Synthesis W. Miura et al. Special Topic

Iridium-Catalyzed Site-Selective C–H Borylation of 2-Pyridones

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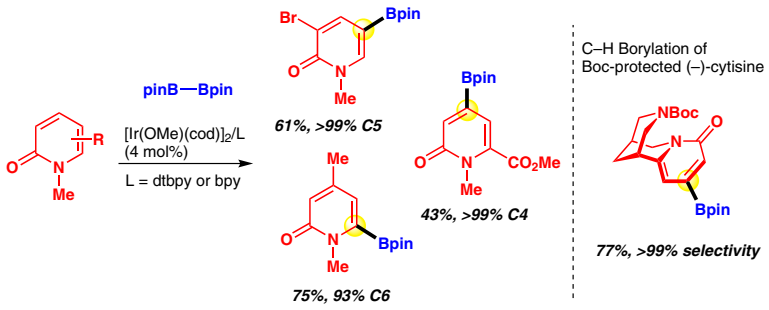

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Abstract An iridium-catalyzed site-selective C–H borylation of 2-pyridones has been developed. The site selectivity is predominantly controlled by steric factors, and we can access C4, C5, and C6 C–H on the 2-pyridone ring by the judicious choice of ligand and solvent. Subsequent Suzuki–Miyaura cross-coupling of the borylated products also proceeds to form the corresponding arylated pyridones in good overall yields.

Key words borylation, C–H functionalization, iridium, 2-pyridones, site selectivity

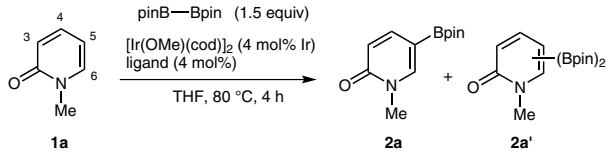
2-Pyridones are frequently occurring heterocyclic substructures in bioactive molecules, natural products, and pharmaceutical agents, including ciclopirox, milrinone, camptothecin, fredericamycin, perampanel, and cytisine.[1] Many synthetic chemists thus have developed synthetic methodologies to construct and functionalize the 2-pyridone ring, particularly by transition-metal catalysts. While traditional strategies largely rely on prefunctionalization, such as halogenation, of the parent 2-pyridone, recent advances in metal-promoted C–H activation[2] can skip the preactivation step and provide a more straightforward approach to densely functionalized 2-pyridone cores. To date, site-selective C–H alkylation,[3] arylation,[4] alkenylation,[5] alkynylation,[6] and thiolation[7] have been reported.

Meanwhile, our research group recently developed the rhodium-catalyzed, pyridine-directed C6-selective C–H borylation of 2-pyridones.[8] The resulting boryl group underwent the Suzuki–Miyaura cross-coupling reaction to form C6-arylated 2-pyridones selectively. Although this is the first successful example of the C–H borylation of 2-pyridone, the tedious installation/removal steps of the directing group are inevitable and the reaction site is also limited to the C6 position. Given the rich and versatile chemistry of the organoboron compounds, further development of C–H borylation catalysis that accesses more diverse C–H on the pyridone ring is strongly appealing. Herein, we report an iridium-catalyzed site selective C–H borylation of 2-pyridones with a diboron reagent: the site selectivity is mainly controlled by the steric nature of substrate, and the judicious choice of catalyst and solvent allows C–H borylation at the otherwise challenging C4 as well as C5 and C6 positions without any directing groups. The borylated products can be readily converted into arylated pyridones via Suzuki–Miyaura reaction with aryl halides. Additionally, the iridium catalysis can be applicable to the C–H borylation of a biologically active (–)-cytisine derivative.

Inspired by the recent rapid progress of iridium-catalyzed aromatic C–H borylation,[9,10] we selected *N*-methyl-2-pyridone (**1a**) and bis(pinacolato)diboron (pinB–Bpin) as model substrates and began optimization studies, in conjunction with $[Ir(OMe)(cod)]_2$ catalyst, by screening ancillary ligands (Table 1, Figure 1). In an initial attempt, treatment of **1a** (0.25 mmol) with pinB–Bpin (0.38 mmol) in the presence of 4 mol% Ir/phen catalyst in THF at 80 °C afforded a 92:8 mixture of the C5-borylated pyridone **2a** and diborylated compounds **2a′** in 39% combined yield (entry 1). The structures of diborylated products **2a′** were not completely determined, but the major isomer was found to be a 3,5-diborylated pyridone. While some related bipyridine-type ligands also promoted the reaction with moderate efficiency and selectivity (entries 3–7, 11), the introduction of substituents at the position α to nitrogen largely suppressed the substrate conversion (entries 2, 8–10). On the other hand, bisphosphine ligands showed remarkably high C5 site selectivity, but the yield of **2a** was lower even at higher temperatures (135–150 °C; entries 12–14). Using pinB-H as the boron reagent also worked to some extent, but the reactivity was somewhat lower (entry 15). In contrast to our

previous work, $[Rh(OMe)(cod)]_2$ instead of $[Ir(OMe)(cod)]_2$ did not catalyze the reaction of **1a** at all, as far as we tested (data not shown).

