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PYRIDINE-DIRECTED Rh-CATALYZED C6-SELECTIVE C–H ACETOXYLATION OF 2-PYRIDONES

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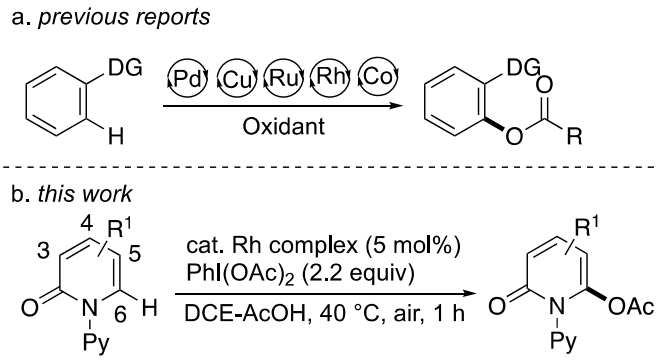
Abstract – A Rh(III)-catalyzed C-H acetoxylation of 2-pyridones with phenyliodine(III) diacetate (PIDA) in a DCE/AcOH mixed solvent system has been developed using *N*-2-pyridyl function as directing group. The reaction occurs under mild conditions, typically in air at 40 ºC, to selectively produce the corresponding C6-acetoxylated 2-pyridones in moderate to good yields.

INTRODUCTION

Transition-metal-catalyzed direct C–O bond formation by means of C–H bond activation strategy[1] has emerged as a useful method to make oxygen-bearing compounds in organic synthesis over the past one and a half decade. In particular, the wide occurrence of acetoxy group[2] in natural products, pharmaceutical agents, and agrochemicals as well as its role as a useful synthetic handle has stimulated synthetic chemists to develop efficient protocols for the direct acetoxylation of C–H bonds. In 2004, Sanford reported the palladium-catalyzed selective acetoxylation of arene and benzylic C–H bonds.[3] Subsequently, Sanford[4a] and Yu[4b] developed palladium-catalyzed acetoxylation methods for unactivated sp^3 C-H bonds. After these reports, palladium[5] and other transition metals such as copper,[6] ruthenium,[7] rhodium,[8] and cobalt[9] catalysts have been employed for the acetoxylation/acyloxylation of C–H bonds (Scheme 1a). The substantial importance of pyridone derivatives[10] in pharmaceutical and medicinal chemistry and our ongoing research[11] on the site-selective functionalization of 2-pyridones prompted us to develop a suitable method for the regioselective acetoxylation of pyridone derivatives. In our blueprint, the pyridyl group in *N*-(2-pyridyl)-2-pyridones would direct a transition metal catalyst to activate the C–H bond at the C6 position, thereby facilitating the C6-selective acetoxylation of the pyridone substrates under appropriate reaction conditions. Herein, we report a pyridine-directed, Rh(III)-catalyzed C6-selective acetoxylation of 2-pyridones using phenyliodine(III) diacetate (PIDA) (Scheme 1b).

The paper is dedicated to Prof. Kaoru Fuji on the occasion of his 80th birthday.



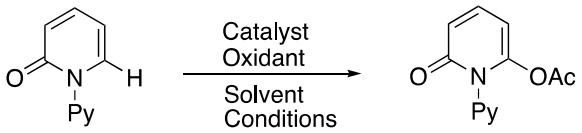
Scheme 1. Directing group-assisted transition-metal-catalyzed acyloxylation via C-H bond activation. DG = directing group, Py = 2-pyridyl.

