

Borylation Reactions

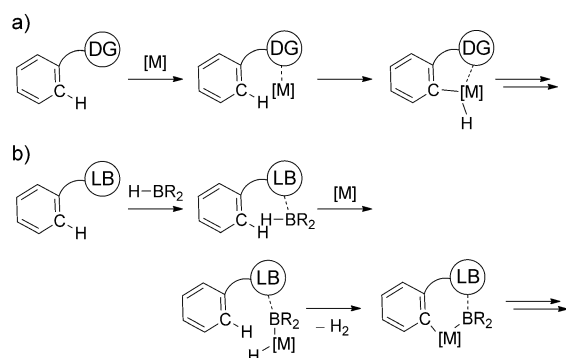
Palladium-Catalyzed *ortho*-Selective C–H Borylation of 2-Phenylpyridine and Its Derivatives at Room Temperature**

Yoichiro Kuninobu,* Takashi Iwanaga, Tetsuya Omura, and Kazuhiko Takai*

Direct C–H bond transformations have received much attention as ideal and highly efficient methods for the synthesis of useful organic compounds. However, several difficulties remain, in particular the issue of regioselectivity. To solve this problem, directing groups bearing the unshared electron pair of a heteroatom have been used, resulting in dramatic development of the chemistry of C–H bond transformations over the last few decades.^[1] The directing group usually acts as a Lewis base to coordinate a transition metal, and thus, the metal center comes close to an appropriate site (a C–H bond) for the reaction, and subsequent C–H activation occurs (Scheme 1 a). Herein, we report the *ortho*-

converted into a reactive species for C–H activation upon treatment with a transition metal (Scheme 1 b). Until recently, it was difficult to promote transition-metal-catalyzed *ortho*-selective C–H borylation, but several examples of such transformations have appeared in the last one or two years.^[4,5]

In C–H borylation, pinacolborane and bis(pinacolate)diboron are usually employed as substrates.^[6] Therefore, we initially investigated the reactions between 2-phenylpyridine (**1a**) and various borane reagents in the presence of a catalytic amount of several transition metal compounds. However, the desired reaction did not occur at all.^[7–9] The reason for the low reactivity was thought to be that the Lewis acidity of the borane reagents was not enough to promote the Lewis acid–base interaction between the pyridyl group of **1a** and the boron atom of pinacolborane or bis(pinacolate)diboron. Consequently, 9-borabicyclo[3.3.1]nonane (9-BBN, **2a**) was selected as a promising substrate, because 9-BBN has higher Lewis acidity than pinacolborane and bis(pinacolate)diboron. Treatment of 2-phenylpyridine (**1a**) with 9-BBN (**2a**) in the presence of a catalytic amount of a palladium salt, Pd(OAc)₂, in 1,2-dichloroethane at 25 °C for 24 h gave *ortho*-borylated 2-phenylpyridine **3a** in 87 % yield [Eq. (1)].^[10–14] To verify the



Scheme 1. C–H bond functionalization. a) Using the coordination of a directing group to a metal center. b) By Lewis acid–base interaction. DG = directing group, LB = Lewis basic heteroatom, [M] = metal catalyst.

selective borylation of aromatic C–H bonds with a palladium catalyst using the interaction between a Lewis basic nitrogen and Lewis acidic boron atoms.^[2,3] This is a new concept for the directing group; the group also has an electron pair, but coordinates to a Lewis acidic main-group metal, and a boron atom that also bears a hydrogen atom, which is then



existence of the Lewis acid–base interaction, the following experiment was carried out: a mixture of 2-phenylpyridine (**1a**) and 9-BBN (**2a**) in CD₂Cl₂ was stirred at 25 °C for 24 h, and ¹¹B NMR analysis of the reaction mixture was then conducted. As a result, a new signal was observed at 0.3 ppm (vs. 27.7 ppm for **2a**), which is consistent with signals observed for boranes coordinated to pyridine derivatives.^[15] This result indicates that the borylation reaction proceeded, supported by Lewis acid–base interaction. Moreover, the reaction proceeded even in the absence of the palladium catalyst at higher temperature (135 °C, 73 %). In this reaction, other regioisomers were not formed to the limits of detection by ¹H NMR. This also supports the existence of a Lewis acid–base interaction between the boron and nitrogen atoms. Product **3a** exhibited a light blue fluorescence in CDCl₃ solution and a reddish purple to blue fluorescence as a solid

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under UV irradiation (254 nm).^[16,17] The result in Eq. (1) shows that the directing group, a pyridyl group, acts not only to bring the reactive species close to the C–H bond, but also as a useful component for fluorescence.

