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Ruthenium-Catalyzed *Ortho*-Selective Aromatic C–H Borylation of 2-Arylpyridines with Pinacolborane

Shinsuke Okada, Takeshi Namikoshi, Shinji Watanabe, and Miki Murata*[a]

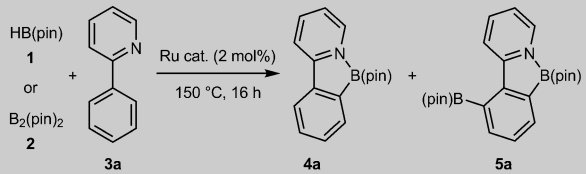
The ruthenium-catalyzed dehydrogenative borylation of 2-arylpyridines with pinacolborane took place at *ortho*-positions of the benzene ring. Density functional theory calculations and kinetic isotope effect experiments suggest that the catalytic cycle should involve oxidative addition of the C–H bond, the rate-determining σ-bond metathesis of pinacolborane with the ruthenium hydride complex, and reductive elimination of the C–B bond.

As arylboronates are an important class of organometallics, which can be widely used as versatile building blocks in modern organic synthesis, the development of transition metal-catalyzed aryl C–B bond-forming reactions has sustained ongoing interest.[1] From an environmental and economic point of view, there is no doubt that the direct borylation of ubiquitous C–H bonds of aromatic hydrocarbons is an ultimate goal in this area.[2] Numerous catalyst systems, most of which were rhodium and iridium complexes, have been proposed for utilization in the C–H borylation of arenes with pinacolborane (4,4,5,5-tetramethyl-1,3,2-dioxaborolane, **1**) or bis(pinacolato)diboron (4,4,4′,4′,5,5,5′,5′-octamethyl-2,2′-bi-1,3,2-dioxaborolane, **2**) as a boron source. In contrast, an example of such transformation using ruthenium catalysts is rare. In 2006, the $[Cp^*RuCl_2]_2$-catalyzed C–H borylation of alkanes with bis(pinacolato)diboron (**2**) has been reported by Hartwig's group; however, benzene was not the suitable substrate under these conditions.[3] Although the ruthenium-catalyzed C–H borylation of indoles with pinacolborane (**1**) has been achieved by Tatsumi, Oestreich, and co-workers, the borylation of other substrates has not been disclosed.[4] Very recently, Nolan and co-workers have described an efficient ruthenium catalyst for the C–H borylation of 2-arylpyridines with bis(pinacolato)diboron (**2**).[5]

During the past few years, considerable attention has been devoted to the *ortho*-selective C–H borylation of arenes bearing various oxygen and nitrogen functionalities as directing groups.[2,5–7] The pioneer studies that introduced the concept of chelation-assisted catalytic C–H functionalization relied on ruthenium catalysts.[8] For example, the ruthenium-catalyzed C–H silylation of arenes bearing *ortho*-directing groups has been reported.[9] Despite the success of ruthenium catalysts for related C–H functionalization, there is only one report about ruthenium catalysts to affect the direct C–H borylation.[5] Herein, we wish to report on an alternative approach using pinacolborane (**1**) as a boron source for the ruthenium-catalyzed C–H borylation of 2-arylpyridines.

To evaluate potential ruthenium catalysts for this transformation, we investigated the C–H borylation of 2-phenylpyridine (**3a**). The results are summarized in Table 1. When **3a** was treated with an excess amount of pinacolborane (**1**, 3 equiv) in the presence of 2 mol% of $[RuH_2(CO)(PPh_3)_3]$ in THF at 150 °C for 16 h, a full conversion of **3a** was observed (entry 1). The reaction was completely *ortho*-regioselective affording monoborylated **4a** and diborylated **5a**. Analysis of the ^{11}B NMR spectra indicated that, as expected, **4a** has the tetrahedral boron–nitrogen interaction in the solution state.[6h,7c] Alternatively, the ^{11}B NMR signal of **5a** was observed at 21.8 ppm, which is the middle value of trigonal and tetrahedral boron atom. The presence of only one signal for the boron atoms of **5a** can be explained by a dynamic behavior that involves rapid coordination and dissociation of the boron and nitrogen atoms. In contrast to Nolan's report,[5] several attempts at the selective formation of monoborylated **4a**, including using lower reaction temperatures or lower quantities of **1**, were unsuccessful, probably because the higher temperature would be sufficient to

Table 1. Optimization of Ru-catalyzed borylation of 2-phenylpyridine (**3a**) with pinacolborane (**1**).[a]



