicable as an effective boron source for the present C-H borylation of benzene. We also confirmed that the reaction at a lower temperature such as 80 °C gave only a lower yield of PhBpin **4** (Table 1, entry 9). Experimental results shown in Table 1 suggest that **3-Me** worked as the best catalyst at 100 °C.

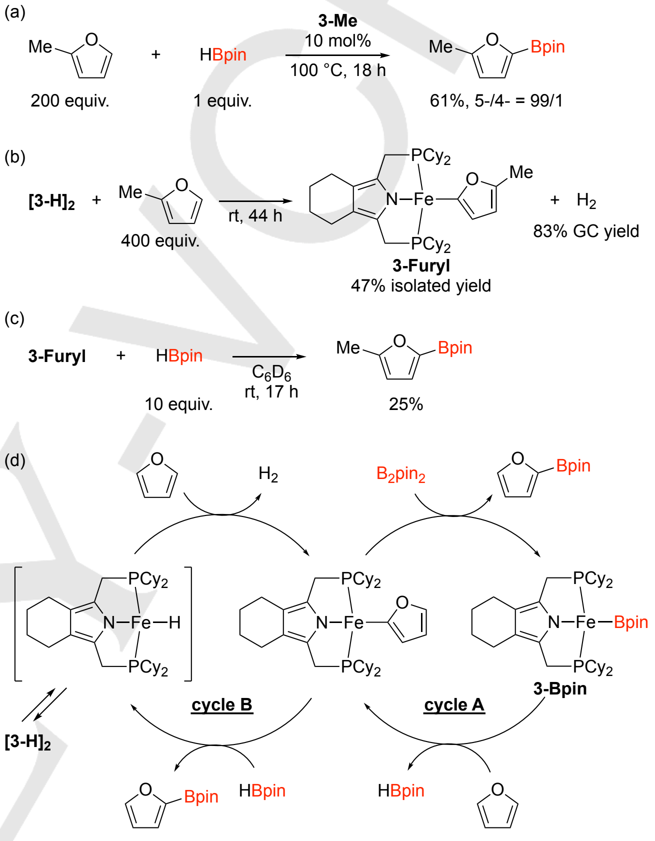
With the optimized conditions in hand, we investigated reactions of various arenes at 100 °C using **3-Me** as a catalyst.[14,15] The reaction of toluene with B_2pin_2 gave the corresponding borylated products in 48% yield as a mixture of *m*- and *p*-isomers with the ratio of 75/25 (Scheme 4a). Not only benzene derivatives but also other five-membered heteroarenes such as pyrrole, thiophen, and furan derivatives were transformed successfully. When *N*-methylpyrrole, *N*-(triisopropylsilyl)pyrrole, and thiophene were used as substrates, the corresponding borylated products were obtained in 60%, 29% and 42% yields, respectively (Schemes 4b and 4c). Interestingly, reactions with furans (2-methylfuran and 2-ethylfuran) afforded the corresponding borylated furans in 149% and 139% yields, respectively, where the yield of borylated furan was estimated based on the mole of B_2pin_2 (Scheme 4d). Thus, the yields over 100% indicate that both two boron fragments in B_2pin_2 were used as a boron source in the reactions with furans.



Scheme 4. C-H boryaltion reactions of various arenes with B_2pin_2.

Several research groups have already reported the iron-catalyzed C-H borylation of arenes with B_2pin_2 and HBpin as boron sources.[10-13] However, development of iron complexes which are applicable to not only benzene derivatives but also five-membered heteroarenes such as pyrroles and furans has not yet been reported until now. In sharp contrast to the previous reports, we can apply the iron complexes bearing a 4,5,6,7-tetrahydroisoindol-2-ide-based PNP pincer ligand to the catalytic C-H borylation of a variety of arenes. Especially, we have succeeded in the first successful examples of C-H borylation of pyrroles using iron complexes as catalysts.

The result of the C-H borylation of furans with B_2pin_2 shown in Scheme 4d prompted us to investigate the borylation of furans in details. The reaction of 2-methylfuran with HBpin in the presence of 10 mol% of **3-Me** at 100 °C for 18 h gave the corresponding borylated product in 61% yield (Scheme 5a). This result indicates that the C-H borylation of furan derivatives with not only B_2pin_2 but also HBpin as boron sources proceeds effectively, in sharp contrast to the C-H borylation of other arenes.