RESULTS AND DISCUSSION

We initially attempted the direct acetoxylation of *N*-(2-pyridyl)-2-pyridone (**1a**) using $[Cp^*RhCl_2]_2$ (5 mol% Rh), PIDA (1.1 equiv), and DCE as catalyst, oxidant, and solvent, respectively at 80 °C for 16 h under air, but no acetoxylated product was obtained even with $AgSbF_6$ as additive (Table 1, Entry 1). On the other hand, the reaction proceeded selectively at the C6 position of **1a** in the presence of a cationic rhodium complex $[Cp^*Rh(MeCN)_3][SbF_6]_2$ in place of the neutral complex $[Cp^*RhCl_2]_2$ to give the expected product **2a**, albeit in 8% isolated yield (Entry 2). We then varied the reaction conditions using the $[Cp^*Rh(MeCN)_3][SbF_6]_2$ catalyst. Screening of solvents revealed that DCE was the best among the examined solvents (Entries 2-5). Increasing the amount of PIDA to 2.2 equiv resulted in the full consumption of **1a** to give **2a** in 22% NMR yield (Entry 6). Lowering the reaction temperature to 40 °C as well as shortening the reaction time to 6 h increased the yield of **2a** further to 39% (Entry 7). It was conceived that the reason why the product yield was still low might be due to the decomposition of both the starting material and product in the presence of the relatively strong oxidant PIDA. However, screening of oxidants suggested that the use of PIDA was crucial for the reaction; other oxidants such as $K_2S_2O_8$/AcOH, $Cu(OAc)_2 \cdot H_2O$, AgOAc, and $Mn(OAc)_3 \cdot 2H_2O$ were unsuccessful (Entries 8-11). We then tried in situ generation of PIDA in the reaction system. The use of PhI[12] in the presence of *m*-CPBA to generate PIDA in the reaction medium and the subsequent attempt of acetoxylation remained unsuccessful (Entry 12). Use of PhIO[13] for in situ generation of PIDA was also found to be inferior (Entry 13). Subsequently, we investigated other reaction parameters to improve the reaction efficiency. Increasing the concentration to 0.2 M slightly improved the product yield to 42% (entry 14). Further shortening the reaction time to 1 h decreased the yield to 22% (entry 15). To our delight, when we added 0.1 mL of AcOH as additive, the product **2a** was obtained in 87% yield within 1 h (Entry 16). When the same reaction was carried out under N_2, the yield was somewhat decreased (Entry 17). No acetoxylation

reaction took place without the Rh catalyst (Entry 18) or PIDA (Entry 19). Based on these results, we chose the reaction conditions in Entry 16 of Table 1 for further experiments.

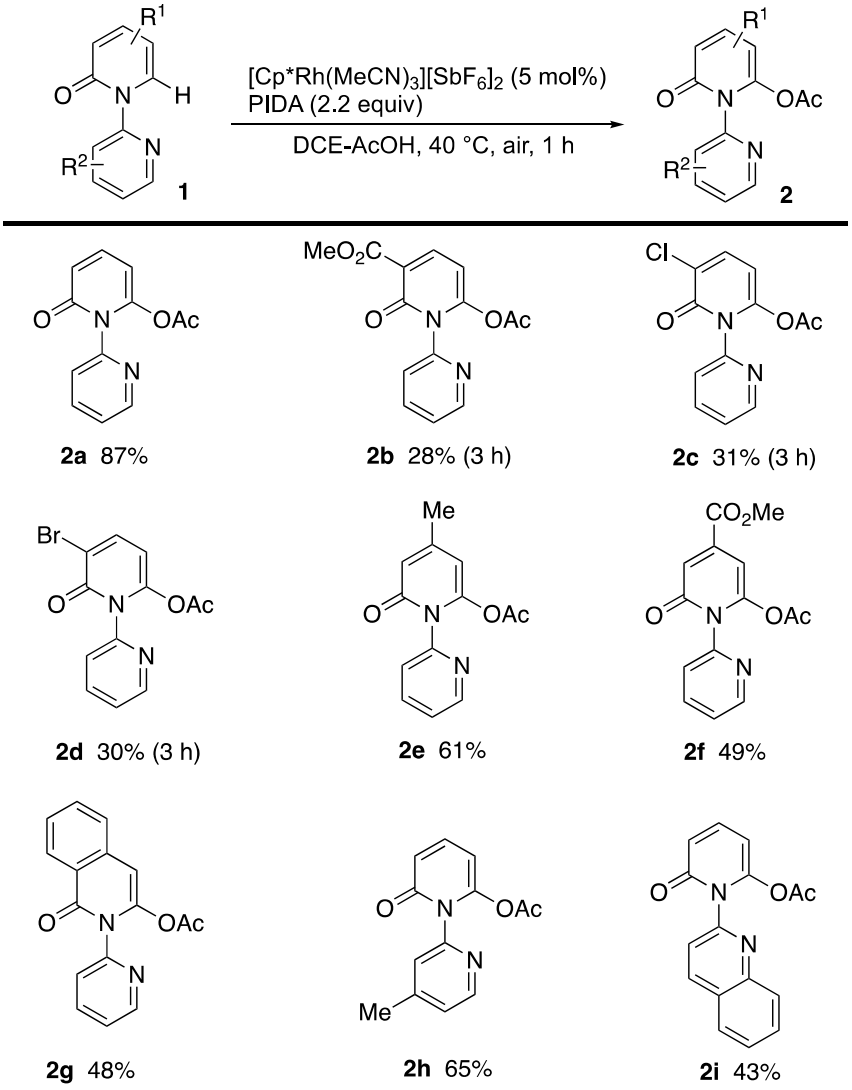
Table 1. Optimization studies for Rh-catalyzed C6-selective acetoxylation of *N*-pyridyl-2-pyridone (**1a**)