Next, we investigated the scope and limitations of aromatic compounds with an sp² nitrogen atom. 2-Phenylpyridine with an electron-donating group at the *para*-position of the benzene ring, **1b**, produced *ortho*-borylated 2-phenylpyridine **3b** in 83 % yield in the presence of a palladium catalyst, Pd(OAc)₂ (Table 1, entry 1). The yield of the *ortho*-

Table 1: Reactions between several N-heteroaromatic compounds **1** and 9-BBN (**2a**).^[a]

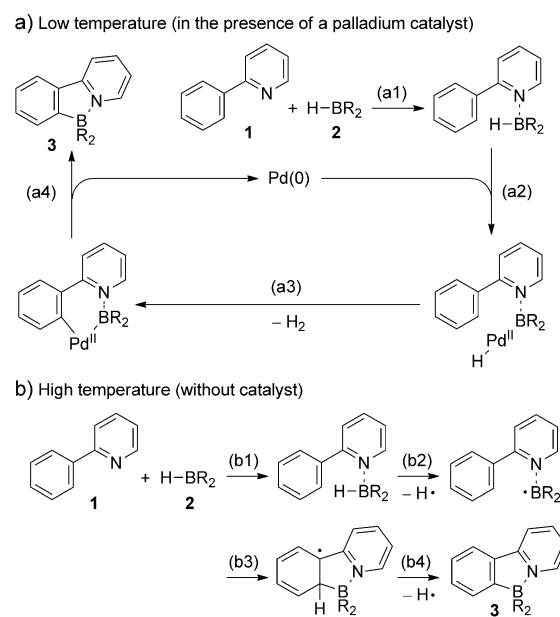
Entry	1	3	Yield [%] ^[b]
1	1b : R ¹ = 4-MeO		83 (69)
2	1c : R ¹ = 4-CF ₃		41 (0)
3	1d : R ¹ = 2-Me		93 (59)
4	1e		77 (68)
5	1f		50 ^[c] (52)
6	1g		19 (0)
7	1h		89 (69)
8			97 (0)
9			27 (0)

[a] **2a** (0.70 equiv). [b] Yields shown are for reactions using Pd(OAc)₂ (3.0 mol%) at 25 °C. Data given in parentheses are for reactions conducted at 135 °C without catalyst. [c] Reaction conducted at 50 °C.

borylated product decreased when 2-phenylpyridine **1c**, which bears an electron-withdrawing group, was used as a substrate (Table 1, entry 2). The reaction was not inhibited by a methyl group at the 2-position, and the desired product **3d** was afforded in 93 % yield (Table 1, entry 3). The borylation also proceeded at the C–H bond of a naphthyl

moiety when 2-(1-naphthalenyl)pyridine (**1e**) was employed as a substrate (Table 1, entry 4). In the case of 2-(2-naphthalenyl)pyridine (**1f**), there are two possible reaction sites. However, the borylation reaction occurred only at the α -position of the naphthalene skeleton (Table 1, entry 5). Treatment of benzo[*h*]quinoline (**1g**) with 9-BBN (**2a**) provided the corresponding borylated product **3g** in low yield (Table 1, entry 6). 2-Phenylpyridine having a methyl group on the pyridyl group, **1h**, also gave *ortho*-borylated 2-phenylpyridine **3h** in 89 % yield (Table 1, entry 7). Another directing group, a pyrazolyl group, was effective for the borylation, providing the corresponding borylated product **3i** in 97 % yield (Table 1, entry 8). 2-Phenyl-4,5-dihydrooxazole (**1j**) also provided the borylated product **3j** in low yield (Table 1, entry 9). In the case of reactions at 135 °C without any catalysts, the yields of the borylated products tended to be similar to the palladium-catalyzed reactions.^[18] The reaction did not proceed using 2-phenylpyrimidine, 2,6-diphenylpyridine, 2-benzylpyridine, ketimine, benzophenone, methyl benzoate, or *trans*-azobenzene.

