Organic LETTERS

Letter

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Rhodium-Catalyzed C6-Selective C−H Borylation of 2-Pyridones

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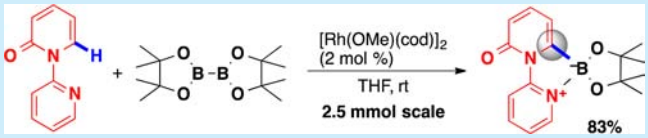
Supporting Information

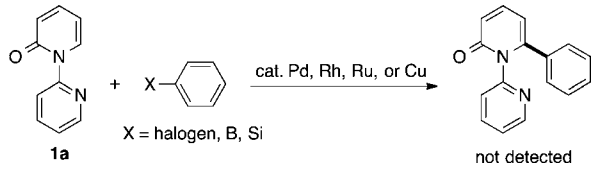
ABSTRACT: A pyridine-directed, rhodium-catalyzed C6-selective C−H borylation of 2-pyridones with bis(pinacolato)-diboron (pinB−Bpin) has been developed. The reaction proceeds smoothly under relatively mild conditions, and the corresponding C6-borylated 2-pyridones are obtained with perfect site selectivity. Subsequent palladium-catalyzed Suzuki−Miyaura cross-coupling is followed by the removal of the pyridine directing group to form the C6-arylated NH-pyridone in an acceptable overall yield.



Owing to the ubiquity in pharmaceutical targets and biologically active natural and unnatural products,[1] the development of protocols for the functionalization of a 2-pyridone ring has received significant attention in organic synthetic chemistry. While the traditional strategies rely on the halogenated 2-pyridone as the starting material, recent advances in metal-promoted C−H functionalization[2] allow for the direct bond-forming reaction without preactivation steps such as halogenation. However, there are four possible reactive C−H bonds on the pyridone ring, and thus the control of the site selectivity is the major challenging issue. To date, the site-selective C−H alkylation and arylation reactions at the relatively electron-rich C5-[3] and C3-positions[4] have been developed with the aid of transition metal catalysts as well as the unique nature of radical intermediates. On the other hand, the selective access to the more electron-deficient C6 position is still underdeveloped. Nakao and Hiyama reported an elegant nickel/aluminum cooperative catalysis for the otherwise difficult C6-selective C−H alkylation and alkenylation of the 2-pyridone.[5,6] Our group also developed the copper-mediated C6-selective C−H heteroarylation with 1,3-azoles by the introduction of the pyridine-based directing group on the nitrogen atom of the 2-pyridone.[7] Since then, some research groups reported the rhodium-catalyzed C−H alkylation and alkynylation at the C6 position by using the same pyridine-directed strategy.[8] Despite the above-mentioned certain progress, there still remains a demand for more diverse direct functionalization at the C6 position. In this letter, we report a rhodium-catalyzed C6-selective C−H borylation of 2-pyridones. The resulting C−B moiety can be a useful synthetic handle for further manipulations. As such an example, the Suzuki−Miyaura cross-coupling of the borylated pyridone is also described herein.

During our continuous studies on the site-selective C−H functionalization of 2-pyridones,[4a−c,7] we initially attempted the catalytic direct arylation of *N*-(2-pyridyl)-2-pyridone (**1a**) at the C6 position. Various transition metal catalysts, particularly effective for the direct arylation of a structurally similar 2-phenylpyridine, were investigated, but no desired arylated product was detected as far as we tested (Scheme 1).[9]

Scheme 1. Unsuccessful Attempts of Catalytic C6-Selective C−H Arylation of *N*-(2-Pyridyl)-2-pyridone (1a)