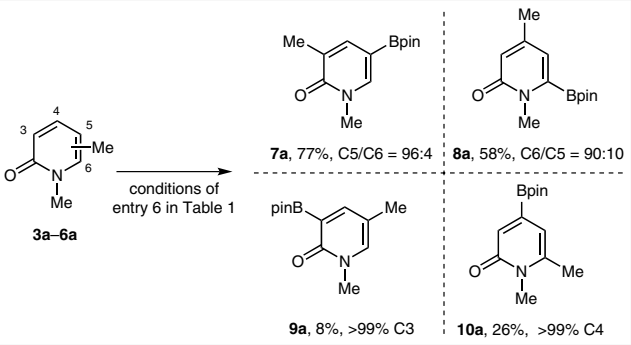
Table 1 Optimization Studies for Iridium-Catalyzed Site-Selective C–H Borylation of *N*-Methyl-2-pyridone (**1a**) with pinB–Bpin[a]



1a **2a** **2a'**

Entry	Ligand	Yield[b] (%) of **2a** + **2a'**	Ratio[c] **2a**/**2a'**
1	phen	39	92:8
2	Me_2-phen	4	>99:1
3	Me_4-phen	9	85:15
4	bathophen	24	42:58
5	bpy	35	83:17
6	dtbpy	49	44:56
7	MeO-bpy	51	75:25
8	Me_2-bpy	0	–
9	**N1**	0	–
10	**N2**	0	–
11	**N3**	36	89:11
12[d]	dppf	7	>99:1
13[e]	*rac*-Binap	5	>99:1
14[e]	(*R*)-DTBM-Segphos	14	>99:1
15[f]	dtbpy	24	88:12

[a] Reaction conditions: **1a** (0.25 mmol), pinB–Bpin (0.38 mmol), $[Ir(OMe)(cod)]_2$ (0.0050 mmol), ligand (0.010 mmol), THF (1.5 mL), 80 °C, 4 h, N_2.
[b] Determined by ^1H NMR with dibenzyl ether as an internal standard.
[c] Determined by ^1H NMR of the crude mixture.
[d] In CPME at 150 °C.
[e] In octane at 135 °C.
[f] With pinB-H (0.75 mmol) instead of pinB–Bpin.



Scheme 1 Initial attempts of Ir/dtbpy-catalyzed C–H borylation of 3-, 4-, 5-, and 6-methyl-2-pyridones **3a–6a**; ^1H NMR yields are given

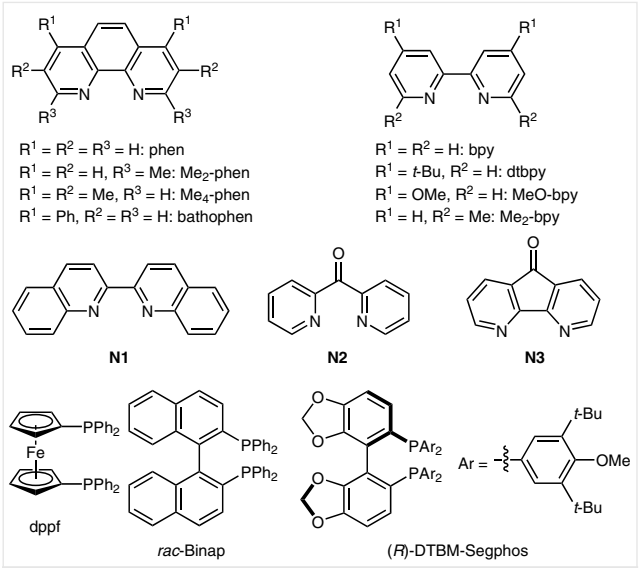
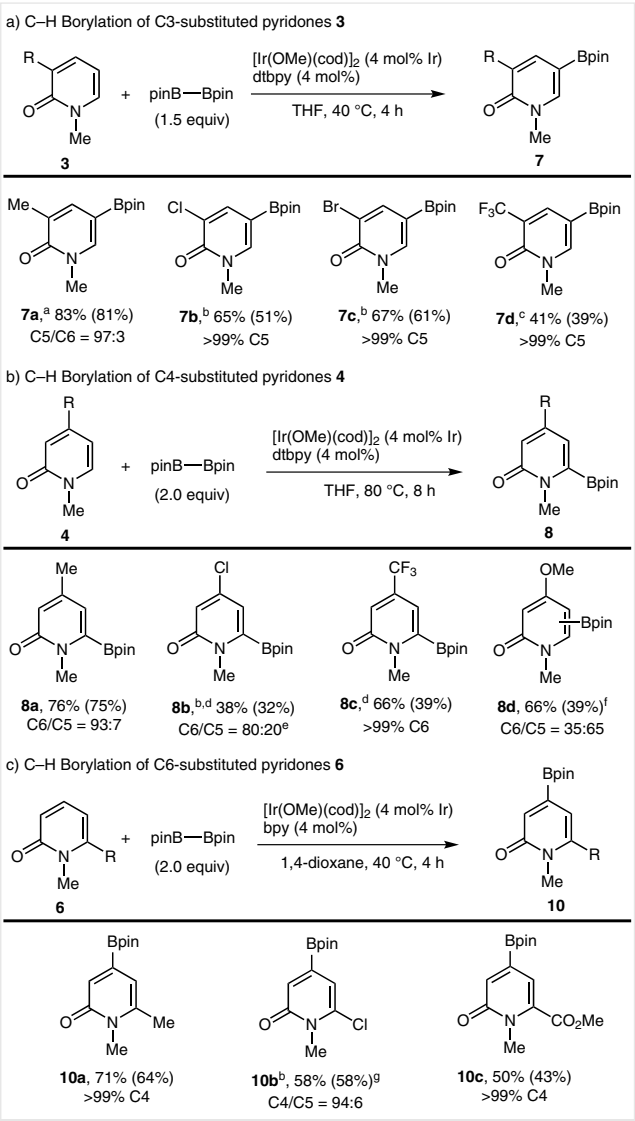