1a **2a**

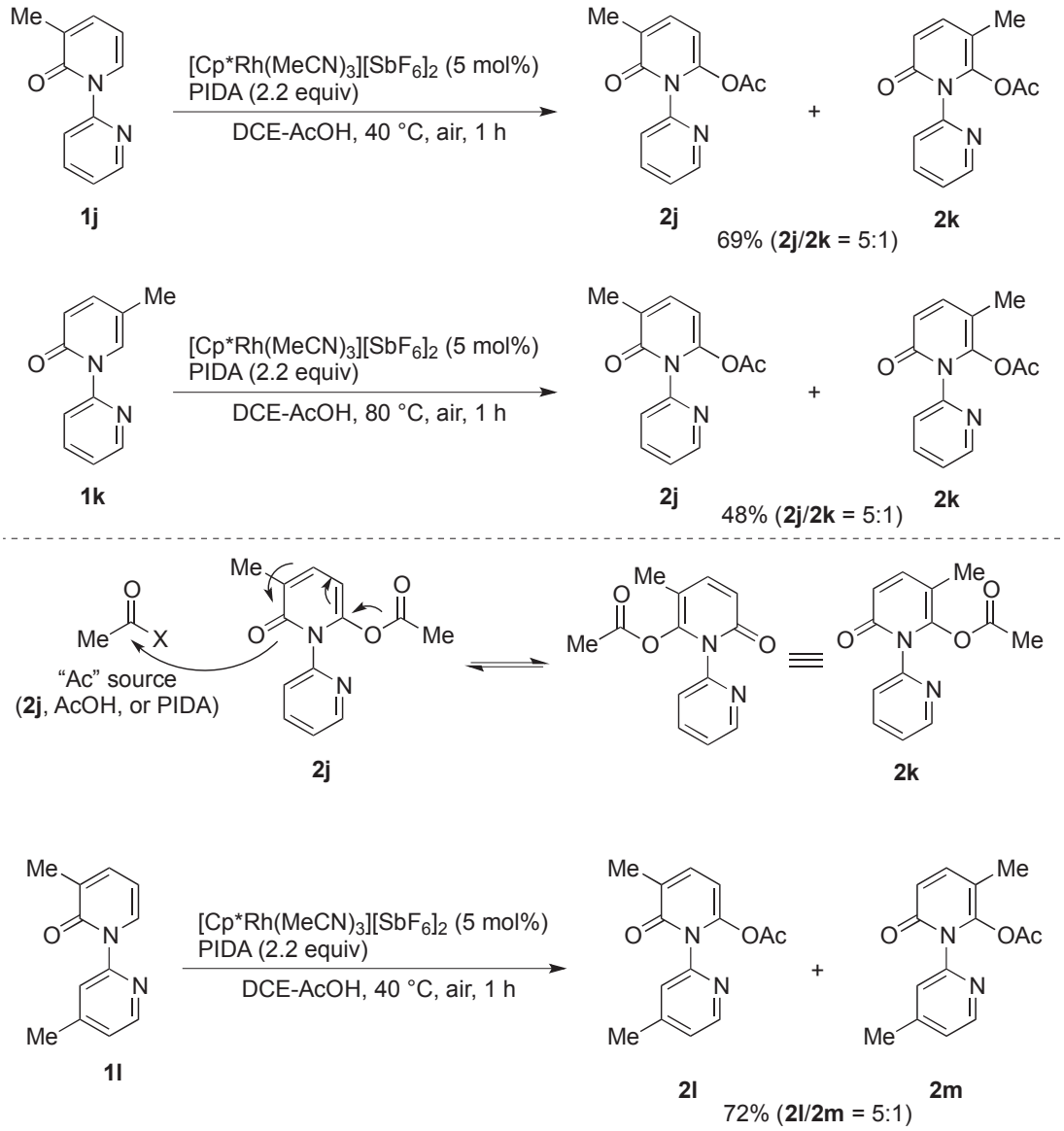
Entry	Catalyst	Oxidant (equiv)	Solvent (mL)	Yield[j] (%)
1[a,b]	$[Cp^*RhCl_2]_2$	PIDA (1.2)	DCE (1.0)	0
2[b]	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	PIDA (1.2)	DCE (1.0)	(8)
3[b]	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	PIDA (1.2)	MeCN (1.0)	0
4[b]	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	PIDA (1.2)	1,4-dioxane (1.0)	0
5[b]	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	PIDA (1.2)	toluene (1.0)	0
6[b]	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	PIDA (2.2)	DCE (1.0)	22
7[c]	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	PIDA (2.2)	DCE (1.0)	39
8[b, d]	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	$K_2S_2O_8$ (2.0)	DCE (1.0)	0
9[b]	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	$Cu(OAc)_2 \cdot H_2O$ (2.0)	DCE (1.0)	0
10[b]	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	AgOAc (2.0)	DCE (1.0)	0
11[b]	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	$Mn(OAc)_3 \cdot 2H_2O$ (2.0)	DCE (1.0)	0
12[e]	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	*m*-CPBA (2.0)	AcOH (1.0)	0
13[f]	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	PhIO (2.0)	DCE (1.0)	16
14[c]	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	PIDA (2.2)	DCE (0.5)	42
15[g]	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	PIDA (2.2)	DCE (0.5)	22
16[h]	**$[Cp^*Rh(MeCN)_3][SbF_6]_2$**	**PIDA (2.2)**	**DCE (0.5)**	**(87)**
17[h, i]	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	PIDA (2.2)	DCE (0.5)	80
18[g]	-	PIDA (2.2)	DCE (0.5)	0
19[g]	$[Cp^*Rh(MeCN)_3][SbF_6]_2$	-	DCE (0.5)	0