Thus, we turned our attention into the corresponding C−H borylation: given the rich chemistry based on the organoboron compounds, it can provide a useful synthetic platform for versatile C6-functionalized 2-pyridones. To our delight, the reaction of **1a** (0.25 mmol) with bis(pinacolato)diboron (pinB−Bpin, 0.38 mmol) proceeded in the presence of 2 mol % $[Ir(OMe)(cod)]_2$, the representative catalyst for the aromatic C−H borylation,[10] in refluxing octane, and the C6-borylated 2-pyridone **2a** was formed albeit with an 18% NMR yield (Table 1, entry 1). The structure of **2a** involving the intramolecular N−B coordination was determined by ^{1}H, ^{13}C, ^{11}B NMR,[11] HRMS, and X-ray analysis.[12] To improve the reaction efficiency, we added several nitrogen-based ligands, which are well-known to accelerate the iridium-catalyzed C−H borylation.[10,13] However, they gave negative or negligible impact on the yield of **2a** (entries 2−5). After a brief screening of solvents, toluene was found to be better, but the yield was still moderate (entries 6 and 7). Thus, we then tested the alternative $[Rh(OMe)(cod)]_2$ catalyst.[14] Pleasingly, the full conversion of **1a** was observed, and the NMR yield of **2a** increased to 60% (entry 8). The rhodium catalyst promoted the reaction even at lower temperature (entries 9 and 10), and finally the best result was obtained in THF at room temperature (74% isolated yield;

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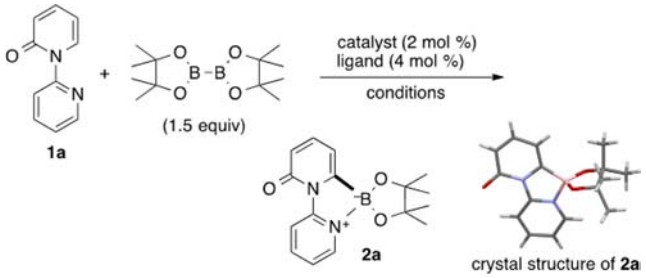
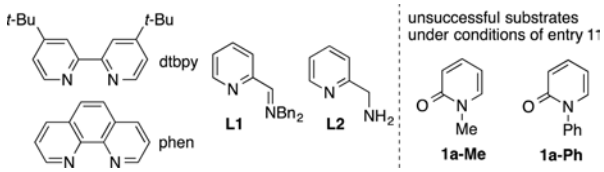
Table 1. Optimization Studies for Catalytic C6-Selective C–H Borylation of *N*-(2-Pyridyl)-2-pyridone (1a)[a]



entry	catalyst/ligand	conditions	yield (%)[b]
1	$[Ir(OMe)(cod)]_2$/none	octane, reflux, 4 h	18
2	$[Ir(OMe)(cod)]_2$/dtbpy	octane, reflux, 4 h	0
3	$[Ir(OMe)(cod)]_2$/phen	octane, reflux, 4 h	0
4	$[Ir(OMe)(cod)]_2$/**L1**	octane, reflux, 4 h	14
5	$[Ir(OMe)(cod)]_2$/**L2**	octane, reflux, 4 h	12
6	$[Ir(OMe)(cod)]_2$/none	THF, reflux, 4 h	15
7	$[Ir(OMe)(cod)]_2$/none	toluene, reflux, 4 h	23
8	$[Rh(OMe)(cod)]_2$/none	toluene, reflux, 4 h	60
9	$[Rh(OMe)(cod)]_2$/none	toluene, 80 °C, 24 h	40
10	$[Rh(OMe)(cod)]_2$/none	toluene, rt, 24 h	68
11	$[Rh(OMe)(cod)]_2$/none	THF, rt, 24 h	(74, 83[c])
12	$[Rh(OMe)(cod)]_2$/dtbpy	THF, rt, 24 h	0
13	$[Rh(OMe)(cod)]_2/PPh_3$	THF, rt, 24 h	19

