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Regioselective *ortho*-hydroxylation of aryl moiety of 2-arylpyridines using $Pd(OAc)_2$/Oxone in PEG-3400/*tert*-BuOH

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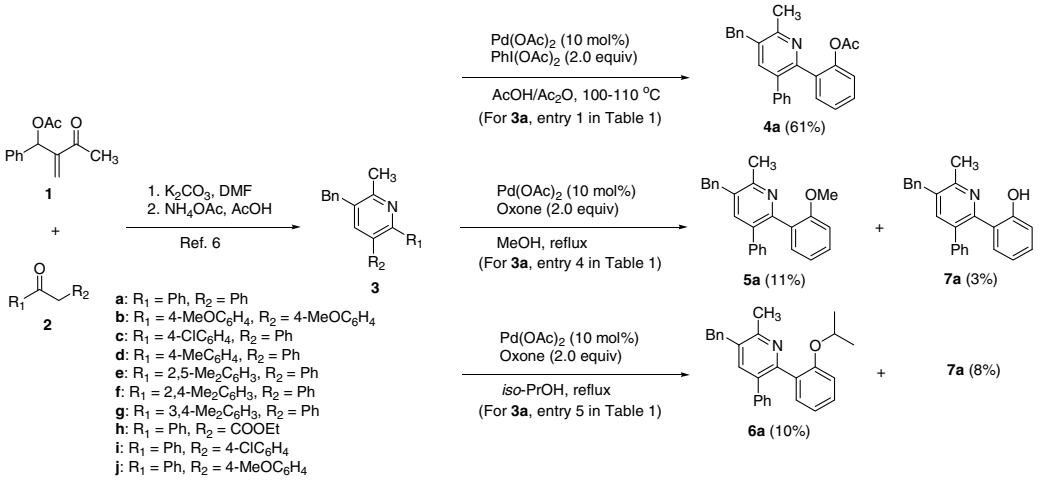
ABSTRACT

Regioselective *ortho*-hydroxylation of aryl moiety of 2-arylpyridines was carried out under the influence of $Pd(OAc)_2$/Oxone (potassium peroxymonosulfate) in PEG-3400/*t*-BuOH in moderate yields.

Recently, palladium-mediated C–H bond activations of 2-arylpyridines and related systems are regarded as one of the hot topics.[1–4] Introductions of various functional groups have been reported, including alkyls,[1] aryls,[2] halogens[3] and acetoxy group.[4] Although many types of functionalizations have been reported, direct hydroxylation is unprecedented to the best of our knowledge.[1–5]

Very recently we reported an efficient synthetic method of poly-substituted pyridines from Baylis-Hillman adducts via the [3+2+1] annulation protocol.[6] Further functionalization of the



Scheme 1.

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Table 1
Optimization for the synthesis of **7a**

Entry	Conditions	Products (%)				**3a** (%)
		4a	**5a**	**6a**	**7a**	
1	$Pd(OAc)_2$ (10 mol %), $PhI(OAc)_2$ (2.0 equiv), AcOH, Ac_2O, 100–110 °C, 1 h	61	nd	nd	nd	nd
2	$Pd(OAc)_2$ (10 mol %), Oxone (2.0 equiv), AcOH, Ac_2O, 100–110 °C, 3 h	44	nd	nd	nd	nd
3	$Pd(OAc)_2$ (10 mol %), $PhI(OAc)_2$ (2.0 equiv), *t*-BuOH, reflux, 10 h	45	nd	nd	3	nd
4	$Pd(OAc)_2$ (10 mol %), Oxone (2.0 equiv), MeOH, reflux, 2 h	nd	11	nd	3	60
5	$Pd(OAc)_2$ (10 mol %), Oxone (2.0 equiv), iso-PrOH, reflux, 2 h	nd	nd	10	8	53
6	$Pd(OAc)_2$ (10 mol %), Oxone (2.0 equiv), *t*-BuOH, reflux, 4 h	nd	nd	nd	64	nd
7	$Pd(OAc)_2$ (10 mol %), Oxone (2.0 equiv), *t*-amyl alcohol, 80–90 °C, 2 h	nd	nd	nd	47	nd
8	$Pd(OAc)_2$ (10 mol %), Oxone (5.0 equiv), PEG-3400/*t*-BuOH, 80–90 °C, 2 h	nd	nd	nd	76	nd
9	$Pd(OAc)_2$ (10 mol %), Oxone (2.0 equiv), CH_3CN, reflux, 8 h	nd	nd	nd	nd	20
10	$Pd(OAc)_2$ (10 mol %), $K_2S_2O_8$ (2.0 equiv), *t*-BuOH, reflux, 16 h	nd	nd	nd	11	23