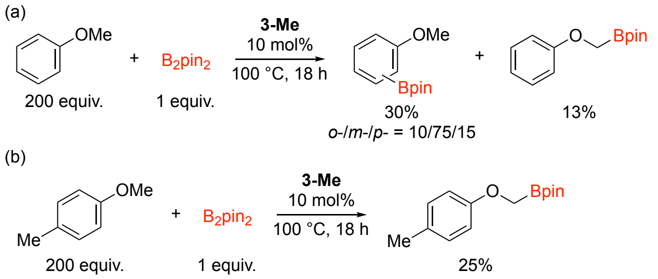


Scheme 5. Reactivity of iron complexes toward furan derivatives.

To check the different reactivity of furans, we carried out the following stoichiometric reactions. The reaction of hydride-bridged diiron complex with an excess amount of 2-methylfuran at room temperature for 44 h gave the corresponding iron-furyl complex (**3-Furyl**) in 47% yield together with the formation of H_2 in 83% GC yield (Scheme 5b). On the other hand, the reaction of **3-Furyl** with 10 equiv of HBpin in C_6D_6 at room temperature for 17 h gave the corresponding borylated furan in 25% yield together with a mixture of unidentified iron complexes (Scheme 5c). Based on the results of the stoichiometric reactions in Schemes 5b and 5c, we proposed a reaction pathway for the C-H borylation of furan shown in Scheme 5d. In addition to the **Cycle A** shown in Scheme 3c, the C-H borylation of furan with HBpin proceeds via the **Cycle B**. In the **Cycle B**, **3-Furyl** reacts with HBpin to give the corresponding mononuclear iron-hydride complex, which is presumably in equilibrium with **[3-H]$_2$**, and the borylated furan. Then, the resulting iron-hydride species may react with furan to give **3-Furyl** together with the formation of H_2. Thus, the C-H borylation of furan with B_2pin_2 proceeds via **Cycle A** and that with HBpin proceeds via **Cycle B**.

Separately, we confirmed that no reaction of **[3-H]$_2$** with benzene at room temperature for 44 h occurred at all. This result indicates that iron-hydride species derived from **[3-H]$_2$** are reactive not toward benzene but toward furan under the present reaction conditions. We consider that this different reactivity is due to higher acidity of the C-H bond of furan than that of benzene.[16,17]

During our investigation of the reactivity of the iron complexes, we have found that the reaction of anisole with 1 equiv of B_2pin_2 in the presence of 10 mol% of **3-Me** at 100 °C for 18 h gave a mixture of the sp^2 C-H borylated products in 30% yield together with the sp^3 C-H borylated product in 13% yield (Scheme 6a). This result indicates the superstoichiometric amount of the sp^3 C-H borylation product was produced. On the other hand, when 4-methylanisole was used to avoid the sp^2 C-H borylation of the benzene ring under the same reaction conditions, the sp^3 C-H borylation of methoxy group proceeded selectively to give the sp^3 C-H borylated product in 25% yield as a sole product (Scheme 6b). To the best of our knowledge, this is the first successful example of the iron-catalyzed sp^3 C-H borylation.



Scheme 6. sp^3 C-H borylation of anisole derivatives.

In summary, we have newly designed the iron-catalyzed C-H borylation using iron complexes bearing a 4,5,6,7-tetrahydroisoindol-2-ide-based PNP pincer ligand, based on results of stoichiometric reactions of the iron complexes. As a result, we can apply a variety of arenes, not only benzene derivatives but also 5-membered heteroarenes such as pyrrole derivatives, to the C-H borylation. We have also found the first successful example of the iron-catalyzed sp^3 C-H borylation in the reaction of 4-methylanisole. Further work is currently in progress in our laboratory.

Keywords: iron complex • pincer complex • C-H borylation • heterocycles

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[15] We investigated reactions of other heterocycles such as pyridine, 2,6-lutidine, *N*-methylimidazole, *N*-methylindole, 1,3-oxazole. However, the corresponding C-H borylation products were not observed in all cases.

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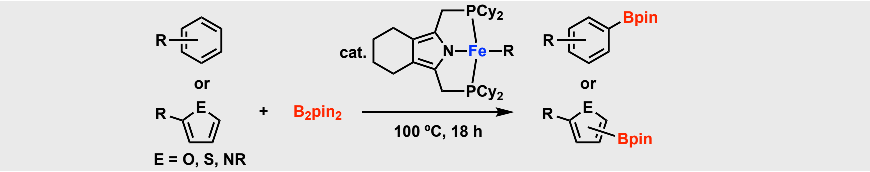

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