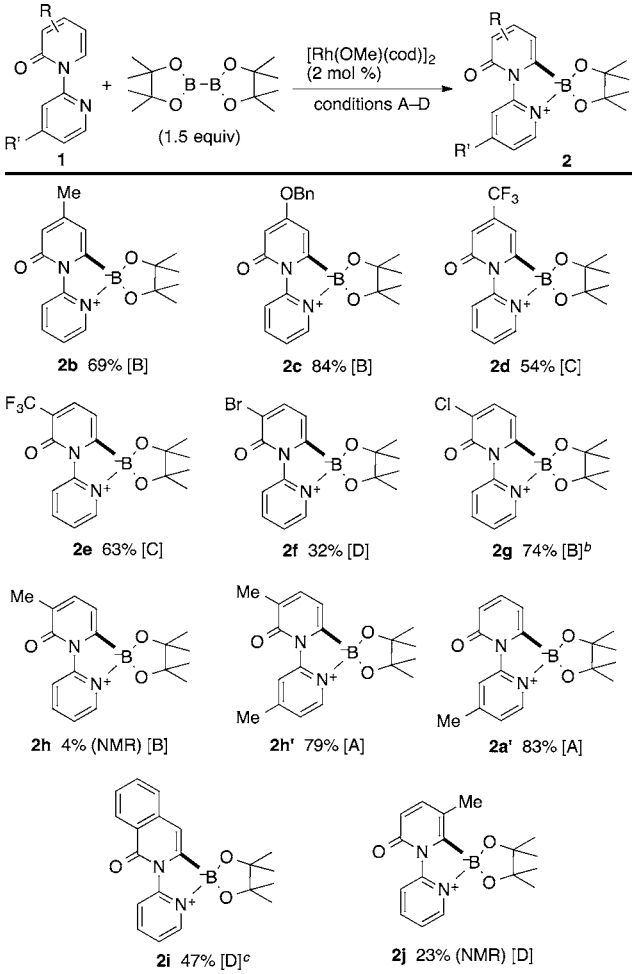
[a]Reaction conditions: **1a** (0.25 mmol), pinB–Bpin (0.38 mmol), catalyst (0.0050 mmol), ligand (0.010 mmol), solvent (1.5 mL), N_2. [b]^{1}H NMR yield. Isolated yields are given in parentheses. [c]2.5 mmol scale.



entry 11). The rhodium-catalyzed C–H borylation could also be easily performed on a 10-fold larger scale, and **2a** was isolated in 83% yield. As shown in the case of $[Ir(OMe)(cod)]_2$, the addition of dative ligands such as dtbpy and PPh_3 was detrimental (entries 12 and 13). Additionally, simpler **1a-Me** and **1a-Ph** gave no borylated products under the rhodium catalysis, thus indicating the necessity of the coordination ability of the pyridyl group in **1a**.[15]

We next investigated the scope and limitation of the 2-pyridone. Representative C6-borylated products are shown in Scheme 2. The rhodium catalysis was compatible with electron-donating methyl and benzyloxy groups as well as an electron-withdrawing trifluoromethyl group at the C4 position, and the corresponding **2b–2d** were obtained in good yields. In the cases of the C3-substituted pyridones, electron-poor substrates showed better reactivity (**2e–2g**), although the $[Ir(OMe)(cod)]_2$ catalyst was found to be uniquely effective for the 3-chloropyridone derivative (**2g**).[16] The electron-rich 3-methylpyridone was reluctant under any tested conditions (**2h**); however, modification of the directing group to a more strongly coordinating 4-methylpyridyl moiety dramatically improved the reaction efficiency (**2h′**).[17] This directing group was also promising for the simple pyridone (**2a′**). The benzene-fused isoquinolinone could also be employed for this transformation to form the desired **2i** in an acceptable yield. A current

Scheme 2. Catalytic C6-Selective C–H Borylation of Various 2-Pyridones 1[a]



[a]Reaction stoichiometry: **1** (0.25 mmol), pinB–Bpin (0.38 mmol), $[Rh(OMe)(cod)]_2$ (0.0050 mmol), solvent (1.5 mL). Isolated yields are given. Conditions employed are in parentheses (A–D). Conditions A: THF, rt, 24 h. Conditions B: THF, reflux, 4 h. Conditions C: *o*-xylene, 150 °C, 2 h. Conditions D: THF, 150 °C, μw, 2 h. [b]With $[Ir(OMe)(cod)]_2$ instead of $[Rh(OMe)(cod)]_2$. [c]With 0.010 mmol of $[Rh(OMe)(cod)]_2$.

limitation is the inaccessibility to C5-substituted pyridones, probably due to steric factors (**2j**). Overall, the reactivity was highly dependent on the electronic nature of the substituent, and fine-tuning of the reaction temperature (conditions A–D) was essential for a satisfactory yield in each case. However, most borylated products were formed with synthetically useful yields, and the site selectivity was perfectly controlled.