pyridines would provide valuable pyridine derivatives, which could be used for many purposes.[7–9] In this respect, we decided to examine the feasibility for the regioselective introduction of acetoxy or alkoxy group at the *ortho*-position of 2-aryl moiety (vide infra, Scheme 1).

Starting material **3a** was prepared as reported in good yield.[6] With this compound **3a**, we examined acetoxylation as the first trial under the reported conditions which comprised $Pd(OAc)_2$/$PhI(OAc)_2$/AcOH/Ac_2O at 100–110 °C.[4] Compound **4a** was synthesized in 61% yield in 1 h (Scheme 1, entry 1 in Table 1). The use of Oxone (potassium peroxymonosulfate) or the reaction in *tert*-BuOH resulted in lower yield of product **4a** (entries 2 and 3).

Table 2
Synthesis of *ortho*-hydroxyaryl pyridines **7a–j**

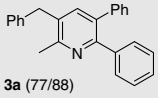
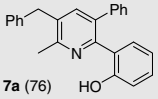
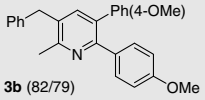
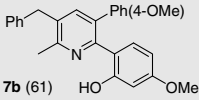
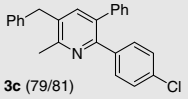
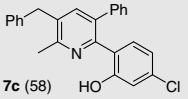
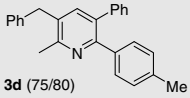
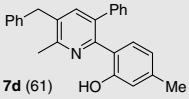
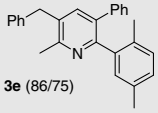
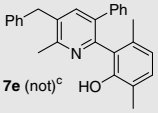
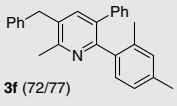
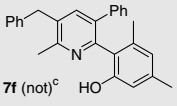
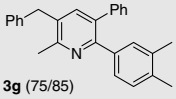
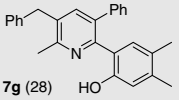
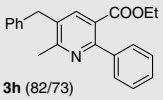
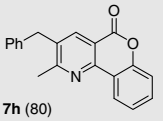
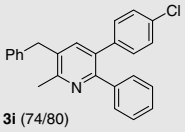
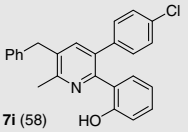
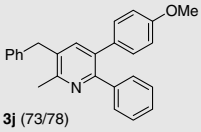
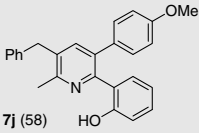
Entry	Substrate[a] (%)	Product[b] (%)
1	 **3a** (77/88)	 **7a** (76)
2	 **3b** (82/79)	 **7b** (61)
3	 **3c** (79/81)	 **7c** (58)
4	 **3d** (75/80)	 **7d** (61)
5	 **3e** (86/75)	 **7e** (not)[c]
6	 **3f** (72/77)	 **7f** (not)[c]

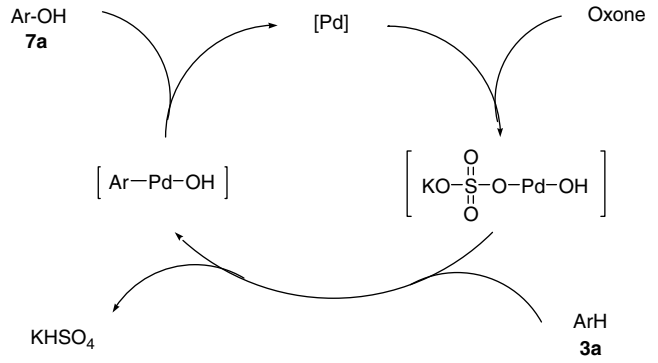
Table 2 (*continued*)

Entry	Substrate[a] (%)	Product[b] (%)
7	 **3g** (75/85)	 **7g** (28)
8	 **3h** (82/73)	 **7h** (80)
9	 **3i** (74/80)	 **7i** (58)
10	 **3j** (73/78)	 **7j** (58)

[a] Prepared according to Ref. 6 and the first yield refer to the first S_N2' step and the second one to the synthesis of pyridine.
[b] Conditions: Substrate 3 (1.0 equiv), $Pd(OAc)_2$ (10 mol %), PEG-3400/*t*-BuOH, Oxone (5.0 equiv), 80–90 °C, 2 h.
[c] No reaction even at 120 °C.