Figure 1

Unfortunately, we could not obtain a satisfactory yield and selectivity with the parent **1a**, but 3-, 4-, 5-, and 6-methyl-2-pyridones **3a**, **4a**, **5a**, and **6a** were then tested under conditions identical to entry 6 in Table 1 (Scheme 1). To our delight, remarkable increase in the yield and/or selectivity was observed for **3a**, **4a**, and **6a** to afford C5- (**7a**), C6- (**8a**), and C4-borylated (**10a**) products with >90:10 site selectivity. Exceptionally, the reaction of 5-methyl-2-pyridone (**5a**) was sluggish and gave **9a** in 8% yield albeit with >99% C3 selectivity. Additional fine tuning of ligand, solvent, temperature, and stoichiometry identified optimal conditions for each substitution pattern. Representative results are shown in Scheme 2. Various C3-substituted 2-pyridones **3** underwent C–H borylation smoothly under the Ir/bpy or dtbpy catalyst system at 40 °C to deliver the corresponding C5-borylated compounds **7a–d** in good yields with >97:3 site selectivity [Scheme 2 (a)]. Notably, halogenated substrates **3b** and **3c** necessitated the preactivation of iridium catalyst for satisfactory conversion (see the experimental section for details): without the preactivation, the reaction stopped at an early stage of reaction, although we did not observe any borylation products at the C–halogen bond. Similar trends were observed for other halogen-substituted pyridones (*vide infra*). The combination of $[Ir(OMe)(cod)]_2$ and dtbpy efficiently catalyzed the reaction of C4-substituted pyridones **4** [Scheme 2 (b)]. While methyl- and trifluoromethyl-substituted **4a** and **4c** formed the C6-borylated products **8a** and **8c** with 93% and >99% C6 selectivity, respectively, chloro and methoxy substituents decreased the site selectivity for **8b** and **8b**. It is noteworthy that the C6-substituted pyridones **6** were borylated in the presence of the Ir/bpy catalyst[11] selectively at the more electron-deficient C4 position [Scheme 2 (c); **10a–c**], which is otherwise difficult to access by other C–H activation

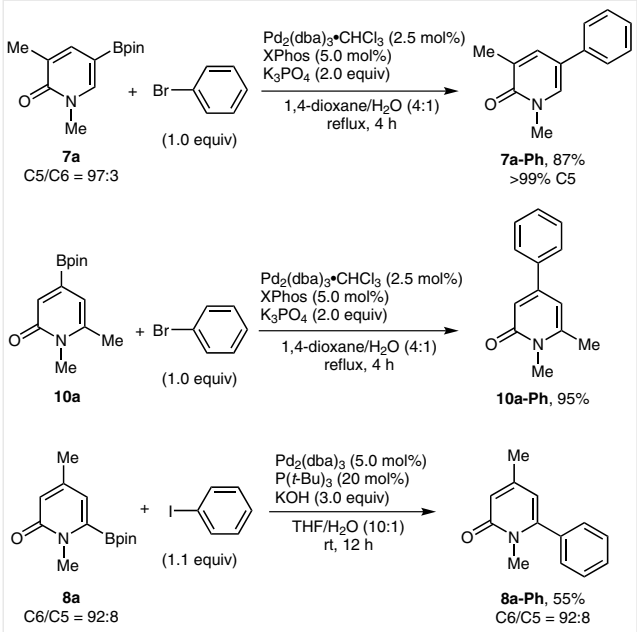


Scheme 2 Iridium-catalyzed site-selective C–H borylation of C3-, C4-, and C6-substituted 2-pyridones; ^{1}H NMR yields are shown, combined isolated yields are given in parenthesis. The site selectivity was determined by ^{1}H NMR analysis of the crude mixture. [a] With 2.0 equiv of pinB–Bpin and bpy in 1,4-dioxane. [b] Preactivation of the catalyst was performed. See the experimental section for details. [c] 24 h. [d] 40 °C, 4 h. [e] The C6/C5 ratio of the isolated product was 77:23. [f] Isolated yield of the pure C5-borylated isomer. [g] Isolated yield of the pure C4-borylated isomer.