Reactions were carried out using 0.1 mmol of **1a**, Rh-catalyst (5 mol%), oxidant, and solvent, under air (unless otherwise noted) at specified temperature and time. [a] 10 mol% of $AgSbF_6$ was added as additive. [b] Reaction at 80 °C for 16 h. [c] Reaction at 40 °C for 6 h. [d] Reaction in the presence of 0.5 mL of AcOH. [e] Reaction in the presence of 2.0 equiv PhI at 60 °C for 24 h. [f] Reaction in the presence of 20 equiv of Ac_2O at 40 °C for 6 h. [g] Reaction at 40 °C for 1 h. [h] Reaction at 40 °C for 1 h in the presence of 0.1 mL of AcOH. [i] Reaction under N_2. [j] Yield was determined by ^1H NMR of each crude reaction mixture using CH_2Br_2 as internal standard. Isolated yields are given in parentheses.



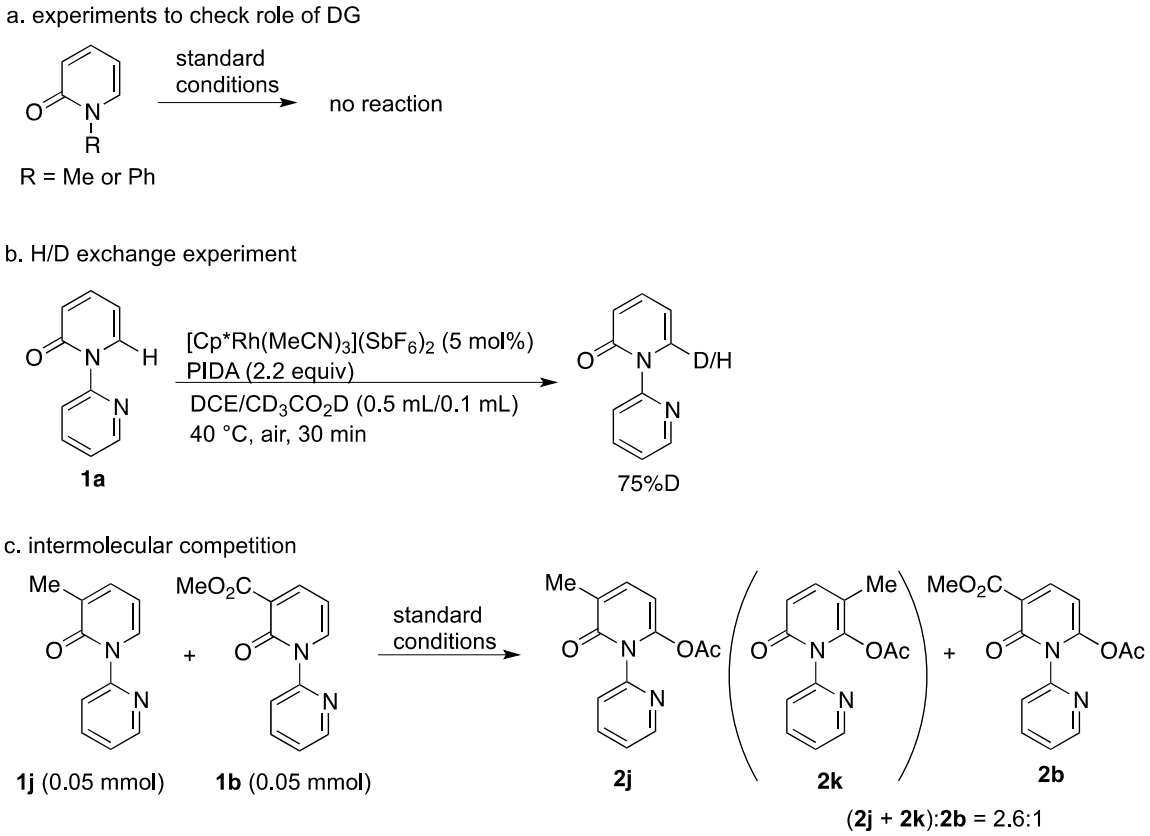
Scheme 2. Rh-Catalyzed C6-selective acetoxylation of *N*-(2-pyridyl)-2-pyridones **1**. Isolated yields are given.