Entry	Catalyst	Solvent	Yield[b] [%]	
			4a	**5a**
1	$[RuH_2(CO)(PPh_3)_3]$	THF	6	94
2[c]	$[RuH_2(CO)(PPh_3)_3]$	THF	47	43
3[d]	$[RuH_2(CO)(PPh_3)_3]$	THF	40	18
4	$Ru_3(CO)_{12}$	THF	42	31
5	[Ru(cod)(cot)]	THF	15	39
6	$[Cp^*RuCl]_4$	THF	23	18
7	$[RuCl_2(p\text{-cymene})]_2$	THF	13	59
8	$[RuH_2(CO)(PPh_3)_3]$	toluene	41	18
9	$[RuH_2(CO)(PPh_3)_3]$	cyclohexane	22	42
10[e]	$[RuH_2(CO)(PPh_3)_3]$	THF	6	93

[a] Reaction conditions: **1** (0.75 mmol), **3a** (0.25 mmol), Ru catalyst (2 mol% Ru atom), and solvent (0.5 mL), 150 °C, 16 h. [b] GC yields are based on **3a**. [c] At 120 °C. [d] **1** (0.30 mmol) was used. [e] **2** (0.38 mmol) was used instead of **1**.

[a] *S. Okada, Dr. T. Namikoshi, Prof. Dr. S. Watanabe, Prof. Dr. M. Murata*
Department of Materials Science and Engineering
Kitami Institute of Technology
165 Koen-Cho, Kitami, Hokkaido 090-8507 (Japan)
Fax: (+81) 157-26-4973
E-mail: muratamk@mail.kitami-it.ac.jp

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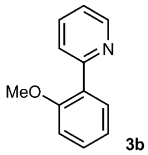
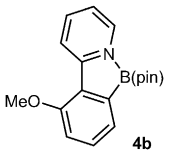
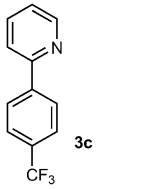
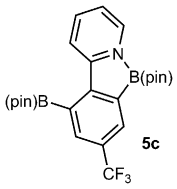
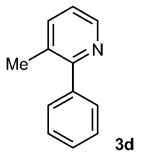
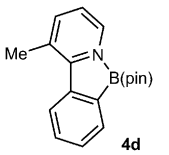
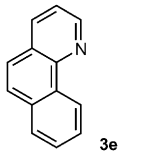
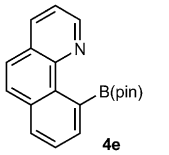
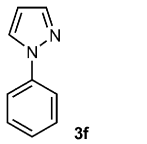
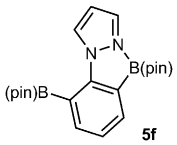
promote the equilibrium of B–N interaction (entries 2 and 3). Although several ruthenium complexes, including $Ru_3(CO)_{12}$, [Ru(cod)(cot)], $[Cp^*RuCl]_4$, and $[RuCl_2(p\text{-cymene})]_2$, showed some catalytic activity for the C–H borylation (entries 4–7), $[RuH_2(CO)(PPh_3)_3]$ was the catalyst of choice. Different reaction media were subsequently investigated, and THF proved to be the best solvent (entries 1, 8, and 9). Thus, the optimized reaction conditions utilized $[RuH_2(CO)(PPh_3)_3]$ in THF. Under the condition, bis(pinacolato)diboron (**2**) also participated in the C–H borylation (entry 10).[5]

The results obtained with some other substrates **3**, giving arylboronates **4** or **5** similarly as above, are listed in Table 2. The

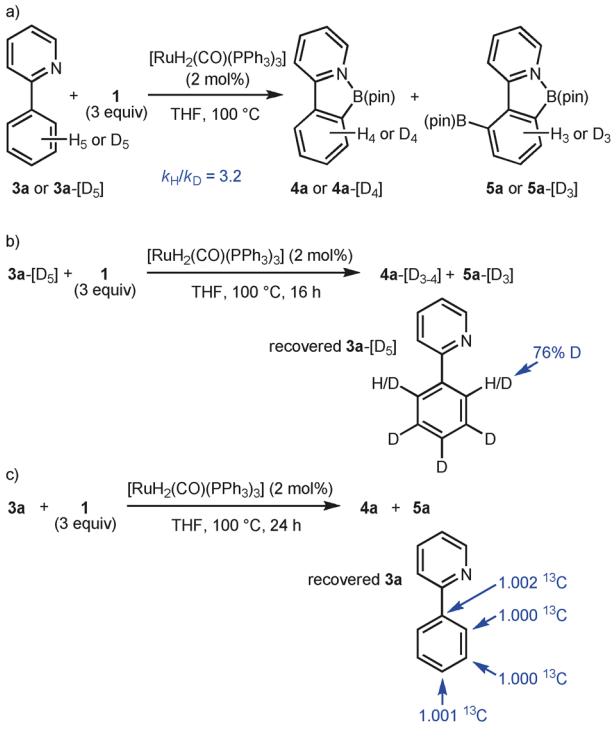
Table 2. Ru-catalyzed Borylation of **3** with Pinacolborane (**1**).[a]