The obtained C6-borylated 2-pyridone **2a** could be readily converted to the corresponding difluoroborane **2a-BF$_2$** upon treatment with KHF_2 in THF/H_2O (Scheme 3). Notably, even in the presence of excess fluoride anion, the intramolecular N–B interaction was retained, which was assigned by ^{11}B NMR as well as X-ray analysis.[12] Moreover, the $Pd(OAc)_2$/P[3,5-$(CF_3)_2C_6H_3]_3$-catalyzed Suzuki–Miyaura cross-coupling with iodobenzene was also possible, and the C6-arylated 2-pyridone **3a** was obtained in 72% isolated yield.[18] The exclusive C6-arylation was unambiguously confirmed by the crystallographic analysis.[12] Subsequent MeOTf-driven reductive removal of the

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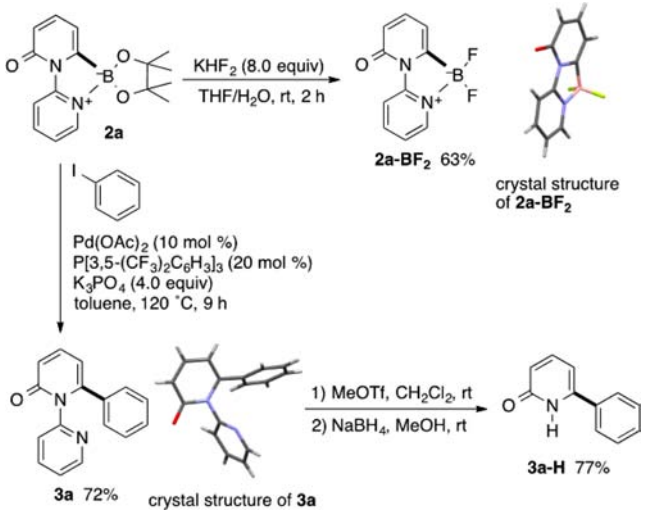
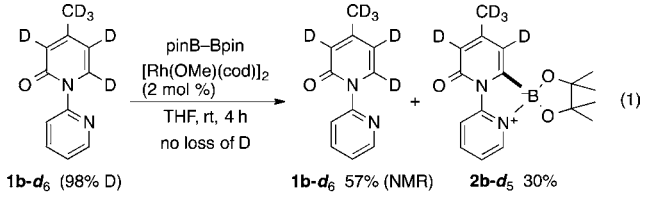
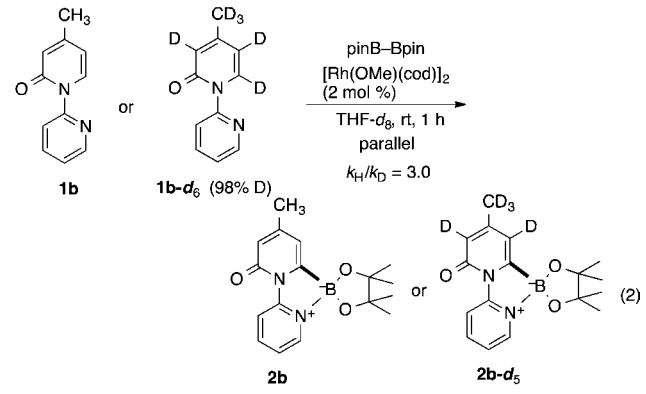
Scheme 3. Derivatization of C6-Borylated 2-Pyridone 2a

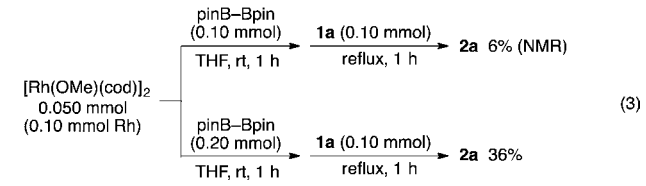


pyridine directing group afforded the 6-phenyl-NH-2-pyridone (**3a-H**) in an acceptable overall yield.[19]

The following control experiments with the deuterium-labeling pyridone **1b-*d*$_6$** indicate that the irreversible and selective C−H cleavage occurs at the C6 position (eq 1) and