Having the optimized reaction conditions, we then examined the generality and limitations of the present acetoxylation of 2-pyridones **1** (Scheme 2). Substrates containing an electron-withdrawing group such as ester (CO_2Me) and halogen (Cl, Br) at the C3 position were found to be less reactive; the reactions of these substrates were carried out for a longer time of 3 h, and the corresponding C6-acetoxylated products **2b–2d** were obtained selectively albeit with lower yields. The reaction protocol was also applicable to substrates containing an electron-donating (Me) or electron-withdrawing (CO_2Me) substituent at the C4 position (**2e**, **2f**). Additionally, an isoquinolone substrate underwent the acetoxylation under the standard conditions to give the corresponding product **2g** in a moderate yield. The substituent effect on the pyridyl directing group was also tested: the 4-methylpyridyl group also directed the C6-selective acetoxylation reaction, giving the products **2h** in 65% isolated yield. The 2-quinolinyl directing group also worked, and thus, the acetoxylated product **2i** was obtained in 43% yield.



Scheme 3. Reactions of C3- or C5-methylated substrates

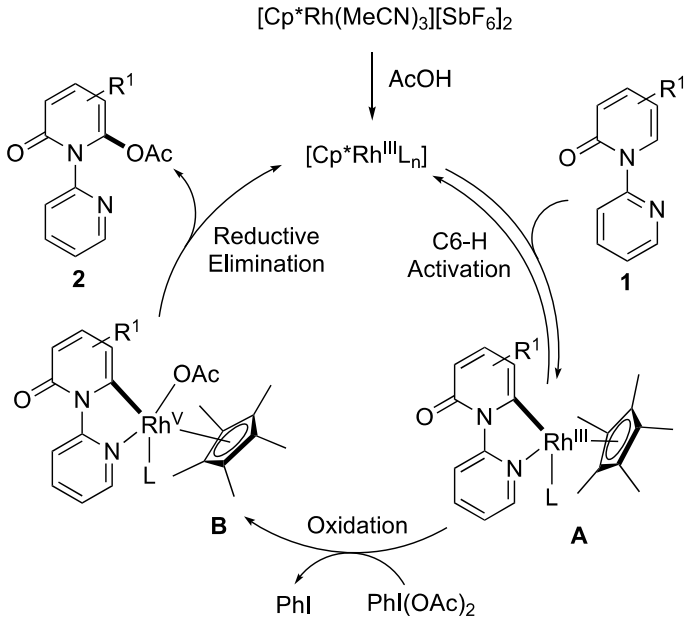
Somewhat unique phenomena were observed in the reactions of C3- or C5-methylated substrates (Scheme 3). Under identical conditions, the C3-methylated **1j** was converted to a 5:1 mixture of the expected product **2j** and unexpected C5-methylayed C6-acetoxylated product **2k** in 69% total yield. Similarly, the reaction of C5-methylated **1k** gave **2j** as well as **2k** in the same 5:1 ratio of **2j** and **2k**. The outcomes suggest the equilibrium between **2j** and **2k** via an Ac transfer under the standard reaction conditions. The same result was also obtained from the C3-methylated **1l** that bears the 4-methylpyridyl directing group. Thus, the Ac transfer process is general for the C3- and C5-methylated pyridones and regardless of the nature of directing group.



Scheme 4. Control experiments

We then performed a series of control experiments to gain some insight into the reaction mechanism (Scheme 4). When the reaction was carried out with *N*-methyl-2-pyridone or *N*-phenyl-2-pyridone, no acetoxylation occurred, which confirmed that the presence of pyridyl directing group is essential for the acetoxylation reaction (Scheme 4a). The hydrogen-deuterium (H/D) scrambling experiment (Scheme 4b) with **1a** in the presence of CD_3CO_2D resulted in H/D exchange at the C6 position of recovered substrate (75% D), which implies that the C–H activation step is facile and reversible. The electronic preference in the substrate was next examined through an intermolecular competition experiment using an equimolar mixture of **1j** and **1b**. The result suggested that the electron-rich substrate **1j** reacted at a higher rate (Scheme 4c).