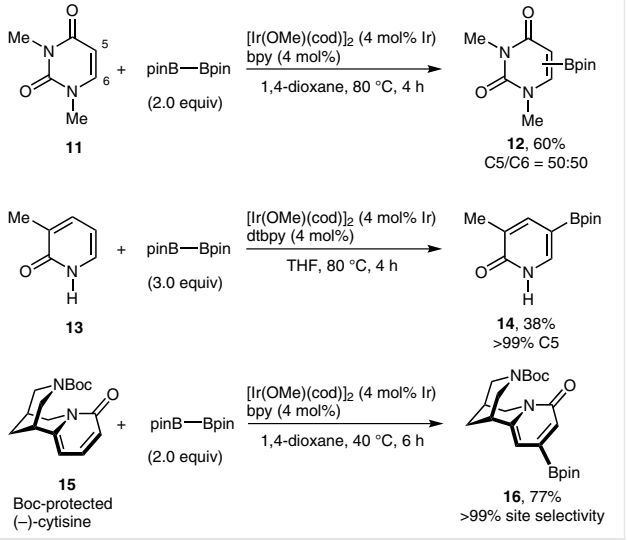
strategies;[3–8] just a single example under Ni/Al cooperative catalysis has been reported.[3a] In general, the site selectivity was controlled by the innate steric nature of the pyridone substrates. However, exceptionally lower selectivity was observed in the C6-selective borylation of 4-chloro-, and methoxy-substituted pyridones [Scheme 2 (b), **8b** and **8d**]. This is probably because of the directing effect of the chloro group[12] and the higher acidity of C–H *ortho* to the methoxy group[13] as well as higher electron density at the C5 position. However, detailed reasons are not clear at this stage. On the other hand, we could not optimize conditions for the borylation of C5-substituted pyridones such as **5a**. Further efforts are essential.

The obtained borylated pyridones easily participated in the Suzuki–Miyaura cross-coupling reaction with aryl halides (Scheme 3). The C5- and C4-borylated pyridones **7a** and **10a** coupled with bromobenzene under Pd/XPhos (XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl) catalysis[14] to furnish the corresponding arylpyridones **7a-Ph** and **10a-Ph** in 87% and 95% yields, respectively. For C6-borylated **8a**, a Pd/P(*t*-Bu)$_3$ catalyst[15] and iodobenzene were more suitable, and the desired **8a-Ph** was obtained in 55% yield.

Finally, we applied this protocol to conceivably more challenging pyridone derivatives (Scheme 4). While less site selective, the Ir/bpy-catalyzed C–H borylation of 1,3-dimethyluracil (**11**) proceeded to form the boryluracil **12** in a good combined yield (60%). Under slightly modified conditions, the NH-pyridone **13** could also be employed, and desired C5-borylated **14** was obtained in 38% yield with >99% C5 selectivity, probably via in situ *N*- or *O*-borylation of the CONH moiety.[10g] Moreover, Boc-protected (–)-cytisine **15** was effectively borylated to give **16** in 77% yield and with >99% site selectivity. The boryl group can be a good handle for further modification of biological activity of the parent cytisine.[16]



Scheme 3 Suzuki–Miyaura cross-coupling of borylated 2-pyridones; isolated yields are given



Scheme 4 Iridium-catalyzed C–H borylation of uracil, NH-pyridone, and Boc-protected (–)-cytisine; isolated yields are given

In conclusion, we have developed an iridium-catalyzed site-selective C–H borylation of 2-pyridones. The site selectivity is mainly controlled by steric factors of substrates. This catalysis can provide a more straightforward approach to C4-, C5-, and C6-borylated pyridones; some of which are traditionally prepared by two-step procedures, i.e., halogenation and Pd-catalyzed Miyaura borylation. Additionally, subsequent Suzuki–Miyaura coupling readily converts the borylated pyridones into the corresponding aryl-substituted pyridones of great potential in medicinal chemistry. Related metal-catalyzed site-selective C–H functionalizations of 2-pyridones are currently underway and will be reported in due course.

^{1}H, ^{13}C{^{1}H}, ^{19}F{^{1}H}, and ^{11}B NMR spectra were recorded at 400, 100, 376, and 128 MHz, respectively, for $CDCl_3$ solutions. HRMS data were obtained by APCI using TOF. Silica gel (Wakosil C-200) was used for column chromatography. Gel permeation chromatography (GPC) was performed by LC-20AR (pump, Shimadzu, 7.5 mL/min) and RID-20A (RI detector, Shimadzu) with two in-line YMC-GPC T2000 (20 × 600 mm, particle size: 10 µm) (preparative columns, YMC, EtOAc eluent) or two in-line GPC H-2001 (20 × 500 mm, particle size: 15 µm) and H-2002 columns (20 × 500 mm, particle size: 15 µm) (preparative columns, Shodex, $CHCl_3$ eluent). Unless otherwise noted, materials obtained from commercial suppliers were used as received. Anhyd THF was purchased and used out of the bottle without further purification. 1,4-Dioxane was dried on a Glass Contour Solvent dispensing system (Nikko Hansen & Co., Ltd.) prior to use. $[Ir(OMe)(cod)]_2$ was prepared according to the literature procedure.[17] Pyridone **1a** is commercially available, and others were synthesized from the corresponding NH-pyridones by reported methods.[5b,18]