Entry	3	Product	Yield[b] [%]
1	 **3b**	 **4b**	87
2	 **3c**	 **5c**	68
3[c]	 **3d**	 **4d**	65
4	 **3e**	 **4e**	82
5	 **3f**	 **5f**	79

[a] Reaction conditions: **1** (0.75 mmol), **3** (0.25 mmol), $[RuH_2(CO)(PPh_3)_3]$ (2 mol%), and THF (0.5 mL), 150 °C, 16 h. [b] Isolated yield. [c] At 100 °C.

reaction of **3b**, bearing only one *ortho* C–H bond on the aromatic ring, afforded the corresponding **4b** as the sole product (entry 1). In the case of **3c**, the ^{11}B NMR signals of the diborylated product **5c** were observed at 9.4 and 30.5 ppm (entry 2). The stronger boron–nitrogen interaction than **5a** should arise from the electron-withdrawing group on the aromatic ring. The monoborylation of 2-phenyl-β-picoline (**3d**) was achieved selectively at 100 °C to give the corresponding **4d** (entry 3), whereas the reaction at 150 °C resulted in a 1:1 mixture of **4d** and diborylated product. The borylation of benzo[*h*]quinoline (**3e**) selectively occurred at the 10-position (entry 4). The normal trigonal boron atom of **4e** was characterized by ^{11}B NMR analysis. Furthermore, the pyrazol ring can also function as a directing group (entry 6).

To gain mechanistic insights into the ruthenium-catalyzed C–H borylation, we conducted some preliminary isotope experiments with pinacolborane (**1**). Comparison of the observed pseudo-first-order rate constants for individual experiments with **3a** and a deuterated substrate **3a**-$[D_5]$ yielded a kinetic isotope effect of 3.2 (Scheme 1a). However, when the reaction



Scheme 1. Isotope experiments to reveal the catalytic cycle.

of **3a**-$[D_5]$ was taken to 62% conversion, ^1H NMR spectra of the recovered starting material **3a**-$[D_5]$ showed that partial H/D exchange occurred at the *ortho* positions of the phenyl ring (Scheme 1b). This result indicates that the C–H bond activation step is an equilibrium process. Next, the unreacted **3a** was recovered at 87% conversion (Scheme 1c). The ^{13}C ratio of each carbon in the recovered **3a** to the same carbon in a virgin **3a** was measured by Singleton's NMR technique at natural abundance, but no significant carbon isotope effect was observed.[10,11] These results suggest that neither the C–H bond activation step nor the C–B bond formation step would be the rate-determining for the present C–H borylation.

The present C–H borylation was then addressed computationally by density functional theory (DFT) calculations. We have adopted the reaction of phenylmethanimine with HB(eg) (1,3,2-dioxaborolane) as a model reaction, and the PPh_3 ligand of $[RuH_2(CO)(PPh_3)_3]$ was replaced by PH_3 in the computed structures.[12] The energy profile of a proposed catalytic cycle is depicted in Figure 1. On the basis of the theoretical study by Morokuma and co-workers on the ruthenium-catalyzed addi-