Based on the control experiments performed and previous literature reports,[8b,8c] a plausible mechanism for the present reaction is illustrated in Scheme 5. First, the $[Cp^*Rh(MeCN)_3][SbF_6]_2$ precatalyst is converted with AcOH to the active $[Cp^*RhL_n]$, where one of L_n is OAc. The pyridone substrate **1** then undergoes the reversible C6–H bond cleavage with the cationic $[Cp^*RhL_n]$ species to produce a rhodacycle intermediate **A**.[14] Subsequent oxidation of **A** with PIDA generates a rhodium(V) intermediate **B** and final reductive elimination in **B** leads to the product **2** and regenerates the starting Rh(III) catalytic species.



Scheme 5. Plausible mechanism of acetoxylation of **1**. L = SbF_6 or OAc.

CONCLUSION

In summary, we have demonstrated a catalytic method for the C6-selective acetoxylation through pyridine-directed C-H bond cleavage of 2-pyridones under rhodium catalysis using PIDA as oxidizing agent. The method is operationally simple, performed under air, and allows the synthesis of various C6-acetoxylated 2-pyridones in moderate to good yields under mild reaction conditions. Thus, the present method appears to be useful for synthesizing the oxygenated pyridones, which are of interest in pharmaceutical and medicinal chemistry.[15] Further development of related direct C-O bond formation reactions is currently underway in our group.

EXPERIMENTAL

General. Nuclear magnetic resonance spectra were measured at 400 MHz (^{1}H NMR) and at 100 MHz (^{13}C NMR). All ^{1}H NMR chemical shifts were reported in ppm relative to the resonance in TMS at δ 0.00. All ^{13}C NMR chemical shifts were reported in ppm relative to carbon resonance in chloroform-d_1 at δ 77.16. High resolution mass spectra (HRMS) were measured by APCI-TOF. Gel permeation chromatography (GPC) was performed by LC-20AR (pump, SHIMADZU, 7.5 mL/min) and SPD-20A (UV detector, SHIMADZU, 254 nm) with two in-line YMC-GPC T2000 (20 x 600 mm, particle size: 10 μm) (preparative columns, YMC, $CHCl_3$ eluent). All starting materials were prepared according to the previous literature report.[11c] $[Cp^*Rh(MeCN)_3][SbF_6]_2$ was prepared according to the literature procedure.[16] All other reagents were purchased from commercial resources.

Rh-Catalyzed C6-selective acetoxylation of *N*-(2-pyridyl)-2-pyridones 1. The reaction of **1a** is representative (Table 1, entry 16): *N*-(2-pyridyl)-2-pyridone (**1a**, 17.2 mg, 0.1 mmol), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (4.1 mg, 0.005 mmol), and PIDA (71.0 mg, 0.22 mmol) were placed in a 20 mL screw vial. DCE (0.5 mL) and AcOH (0.1 mL) were added via syringe. The vial was closed under air, and the resulting mixture was stirred at 40 °C for 1 h. After cooling to room temperature, the solvent was evaporated at room temperature, and the residue was diluted with EtOAc (10 mL) and filtered through a short silica gel column neutralized with 5% Et_3N in EtOAc, using EtOAc/$CHCl_3$/Et_3N eluent (1/1/0.05, v/v/v, 3 x 25 mL). The combined organic layers were evaporated, and the residue was subjected to silica gel column chromatography using EtOAc/Hexane = 1/5 to EtOAc/$CHCl_3$/Et_3N = 1/1/0.05 (v/v/v) followed by GPC ($CHCl_3$) purification to afford **2a** (20 mg, 87% yield) as a light green liquid. Note: Yields varied if the reaction mixture was not purified within 30 min after quenching the reaction, but the isolated product was stable.

Characterization Data for Products

2-Oxo-2*H*-[1,2'-bipyridin]-6-yl acetate (**2a**)**:** Light green liquid, 20 mg (87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.87 (s, 3H), 6.05 (dd, J = 1.0, 4.2 Hz, 1H), 6.56 (dd, J = 1.0, 5.2 Hz, 1H), 7.35-7.46 (m, 3H), 7.89 (td, J = 1.9, 7.8 Hz, 1H), 8.64-8.66 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 97.5, 118.8, 124.0, 124.3, 138.6, 140.3, 147.4, 149.2, 149.8, 162.8, 166.8. HRMS (APCI) *m/z* ($[M+H]^+$) calcd for $C_{12}H_{11}N_2O_3$: 231.0764, found: 231.0753.