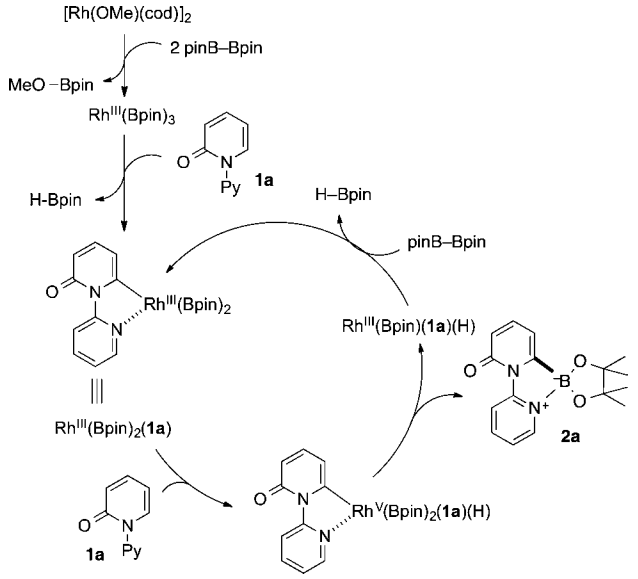






this step can be involved in the rate-limiting step (k_H/k_D = 3.0, eq 2). Additionally, two stoichiometric reactions in a ratio of Rh/pinB−Bpin = 1/1 or 1/2 suggest a tris(boryl)rhodium complex [Rh^{III}(Bpin)$_3$] to be an active species (eq 3). The above findings and literature information[20] can support the Rh(III)/Rh(V) redox mechanism involving (i) initial generation of Rh^{III}(Bpin)$_2$(**1a**) via Rh^{III}(Bpin)$_3$-promoted C−H rhodation of **1a**, (ii) the directed oxidative addition of C−H of **1a** to Rh^{III}(Bpin)$_2$(**1a**) forming Rh^{V}(Bpin)$_2$(**1a**)$_2$(H), (iii) formation of **2a** and Rh^{III}(Bpin)(**1a**)(H) through reductive elimination, and (iv) regeneration of Rh^{III}(Bpin)$_2$(**1a**) by the metathesis of Rh^{III}(Bpin)(**1a**)(H) with pinB−Bpin (Scheme 4).

Scheme 4. Plausible Mechanism



The observed negative or negligible effect of the external ligands (Table 1, entries 2−5, 12, and 13) also suggests that **1a** is the ligand to the rhodium as well as the substrate to be borylated.[20a] However, an alternative Rh(I)/Rh(III) mechanism cannot be completely excluded, and further efforts are essential for clarification of the exact mechanism.

In conclusion, we have developed a pyridine-directed, rhodium-catalyzed C−H borylation of 2-pyridones at the C6 position. To the best of our knowledge, this is the first successful example of C6-selective direct introduction of the heteroatom substituent. The formed borylated pyridone can be a useful synthetic handle for versatile C6-functionalized 2-pyridones; its capacity is demonstrated by the Suzuki−Miyaura cross-coupling while still preliminary. Additional transformations of the borylated products and more detailed mechanistic studies are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01762.

CIF file of **2a** (CIF)
CIF file of **2a-BF$_2$** (CIF)
CIF file of **3a** (CIF)
^{1}H, ^{13}C{^{1}H}, ^{11}B, and ^{19}F NMR spectra for products and ORTEP drawings (PDF)

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Notes

The authors declare no competing financial interest.

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(12) Crystallographic data for the structures have been deposited with the Cambridge Crystallographic Data Center (CCDC 1483627, 1483628, and 1483629). See the Supporting Information for details.

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(15) See the Supporting Information for more detailed optimization studies.

(16) We have no explanation for the reason at this stage.

(17) On the other hand, 4-fluoropyridyl, 4-methoxypyridyl, and 2-thiazolyl directing groups showed sluggish reactivity (<5% borylated products). Additionally, we also prepared *N*-(4-methylpyridyl)-5-methyl-2-pyridone (**1j′**) and investigated its reactivity. However, the yield was not improved. Thus, the positive effect of the 4-methylpyridyl directing group can be somewhat limited.

(18) Even under the $Pd(OAc)_2$/P[3,5-$(CF_3)_2C_6H_3$]$_3$-promoted conditions, the C−H arylation of **1a** with iodobenzene did not occur at all. See the Supporting Information for details and additional examples of the Suzuki−Miyaura coupling.

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