Iridium-Catalyzed C–H Borylation of 2-Pyridones; General Procedure A (GPA)

Ligand (0.010 mmol) and $[Ir(OMe)(cod)]_2$ (3.3 mg, 0.0050 mmol) were placed in a 20-mL two-necked reaction flask, which was filled with N_2 by using the standard Schlenk technique. Solvent (0.50 mL) was injected via a syringe, and the mixture was stirred for 5 min at r.t. A solution of 2-pyridone (0.25 mmol) and bis(pinacolato)diboron (0.38–0.75 mmol) in solvent (1.0 mL) was then added, and the suspension was stirred under the indicated conditions. The resulting mixture was allowed to cool to r.t., diluted with EtOAc, and filtered through a short pad of neutral alumina and anhyd Na_2SO_4. After concentration under reduced pressure, purification by GPC (EtOAc) afforded the corresponding borylated 2-pyridone.

Iridium-Catalyzed C–H Borylation of Halogenated 2-Pyridones; General Procedure B (GPB, Preactivation Method)

Ligand (0.010 mmol) and $[Ir(OMe)(cod)]_2$ (3.3 mg, 0.0050 mmol) were placed in a 20-mL two-necked reaction flask, which was filled with N_2 by using the standard Schlenk technique. Solvent (0.50 mL) was injected via a syringe, and the mixture was stirred for 5 min at r.t. A solution of bis(pinacolato)diboron (0.38–0.50 mmol) in solvent (0.50 mL) was then added, and the suspension was stirred for an additional 5 min at r.t. A solution of halogenated 2-pyridone (0.25 mmol) in solvent (0.50 mL) was subsequently added, and the solution was stirred under the indicated conditions. The resulting mixture was allowed to cool to r.t., diluted with EtOAc, and filtered through a short pad of neutral alumina and anhyd Na_2SO_4. After concentration under reduced pressure, purification by GPC (EtOAc) afforded the corresponding halogen-containing borylated 2-pyridone.

1,3-Dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one (7a) and 1,3-Dimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one (7a′)

According to GPA, purification by GPC (EtOAc) gave the product (51 mg, 0.20 mmol, 81%) as a white solid; ratio **7a**/**7a′** 97:3; mp 140.3–142.3 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (s, 0.97 × 12 H for **7a**), 1.34 (s, 0.03 × 12 H for **7a′**), 2.13 (d, *J* = 1.0 Hz, 0.97 × 3 H for **7a**), 2.17 (s, 0.03 × 3 H for **7a′**), 3.56 (s, 0.97 × 3 H for **7a**), 3.73 (s, 0.03 × 3 H for **7a′**), 6.70 (d, *J* = 6.7 Hz, 0.03 × 1 H for **7a′**), 7.15 (d, *J* = 6.7 Hz, 0.03 × 1 H for **7a′**), 7.48 (d, *J* = 1.0 Hz, 0.97 × 1 H for **7a**), 7.66 (s, 0.97 × 1 H for **7a**).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): for **7a** δ = 17.03, 24.93, 37.93, 84.04, 128.5, 140.8, 144.2, 164.2. The carbon signal bound to the boron was not observed due to quadrupolar relaxation.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 30.47.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{21}BNO_3$: 250.1611; found: 250.1602.

3-Chloro-1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one (7b)

According to GPB, purification by GPC (EtOAc) gave the product (34 mg, 0.13 mmol, 51%) as a white solid; mp 174.9–176.9 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (s, 12 H), 3.61 (s, 3 H), 7.70 (d, *J* = 1.8 Hz, 1 H), 7.80 (d, *J* = 1.8 Hz, 1 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 24.9, 38.7, 84.5, 125.5, 141.7, 144.8, 159.9. The carbon signal bound to the boron was not observed due to quadrupolar relaxation.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 29.65.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{18}BClNO_3$: 270.1065; found: 270.1077.

3-Bromo-1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one (7c)

According to GPB, purification by GPC (EtOAc) gave the product (48 mg, 0.15 mmol, 61%) as a white solid; mp 172.4–174.4 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (s, 12 H), 3.61 (s, 3 H), 7.74 (d, *J* = 1.8 Hz, 1 H), 8.00 (d, *J* = 1.7 Hz, 1 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 24.9, 39.0, 84.5, 115.6, 145.7 (2 C), 159.9. The carbon signal bound to the boron was not observed due to quadrupolar relaxation.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 30.12.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{18}BBrNO_3$: 314.0560; found: 314.0567.