As a next trial, the synthesis of alkoxy derivatives was examined under the conditions of $Pd(OAc)_2$/Oxone/alcohol (Scheme 1, entries 4 and 5 in Table 1). The reaction was sluggish and the corresponding methoxy- and *iso*-propoxy derivatives, **5a** and **6a**, were obtained in only 10–11% yields. However, we observed the formation of phenol derivative **7a**, albeit in low yields (3–8%), very interestingly. We thought that the yield of **7a** could be increased by using non-oxidizable alcohol solvent such as *tert*-butanol instead of methanol or 2-propanol. Thus, a variety of conditions were examined in order to find an optimized one (entries 6–10 in Table 1). As expected, **7a** was isolated in 64% yield in *tert*-butanol (entry 6). The use of *tert*-amyl alcohol or acetonitrile was less effective (entries 7 and 9). The best yield of **7a** was observed when the reaction was carried out in PEG-3400/*tert*-butanol[10] as reaction medium with 5.0 equiv of Oxone (76%, entry 8). The use of $K_2S_2O_8$ was less effective (entry 10).

Encouraged by the results, we synthesized various 2-arylpyridine derivatives **3b–j** according to our previous Letter.[6] Introduction



Scheme 2.

of ketone compound **2** at the primary position of Baylis-Hillman acetate **1** was carried out with the aid of K_2CO_3 in DMF in good yields (72–86%). Next, pyridine synthesis with NH_4OAc was also carried out as reported in 73–88% yields.[6] With these starting materials we examined the selective *ortho*-hydroxylation under the optimized conditions and the results are summarized in Table 2.

The corresponding 2-hydroxy derivatives were synthesized in moderate to good yields in most cases (**7a**–**d**, **7i**, **7j**). Tricyclic compound **7h** was obtained in good yield (80%) when we used **3h** (entry 8). This compound must be formed *via* the intramolecular lactonization of the initially generated *ortho*-hydroxy intermediate. However, the reaction was completely failed with 2,5-dimethyl and 2,4-dimethyl derivatives, **3e** and **3f** (entries 5 and 6). We could not obtain any trace amounts of desired products (**7e**, **7f**) in these cases even at elevated temperature. Whereas we obtained low yield of product **7g** (28%) from 3,4-dimethyl derivative **3g** (entry 7). Based on the experimental results, the failure for the dimethyl cases, **3e** and **3f**, might be due to the steric effect of the *ortho*-methyl group, which makes the formation of the palladacycle intermediate difficult.

When we add some water to the reaction mixture of **3a**, the yield of **7a** was decreased. When the reaction was carried out under strictly controlled nitrogen atmosphere, compound **7a** was obtained in a similar yield. From these experiments, we tentatively propose the mechanism involving the Oxone as a plausible source of oxygen atom (Scheme 2): Oxidative insertion of Pd(0) into the weak O–O bond of Oxone[1a] and the liberation of product (ArOH) and $KHSO_4$. Further studies on the reaction mechanism and the synthetic applicability of these findings are actively under progress.[11–13]

In summary, we disclosed the synthesis of poly-substituted pyridines functionalized with hydroxyl group regioselectively *via* the Pd-mediated C–H activation process. Further studies on the reaction mechanism and the biological activities of prepared compounds are currently underway.