Although there is no direct evidence for the reaction mechanism, we propose the mechanism for the palladium-catalyzed *ortho*-selective borylation shown in Scheme 2 a.



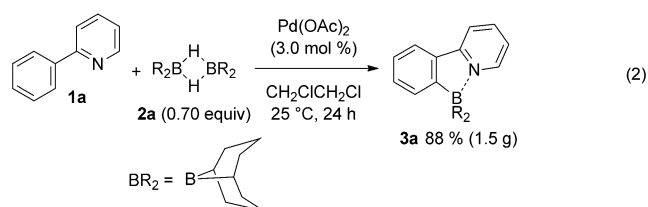
Scheme 2. Proposed mechanism for the formation of *ortho*-borylated 2-phenylpyridines.

Step a1) Lewis acid–base interaction between a boron atom of 9-BBN (**2a**) and a nitrogen atom of 2-phenylpyridine **1**. Step a2) Oxidative addition of a B–H bond to palladium(0) (the oxidation state of the palladium atom is II).^[19,20] Step a3) C–H bond activation by the elimination of H₂ (σ -bond metathesis). Step a4) Reductive elimination to give **3** and regenerate the palladium(0) species. In step a2, the palladium(0) species, which is formed by the reduction of Pd(OAc)₂ with 9-BBN, is likely the active catalytic species

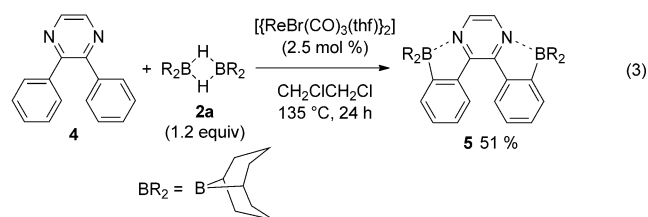
because black precipitates, presumably palladium black, were observed.

For borylation without the palladium catalyst, we propose another reaction mechanism (Scheme 2b). As the reactivity decreases under light shielding, the borylation reaction likely occurs via a radical process. The metal-free process was completely inhibited by radical inhibitors such as 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) and galvinoxyl, leading to the recovery of 89 % and 99 % of 2-phenylpyridine (**1a**), respectively. These results also support the radical pathway. The proposed reaction mechanism is as follows: Step b1) Lewis acid–base interaction between a boron atom of 9-BBN (**2a**) and a nitrogen atom of 2-phenylpyridine **1**. Step b2) Formation of a boryl radical by the elimination of a hydrogen radical.^[21] Step b3) Intramolecular addition. Step b4) Elimination of a hydrogen radical (the hydrogen radical is combined with that formed from another hydrogen radical to generate H₂) to give product **3**.

This reaction also proceeded well on a gram scale [Eq. (2)]. As a result, 1.5 g of the borylated product **3a** was obtained (88 % yield).^[22]



The desired product **5** was not formed upon treatment of 2,3-diphenylpyrazine (**4**) with 9-BBN (**2a**) in the presence of a catalytic amount of a palladium salt, Pd(OAc)₂; instead, a complex mixture was generated. However, when the catalyst was changed to a rhenium complex, [{ReBr(CO)₃(thf)₂}], the double borylation reaction proceeded at both *ortho*-positions and the corresponding product **5** was obtained in 51 % yield [Eq. (3)].^[23,24]



In summary, we have succeeded in the palladium-catalyzed regioselective borylation of 2-phenylpyridine derivatives. This reaction proceeded even at room temperature. The regioselectivity arises from Lewis acid–base interaction between the nitrogen and boron atoms. Using this method, the borylated product can be obtained on a gram scale. As the *ortho*-borylated 2-phenylpyridines exhibit fluorescence under UV irradiation, the products will be useful as functional materials. In addition, the π -conjugated systems could be expanded by double borylation. We hope that this reaction

will provide useful insight into transformations through C–H bond activation.