1-Methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridin-2(1*H*)-one (7d)

According to GPA, purification by GPC (EtOAc) gave the product (30 mg, 0.10 mmol, 39%) as a white solid; mp 142.3–144.3 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (s, 12 H), 3.60 (s, 3 H), 7.94 (d, *J* = 1.7 Hz, 1 H), 8.02 (d, *J* = 1.7 Hz, 1 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 24.9, 38.0, 84.6, 119.6 (q, *J* = 30.4 Hz), 122.9 (q, *J* = 270.0 Hz), 143.1 (q, *J* = 4.8 Hz), 149.8, 159.4. The carbon signal bound to the boron was not observed due to quadrupolar relaxation.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ = –65.85.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 29.87.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{18}BF_3NO_3$: 304.1329; found: 304.1323.

1,4-Dimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one (8a) and 1,4-Dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one (8a′)

According to GPA, purification by GPC (EtOAc) gave the product (46 mg, 0.19 mmol, 75%) as a brown solid; ratio **8a**/**8a′** 97:3; mp 70.5–72.5 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (s, 0.070 × 12 H for **8a′**), 1.35 (s, 0.93 × 12 H for **8a**), 2.15 (d, *J* = 1.0 Hz, 0.93 × 3 H for **8a**), 2.31 (s, 0.070 × 3 H for **8a′**), 3.52 (s, 0.070 × 3 H for **8a′**), 3.68 (s, 0.93 × 3 H for **8a**), 6.33 (s, 0.070 × 1 H for **8a′**), 6.48 (dd, *J* = 1.0, 2.0 Hz, 0.93 × 1 H for **8a**), 6.60 (d, *J* = 2.0 Hz, 0.93 × 1 H for **8a**), 7.71 (s, 0.070 × 1 H for **8a′**).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): for **8a** δ = 24.7, 34.9, 68.0, 85.0, 119.3, 122.0, 149.0, 163.9; for **8a′** δ = 25.6, 37.1, 60.4, 83.5, 118.9, 146.8, 156.0, 163.3. The carbon signal bound to the boron was not observed due to quadrupolar relaxation.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 28.60.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{21}BNO_3$: 250.1611; found: 250.1600.

4-Chloro-1-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one (8b) and 4-Chloro-1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one (8b′)

According to GPB, purification by GPC (EtOAc) gave the product (21 mg, 0.080 mmol, 32%) as a yellow solid; ratio **8b**/**8b′** 77:23; mp 95.8–97.8 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (s, 0.23 × 12 H for **8b′**), 1.36 (s, 0.77 × 12 H for **8b**), 3.53 (s, 0.23 × 3 H for **8b′**), 3.68 (s, 0.77 × 3 H for **8b**), 6.60 (s, 0.23 × 1 H for **8b′**), 6.71 (d, *J* = 2.4 Hz, 0.77 × 1 H for **8b**), 6.76 (d, *J* = 2.4 Hz, 0.77 × 1 H for **8b**), 7.75 (s, 0.23 × 1 H for **8b′**).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): for **8b** δ = 24.8, 35.3, 85.6, 117.9, 121.8, 145.3, 163.1; for **8b′** δ = 24.9, 37.5, 84.3, 119.5, 147.5, 151.0, 162.3. The carbon signal bound to the boron was not observed due to quadrupolar relaxation.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 28.45.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{18}BClNO_3$: 270.1065; found: 270.1073.

1-Methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)pyridin-2(1*H*)-one (8c)

According to GPA, purification by GPC (EtOAc) gave the product (30 mg, 0.10 mmol, 39%) as a yellow solid; mp 131.9–133.9 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.37 (s, 12 H), 3.75 (s, 3 H), 6.87 (d, *J* = 2.0 Hz, 1 H), 6.93 (dd, *J* = 1.0, 2.0 Hz, 1 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 24.8, 35.7, 85.7, 111.2 (q, *J* = 2.6 Hz), 120.6 (q, *J* = 4.2 Hz), 122.3 (q, *J* = 272.4 Hz), 139.8 (q, *J* = 33.5 Hz), 162.8. The carbon signal bound to the boron was not observed due to quadrupolar relaxation.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ = –66.59.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 28.52.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{18}BF_3NO_3$: 304.1329; found: 304.1321.

4-Methoxy-1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one (8d)

According to GPA, purification by GPC (EtOAc) gave the product (26 mg, 0.10 mmol, 39%) as an orange solid; mp 162.2–164.2 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (s, 12 H), 3.49 (s, 3 H), 3.79 (s, 3 H), 5.86 (s, 1 H), 7.66 (s, 1 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 24.8, 36.9, 55.9, 83.7, 96.2, 147.6, 165.1, 171.2. The carbon signal bound to the boron was not observed due to quadrupolar relaxation.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 29.80.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{21}BNO_4$: 266.1561; found: 266.1565.

1,6-Dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one (10a)

According to GPA, purification by GPC (EtOAc) gave the product (40 mg, 0.16 mmol, 64%) as a white solid; mp 133.1–135.1 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (s, 12 H), 2.33 (s, 3 H), 3.52 (s, 3 H), 6.29 (s, 1 H), 6.89 (s, 1 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 20.9, 25.0, 31.3, 84.6, 109.9, 124.8, 145.2, 163.5. The carbon signal bound to the boron was not observed due to quadrupolar relaxation.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 30.13.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{21}BNO_3$: 250.1611; found: 250.1600.