Methyl 6-acetoxy-2-oxo-2*H*-[1,2'-bipyridine]-3-carboxylate (**2b**)**:** Reaction carried out for 3 h. Colorless liquid, 8.1 mg (28%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01 (s, 3H), 3.82 (s, 3H), 6.56 (d, J = 9.8, 1H), 7.31-7.33 (m, 1H), 7.43-7.47 (m, 1H), 7.91 (dd, J = 1.9, 4.84 Hz, 1H), 8.02 (d, J = 9.8 Hz, 1H), 8.66-8.68 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 52.3, 100.8, 118.0, 123.5, 124.8, 138.9, 140.5, 148.6, 150.2, 152.0, 162.4, 163.1, one carbon peak overlapped with another. HRMS (APCI) *m/z* ($[M+H]^+$) calcd for $C_{14}H_{13}N_2O_5$: 289.0819, found: 289.0835.

3-Chloro-2-oxo-2*H*-[1,2'-bipyridin]-6-yl acetate (**2c**)**:** Reaction carried out for 3 h. Colorless liquid, 8.3 mg (31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.88 (s, 3H), 6.05 (d, J = 8.0 Hz, 1H), 7.36-7.38 (m, 1H), 7.42-7.45 (m, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.90 (td, J = 1.9, 8.7 Hz, 1H), 8.63-8.65 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 97.2, 123.9, 124.1, 124.7, 137.9, 138.7, 146.1, 149.0, 149.9, 158.7, 166.6. HRMS (APCI) *m/z* ($[M+H]^+$) calcd for $C_{12}H_{10}ClN_2O_3$: 265.0374, found:265.0353.

3-Bromo-2-oxo-2*H*-[1,2'-bipyridin]-6-yl acetate (**2d**)**:** Reaction carried out for 3 h. Colorless liquid, 9.3 mg (30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.88 (s, 3H), 6.02 (d, J = 8.0 Hz, 1H), 7.35-7.38 (m, 1H), 7.41-7.44 (m, 1H), 7.85 (d, J = 7.9 Hz, 1H), 7.90 (td, J = 1.9, 8.7 Hz, 1H), 8.63-8.65 (m, 1H). ^{13}C NMR

(100 MHz, $CDCl_3$) δ 20.2, 97.9, 113.6, 123.9, 124.6, 138.7, 141.8, 147.0, 149.1, 149.8, 158.8, 166.5. HRMS (APCI) *m/z* ($[M+H]^+$) calcd for $C_{12}H_{10}BrN_2O_3$: 308.9869, found: 308.9856.

4-Methyl-2-oxo-2*H*-[1,2'-bipyridin]-6-yl acetate (2e): Colorless liquid, 15 mg (61%). ^1H NMR (400 MHz, $CDCl_3$) δ 1.86 (s, 3H), 2.25 (s, 3H), 5.90 (d, J = 1.6 Hz, 1H), 6.36-6.37 (m, 1H), 7.34-7.40 (m, 2H), 7.87 (td, J = 1.9, 8.7 Hz, 1H), 8.62-8.64 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 22.0, 100.1, 117.1, 124.17, 124.18, 138.5, 146.4, 149.3, 149.7, 152.3, 162.6, 166.9. HRMS (APCI) *m/z* ($[M+H]^+$) calcd for $C_{13}H_{13}N_2O_3$:245.0921, found: 245.0902.

Methyl 6-acetoxy-2-oxo-2*H*-[1,2'-bipyridine]-4-carboxylate (2f): Colorless liquid, 14.1 mg (49%). ^1H NMR (400 MHz, $CDCl_3$) δ 1.90 (s, 3H), 3.94 (s, 3H), 6.54 (d, J = 1.6 Hz, 1H), 7.22 (d, J = 1.6 Hz, 1H), 7.35-7.37 (m, 1H), 7.41-7.45 (m, 1H), 7.90 (dd, J = 1.9, 8.7 Hz, 1H), 8.65-8.67 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 53.2, 96.5, 121.0, 123.9, 124.6, 138.7, 141.4, 147.7, 148.8, 150.0, 162.5, 164.6, 166.6. HRMS (APCI) *m/z* ($[M+H]^+$) calcd for $C_{14}H_{13}N_2O_5$: 289.0819, found: 289.0806.

1-Oxo-2-(pyridin-2-yl)-1,2-dihydroisoquinolin-3-yl acetate (2g): Colorless liquid, 13.5 mg (48%). ^1H NMR (400 MHz, $CDCl_3$) δ 1.89 (s, 3H), 6.39 (s, 1H), 7.40-7.44 (m, 2H), 7.46-7.50 (m, 1H), 7.53 (d, J = 7.9 Hz, 1H), 7.66-7.70 (m, 1H), 7.90 (td, J = 2.0, 7.9 Hz, 1H), 8.38-8.40 (m, 1H), 8.66-8.68 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 97.3, 124.1, 124.5, 124.8, 126.4, 126.8, 128.5, 133.4, 136.4, 138.5, 142.4, 149.7, 149.8, 162.8, 167.5. HRMS (APCI) *m/z* ($[M+H]^+$) calcd for $C_{16}H_{13}N_2O_3$: 281.0921, found: 281.0940.