Experimental Section

Typical procedure for the palladium-catalyzed synthesis of *ortho*-borylated product **3a**: A mixture of 2-phenylpyridine (**1a**, 77.6 mg, 0.500 mmol), 9-BBN dimer (**2a**, 85.4 mg, 0.35 mmol), and Pd(OAc)₂ (3.4 mg, 0.015 mmol) in 1,2-dichloroethane (1.0 mL) was stirred at 25 °C for 24 h under an argon atmosphere. After purification by silica gel column chromatography (*n*-hexane/benzene = 5:1), 2-[2-(9-borabicyclo[3.3.1]nonyl)phenyl]pyridine (**3a**) was isolated in 87 % yield (60.0 mg).

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- [7] Pinacolborane in CH₂ClCH₂Cl at 135 °C for 24 h gave no reaction with 5 mol % of: [Re₂(CO)₁₀], [ReBr(CO)₅], [ReBr(CO)₃(thf)₂], [RhCl(PPh₃)₃], [IrCl(cod)₂], or Pd(OAc)₂.
- [8] Bis(pinacolate)diboron in CH₂ClCH₂Cl at 135 °C for 24 h gave no reaction with 5 mol % of: [Re₂(CO)₁₀], [ReBr(CO)₅], [ReBr(CO)₃(thf)₂], [RhCl(PPh₃)₃], [IrCl(cod)₂], or Pd(OAc)₂.
- [9] Catecholborane in CH₂ClCH₂Cl at 135 °C for 24 h gave no reaction with 5 mol % of: [Re₂(CO)₁₀], [ReBr(CO)₅], [ReBr(CO)₃(thf)₂], [RhCl(PPh₃)₃], [IrCl(cod)₂], or Pd(OAc)₂.
- [10] CCDC 926839 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. For details, see the Supporting Information.
- [11] Yields from metal catalyst (5.0 mol %) screening with **2a** (0.50 equiv) in toluene at 135 °C for 24 h: [Mn₂(CO)₁₀], trace; [MnBr(CO)₅], trace; [Re₂(CO)₁₀], 0 %; [ReBe(CO)₅], 15 %; [ReBr(CO)₃(thf)₂], 63 %; [RhCl(PPh₃)₃], 9 %; [IrCl(cod)₂], 59 %; Pd/C, 0 %; [Pd₂(dba)₃], 97 %; [Pd(PPh₃)₄], 8 %; Pd(OAc)₂, 65 %; [PdCl₂(NCPH)₂], 50 %; [PdCl₂(PPh₃)₂], 19 %; [PdBr₂(PPh₃)₂], 76 %. Under the conditions in Table 1: [Pd₂(dba)₃], 76 %; [Pd(PPh₃)₄], 0 %.
- [12] Yields from solvent screening with **2** (0.50 equiv) and Pd(OAc)₂ (5.0 mol %) at 135 °C for 24 h: octane, 32 %; toluene, 65 %; 1,2-dichloroethane, 67 %; dioxane, 42 %; acetonitrile, 0 %; neat, 92 %.
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- [17] **3a** turned pink in color under UV light irradiation. After the color changed, the fluorescence of **3a** nearly disappeared. However, after recrystallization, **3a** turned white in color and the fluorescence returned. The reason for this is not clear.
- [18] In the case of substrate **1c**, the coupling reaction between the electron-poor aromatic ring and electron-deficient boryl radical is expected to be difficult. On the other hand, when **1g**, **1i**, and **1j** were employed as substrates, the distances between the carbon atom of the substrates and boron atom of 9-BBN in the Lewis acid–base complexes are longer than those of complexes between 2-phenylpyridine derivatives and 9-BBN.
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- [24] The reaction in Eq. (4) did not proceed without the rhenium catalyst. The possible mechanism for the rhenium-catalyzed double borylation must be the similar to that of palladium-catalyzed borylation; that is: Step a1) Lewis acid–base interaction between a boron atom of 9-BBN (**2**) and a nitrogen atom of 2-phenylpyridine **1**. Step a2) Oxidative addition of a B–H bond to a rhenium(I) atom (the oxidation state of the rhenium atom is III). Step a3) C–H bond activation by the elimination of H₂ (σ-bond metathesis). Step a4) Reductive elimination to give **3** and regenerate the rhenium(I) species. The electron density of pyrazine is lower than that of pyridine, and the Lewis acid–base interaction must be weaker owing to the lower basicity of the pyrazine moiety. Therefore, heating at 135 °C was necessary to promote the reaction.