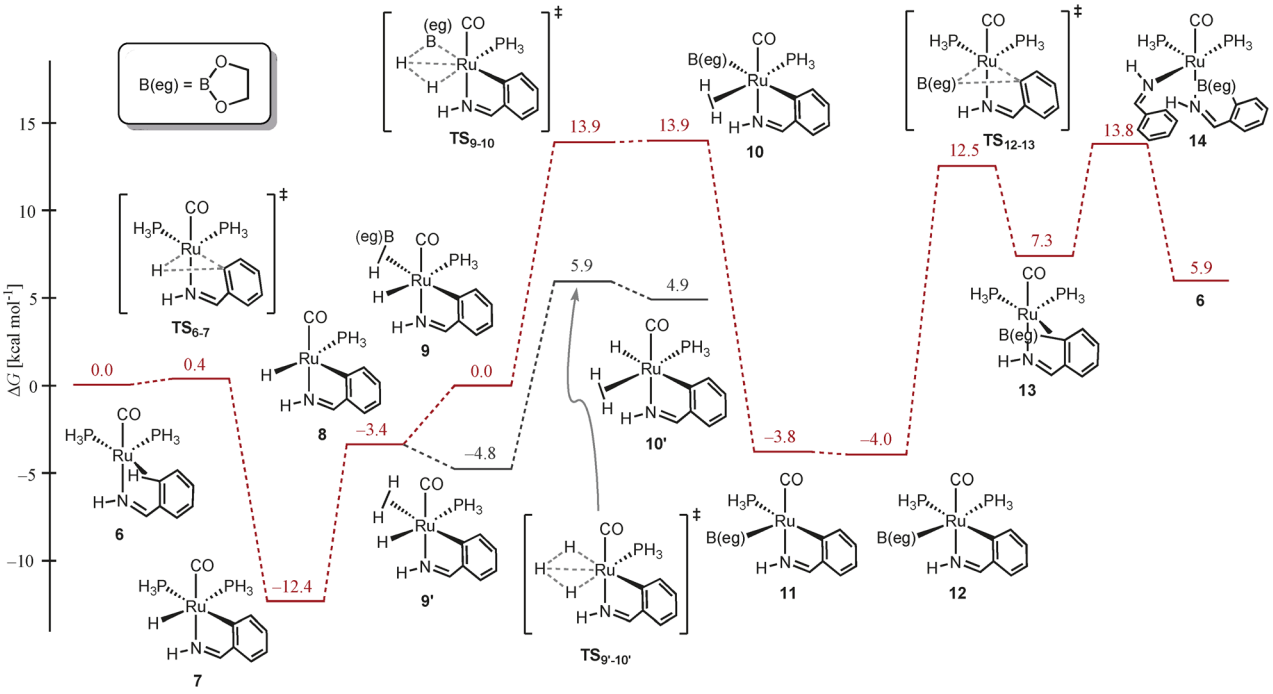


Figure 1. Reaction pathways with calculated relative free energies (kcal mol^{-1}).

tion of arenes to alkenes, a chelation of the substrate to an active ruthenium(0) species "$Ru(CO)(PH_3)_2$" followed by oxidative addition of the *ortho* C–H bond would take place through a transition state $\mathbf{TS_{6-7}}$ to form an intermediate **7**.[13] The activation barrier for the C–H bond activation step is very low.

A ligand substitution reaction includes dissociation of the PH_3 ligand and coordination of HB(eg) forming a σ-borane ruthenium **9**. The σ-complex-assisted metathesis (σ-CAM) with the Ru–H bond takes place through a transition state $\mathbf{TS_{9-10}}$ to form an aryl boryl ruthenium **10**.[14] During the hydrogen dissociation step from **10** to **11**, the Ru–C bond moves from the trans to the cis position to the boron atom due to the strong trans influence.[15] After the coordination of PH_3, the C–B reductive elimination through a transition state $\mathbf{TS_{12-13}}$ takes place to give a ruthenium(0) complex **13**, which contains a coordinated product. An associative ligand exchange between the product and the substrate would regenerate **6**.

As shown in Figure 1, the transition state for the σ-CAM $\mathbf{TS_{9-10}}$ is the highest point on the free energy profile of the catalytic cycle.[16] The rate-determining σ-CAM involving Ru–H (or Ru–D) bond cleavage would be agreement with the deuterium kinetic isotope effect as shown in Scheme 1a.[17] Furthermore, it is possible that H_2 also coordinates with **8** to yield a σ-hydrogen ruthenium **9′**. The σ-CAM of **9′** results in an exchange between dihydrogen and hydride ligands. This transition state $\mathbf{TS_{9'-10'}}$, which would achieve the H/D scrambling as shown in Scheme 1b, is lower in energy than $\mathbf{TS_{9-10}}$.

In conclusion, $[RuH_2(CO)(PPh_3)_3]$ was found to catalyze the *ortho*-selective borylation of 2-arylpyridines **3** with pinacolborane (**1**). Theoretical calculations suggest that the catalytic cycle involves oxidative addition of the C–H bond of **3**, the formation of the boryl ruthenium intermediate **10** through a σ-CAM mechanism, and reductive elimination of the C–B bond. The σ-CAM between the Ru–H and B–H bonds of **9** is the rate-determining step of the catalytic cycle. Further studies, including the expansion of substrate scope as well as detailed kinetic studies, are currently underway.

Experimental Section

General Procedure: $[RuH_2(CO)(PPh_3)_3]$ (4.6 mg, 5.0 μmol) was placed in a resealable Schlenk tube. The tube was evacuated and backfilled with nitrogen, and then charged with THF (0.5 mL), the 2-arylpyridines (**2**, 0.25 mmol), and pinacolborane (**1**; 108 μL, 0.75 mmol). The reaction mixture was then stirred at 150 °C for 16 h. The resulting mixture was allowed to cool to room temperature, diluted with toluene, washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by Kugelrohr distillation to afford the desired product **3**.

Keywords: boranes · C–H activation · density functional calculations · isotope effects · ruthenium

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[16] Figure 1 shows the B3LYP energy profile. The energy profile using the M06 functional is given in the Supporting Information.

[17] As suggested by a reviewer, kinetic studies with deuterated pinacolborane DB(pin)would be more convincing to determine the rate-limiting step. These experiments will be undertaken in the near future.

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