6-Chloro-1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one (10b)

According to GPB, purification by GPC (EtOAc) gave the product (39 mg, 0.15 mmol, 58%) as a white solid; mp 116.2–118.2 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (s, 12 H), 3.67 (s, 3 H), 6.56 (d, *J* = 1.1 Hz, 1 H), 6.92 (d, *J* = 1.1 Hz, 1 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 24.8, 33.2, 84.8, 109.9, 125.4, 137.2, 162.9. The carbon signal bound to the boron was not observed due to quadrupolar relaxation.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 30.22.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{18}BClNO_3$: 270.1065; found: 270.1052.

Methyl 1-Methyl-6-oxo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,6-dihydropyridine-2-carboxylate (10c)

According to GPA, purification by GPC (EtOAc) gave the product (31 mg, 0.11 mmol, 43%) as a white solid; mp 109.8.1–111.8 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (s, 12 H), 3.68 (s, 3 H), 3.91 (s, 3 H), 7.02 (d, *J* = 1.3 Hz, 1 H), 7.18 (d, *J* = 1.3 Hz, 1 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 25.0, 33.7, 53.1, 85.0, 114.1, 132.4, 137.5, 162.6, 163.1. The carbon signal bound to the boron was not observed due to quadrupolar relaxation.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 30.26.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{21}BNO_5$: 294.1510; found: 294.1499.

1,3-Dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione (12) and 1,3-Dimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione (12′)

According to GPA, purification by GPC (EtOAc) gave the product (40 mg, 0.15 mmol, 60%) as an orange solid; ratio **12**/**12′** 50:50; mp 150.6–152.6 °C.

^{1}H NMR (400 MHz, $CDCl_3$): for **12** and **12′** δ = 1.32 (s, 0.50 × 12 H), 1.34 (s, 0.50 × 12 H), 3.34 (s, 0.50 × 3 H), 3.35 (s, 0.50 × 3 H), 3.42 (s, 0.50 × 3 H), 3.53 (s, 0.50 × 3 H), 6.23 (s, 0.50 × 1 H), 7.66 (s, 0.50 × 1 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): for **12** and **12′** δ = 24.7, 24.8, 27.7, 27.9, 35.5, 37.2, 83.9, 85.7, 111.0, 152.0, 152.1, 152.8, 162.7, 164.0. The carbon signal bound to the boron was not observed due to quadrupolar relaxation.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 28.80.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{20}BN_2O_4$: 267.1513; found: 267.1503.

3-Methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one (14)

According to GPA, purification by GPC (EtOAc) gave the product (22 mg, 0.10 mmol, 38%) as an orange solid; mp 216.6–218.6 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (s, 12 H), 2.14 (s, 3 H), 7.59 (s, 1 H), 7.73 (s, 1 H), 12.21 (br, 1 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 16.5, 24.9, 84.0, 128.2, 140.6, 143.1, 166.0. The carbon signal bound to the boron was not observed due to quadrupolar relaxation.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 29.55.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{19}BNO_3$: 236.1455; found: 236.1442.

***tert*-Butyl (1*R*,5*R*)-8-Oxo-10-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,5,6,8-tetrahydro-2*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocine-3(4*H*)-carboxylate (16)**

According to GPA, purification by GPC (EtOAc) gave the product (71 mg, 0.19 mmol, 77%) as a brown solid; mp 108.5–110.5 °C.

^{1}H and ^{13}C NMR spectra of compound **16** are complicated by the presence of rotamers, and all observed signals are thus described.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18 (s, 3 H), 1.32 (s, 17 H), 1.90–1.97 (m, 2.5 H), 2.42 (s, 1 H), 3.02–3.06 (m, 3 H), 3.83 (dd, *J* = 6.0, 15.6 Hz. 1 H), 4.15–4.18 (m, 3 H), 4.36–4.39 (m, 0.5 H), 6.33 (s, 1 H), 6.87 (s, 1 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 24.6, 24.8, 26.1, 27.5, 28.1, 34.6, 48.9, 49.2, 50.2, 50.6, 51.7, 67.0, 80.2, 82.2, 84.4, 108.8, 109.3, 124.4, 147.5, 147.9, 154.6, 162.9.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 30.14.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{34}BN_2O_5$: 417.2559; found: 417.2547.