4'-Methyl-2-oxo-2*H*-[1,2'-bipyridin]-6-yl acetate (2h): Light yellow liquid, 16 mg (65%). ^1H NMR (400 MHz, $CDCl_3$) δ 1.89 (s, 3H), 2.44 (s, 3H), 6.05 (dd, J = 1.0, 4.8 Hz, 1H), 6.56 (dd, J = 1.0, 5.2 Hz, 1H), 7.18 (m, 1H), 7.21-7.23 (m, 1H), 7.42-7.46 (m, 1H), 8.49 (d, J = 5.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 21.2, 97.6, 118.7, 124.5, 125.4, 140.2, 147.4, 149.2, 149.4, 150.3, 162.9, 166.8. HRMS (APCI) *m/z* ($[M+H]^+$) calcd for $C_{13}H_{13}N_2O_3$:245.0921, found: 245.0906.

6-Oxo-1-(quinolin-2-yl)-1,6-dihydropyridin-2-yl acetate (2i): Colorless liquid, 12 mg (43%). ^1H NMR (400 MHz, $CDCl_3$) δ 1.78 (s, 3H), 6.11 (dd, J = 1.0, 4.2 Hz, 1H), 6.60 (dd, J = 1.1, 5.2 Hz, 1H), 7.45-7.51 (m, 2H), 7.63-7.67 (m, 1H), 7.75-7.80 (m, 1H), 7.92 (dd, J = 1.1, 4.6 Hz, 1H), 8.10 (d, J = 8.3 Hz, 1H), 8.33 (d, J = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 97.9, 118.9, 121.2, 127.8, 127.9, 129.4, 130.4, 138.8, 140.4, 147.3, 147.5, 148.6, 163.1, 166.9, one carbon peak overlapped with another. HRMS (APCI) *m/z* ($[M+H]^+$) calcd for $C_{16}H_{13}N_2O_3$:281.0921, found: 281.0933.

A 5:1 mixture of 3-methyl-2-oxo-2*H*-[1,2'-bipyridin]-6-yl acetate (2j) and 5-methyl-2-oxo-2*H*-[1,2'-bipyridin]-6-yl acetate (2k): Light red liquid, 16.9 mg (69%) from **1j** or 11.8 mg (48%) from **1k**. Obtained as (5:1) mixture of two isomers. ^1H NMR (400 MHz, $CDCl_3$) δ 1.87 (d, J = 1.6 Hz, 3H), 1.96 (s, 0.5H), 2.15 (d, J = 1.1 Hz, 2.5H), 5.98 (d, J = 7.4 Hz, 0.83H), 6.56 (d, J = 9.4 Hz, 0.17H), 7.29-7.42 (m, 3H), 7.86-7.90 (m, 1H), 8.64-8.65 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9,

16.9, 19.8, 20.2, 97.0, 105.4, 119.1, 124.0, 124.17, 124.23, 127.9, 137.0, 138.5, 138.6, 143.8, 145.0, 149.65, 149.76, 149.83, 162.3, 163.0, 166.4, 167.2, three carbon peaks were overlapped with other peaks. HRMS (APCI) *m/z* ($[M+H]^+$) calcd for $C_{13}H_{13}N_2O_3$: 245.0921, found: 245.0911.

A 5:1 mixture of 3,4'-dimethyl-2-oxo-2*H*-[1,2'-bipyridin]-6-yl acetate (2l) and 4',5-dimethyl-2-oxo-2*H*-[1,2'-bipyridin]-6-yl acetate (2m): Light yellow liquid, 18.6 mg (72%). Obtained as a (5:1) mixture of two isomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.86 (s, 3H), 1.94 (s, 0.5H), 2.13 (d, J = 1.1 Hz, 2.5H), 2.41 (s, 3 H), 5.96 (d, J = 7.4 Hz, 0.83H), 6.53 (d, J = 9.4 Hz, 0.17H), 7.14-7.16 (m, 1.2H), 7.18-7.20 (m, 1.2H), 7.28-7.33 (m, 1.2H), 8.46-8.48 (m, 1.2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ .13.9, 16.8, 19.8, 20.2, 21.06, 21.11, 97.0, 105.3, 119.0, 124.48, 124.52, 125.2, 125.3, 127.7, 136.9, 143.7, 143.9, 145.1, 149.3, 149.4, 149.6, 150.1, 150.3, 162.3, 163.0, 166.4, 167.2, one carbon peak overlapped with another. HRMS (APCI) *m/z* ($[M+H]^+$) calcd for $C_{14}H_{15}N_2O_3$:259.1077, found: 259.1068.

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