Suzuki–Miyaura Cross-Coupling of 7a and 10a; General Procedure

$Pd_2(dba)_3{\cdot}CHCl_3$ (2.6 mg, 0.0025 mmol), XPhos (2.4 mg, 0.0050 mmol), and K_3PO_4 (42 mg, 0.20 mmol) were placed in a 20-mL two-necked reaction flask, which was filled with N_2 by using the standard Schlenk technique. 1,4-Dioxane (0.20 mL) was injected via a syringe, and the mixture was stirred for 5 min at r.t. A solution of **7a** or **10a** (0.10 mmol) in 1,4-dioxane (1.0 mL), bromobenzene (10 μL, 0.10 mmol), and water (0.30 mL) were sequentially added, and the mixture was stirred for 4 h at 110 °C. The resulting mixture was allowed to cool to r.t. and then quenched with water. The mixture was extracted with EtOAc (3 ×). The combined organic layers were dried (anhyd Na_2SO_4). After concentration under reduced pressure, column purification (silica gel, CH_2Cl_2/EtOAc/Et_3N 1:1:0.02) afforded **7a-Ph** or **10a-Ph**.

1,3-Dimethyl-5-phenylpyridin-2(1*H*)-one (7a-Ph)

Purification by column chromatography (R_f = 0.33) gave the product (17 mg, 0.087 mmol, 87%) as a pale yellow solid; mp 159.2–161.2 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.23 (d, *J* = 1.0 Hz, 3 H), 3.63 (s, 3 H), 7.29–7.35 (m, 1 H), 7.39 (d, *J* = 2.6 Hz, 1 H), 7.40–7.42 (m, 4 H), 7.52 (dd, *J* = 1.0, 2.6 Hz, 1 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 17.6, 38.2, 119.8, 126.0, 127.3, 129.1, 129.8, 133.1, 136.8, 137.0, 162.9.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}NO$: 200.1070; found: 200.1063.

1,6-Dimethyl-4-phenylpyridin-2(1*H*)-one (10a-Ph)

Purification by column chromatography (R_f = 0.20) gave the product (19 mg, 0.095 mmol, 95%) as a white solid; mp 103.6–105.6 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.42 (d, *J* = 1.0 Hz, 3 H), 3.58 (s, 3 H), 6.33 (dd, *J* = 1.0, 1.9 Hz, 1 H), 6.70 (d, *J* = 1.9 Hz, 1 H), 7.41–7.47 (m, 3 H), 7.55–7.58 (m, 2 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 21.4, 31.2, 106.2, 114.0, 126.8, 129.0, 129.4, 138.0, 146.2, 150.9, 164.2.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}NO$: 200.1070; found: 200.1089.

1,4-Dimethyl-6-phenylpyridin-2(1*H*)-one (8a-Ph) and 1,4-Dimethyl-5-phenylpyridin-2(1*H*)-one (8a′-Ph) by Suzuki–Miyaura Cross-Coupling of 8a

In a glovebox filled with N_2, $Pd_2(dba)_3$ (4.6 mg, 0.0050 mmol), P(*t*-Bu)$_3$ (4.0 mg, 0.020 mmol), and KOH (17 mg, 0.30 mmol) were placed in a 20-mL two-necked reaction flask and dissolved in THF (0.50 mL). The reaction flask was sealed with a septum and then taken out of the glovebox. The mixture was stirred for 5 min at r.t. A solution of **8a**/**8a′** (93:7; 25 mg, 0.10 mmol) in THF (1.0 mL), iodobenzene (12 µL, 0.11 mmol), and water (0.15 mL) were sequentially added, and the mixture was stirred for 12 h at r.t. The resulting mixture was quenched with sat. aq NH_4Cl and extracted with EtOAc (3 ×). The combined organic layers were dried (anhyd Na_2SO_4). After concentration under reduced pressure, column purification (silica gel, CH_2Cl_2/EtOAc/Et_3N 1:1:0.02) followed by GPC ($CHCl_3$) afforded a mixture of 1,4-dimethyl-6-phenylpyridin-2(1*H*)-one (**8a-Ph**) and 1,4-dimethyl-5-phenylpyridin-2(1*H*)-one (**8a′-Ph**) (11 mg, 0.055 mmol, 55%) as a yellow oil; ratio **8a-Ph**/**8a′-Ph** 92:8.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.09 (s, 0.080 × 3 H for **8a′-Ph**), 2.19 (d, *J* = 1.0 Hz, 0.92 × 3 H for **8a-Ph**), 3.34 (s, 0.92 × 3 H for **8a-Ph**), 3.56 (s, 0.080 × 3 H for **8a′-Ph**), 5.96 (d, *J* = 2.0 Hz, 0.92 × 1 H for **8a-Ph**), 6.41 (dd, *J* = 1.0, 2.0 Hz, 0.92 × 1 H for **8a-Ph**), 6.49 (s, 0.080 × 1 H for **8a′-Ph**), 7.13 (s, 0.080 × 1 H for **8a′-Ph**), 7.22–7.24 (m, 0.080 × 3 H for **8a′-Ph**), 7.32–7.34 (m, 0.92 × 2 H for **8a-Ph**), 7.39–7.40 (m, 0.080 × 2 H for **8a′-Ph**), 7.45–7.47 (m, 0.92 × 3 H for **8a-Ph**).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): for **8a-Ph** δ = 21.3, 34.1, 110.5, 117.6, 128.5, 128.8, 129.3, 135.8, 149.0, 150.1, 163.9.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}NO$: 200.1070; found: 200.1074.

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Supporting Information

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