Acknowledgements

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10. *The following is typical procedure for the synthesis of* **7a**: A mixture of **3a** (168 mg, 0.5 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), Oxone (1.54 g, 2.5 mmol) in PEG-3400 (1.0 g) and *tert*-butanol (2 mL) was heated to 80–90 °C for 2 h. After cooling to room temperature, the reaction mixture was poured into water and extracted with ether. Pure product **7a** was obtained by column separation process (hexanes/CH_2Cl_2/EtOAc, 20:3:1) as a yellow solid, 134 mg (76%). Other compounds were synthesized analogously and the selected spectroscopic data of **7a**, **7c**, **7d**, **7h**, **4a** and **5a** are as follows.
Compound **7a**: 76%; Yellow solid, mp 146–147 °C; IR (KBr) 3446, 1601, 1450, 1439 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.56 (s, 3H), 4.05 (s, 2H), 6.39–6.45 (m, 1H), 6.81 (dd, J = 8.1 and 1.5 Hz, 1H), 6.99 (dd, J = 8.1 and 1.5 Hz, 1H), 7.08–7.36 (m, 11H), 7.48 (s, 1H), 13.18 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.82, 38.21, 117.82, 117.86, 120.24, 126.55, 127.41, 128.62, 128.71, 128.73, 129.17, 130.06, 131.21, 132.44, 133.93, 138.58, 140.21, 142.14, 152.34, 153.21, 158.39; ESIMS m/z 352 (M^++1). Anal. Calcd for $C_{25}H_{21}NO$: C, 85.44; H, 6.02; N, 3.99. Found: C, 85.21; H, 6.34; N, 3.87.
Compound **7c**: 58%; White solid, mp 137–138 °C; IR (KBr) 3419, 1602, 1568, 1424, 1086 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.55 (s, 3H), 4.04 (s, 2H), 6.38 (dd, J = 8.4 and 2.1 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 6.99 (d, J = 2.1 Hz, 1H), 7.14–7.39 (m, 10H), 7.47 (s, 1H), 13.76 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.77, 38.21, 117.99, 118.09, 118.57, 126.63, 127.66, 128.62, 128.76, 128.94, 129.09, 131.90, 132.77, 133.96, 135.14, 138.42, 139.84, 142.26, 151.45, 153.19, 159.62; ESIMS m/z 386 (M^++1). Anal. Calcd for $C_{25}H_{20}ClNO$: C, 77.81; H, 5.22; N, 3.63. Found: C, 78.03; H, 5.47; N, 3.60.
Compound **7d**: 61%; Pale yellow solid, mp 133–134 °C; IR (KBr) 3419, 1626, 1450, 1426 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.23 (s, 3H), 2.54 (s, 3H), 4.03 (s,

2H), 6.24 (dd, J = 8.0 and 1.5 Hz, 1H), 6.69 (d, J = 8.0 Hz, 1H), 6.81 (d, J = 1.0 Hz, 1H), 7.15 (d, J = 7.5 Hz, 2H), 7.21–7.35 (m, 8H), 7.45 (s, 1H), 13.35 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.29, 21.80, 38.19, 117.41, 118.24, 118.89, 126.52, 127.34, 128.62, 128.70, 128.74, 129.15, 130.94, 131.95, 133.58, 138.68, 140.44, 140.50, 142.12, 152.50, 153.02, 158.47; ESIMS m/z 366 (M^++1). Anal. Calcd for $C_{26}H_{23}NO$: C, 85.45; H, 6.34; N, 3.83. Found: C, 85.37; H, 6.59; N, 3.98.

Compound **7h**: 80%; White solid, mp 186–187 °C; IR (KBr) 1722, 1608, 1173, 1112 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.68 (s, 3H), 4.12 (s, 2H), 7.13–7.16 (m, 2H), 7.22–7.57 (m, 6H), 8.27 (s, 1H), 8.57–8.60 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.78, 38.80, 115.29, 117.05, 119.37, 124.51, 124.68, 126.81, 128.70, 128.84, 131.60, 135.48, 137.86, 137.99, 149.44, 152.50, 161.51, 165.37; ESIMS m/z 302 (M^++1). Anal. Calcd for $C_{20}H_{15}NO_2$: C, 79.72; H, 5.02; N, 4.65. Found: C, 00.00; H, 0.00; N, 0.00.

Compound **4a**: 61%; Pale yellow solid, mp 121–122 °C; IR (KBr) 1764, 1428, 1212, 1191 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.00 (s, 3H), 2.56 (s, 3H), 4.07 (s, 2H), 7.05–7.35 (m, 14H), 7.45 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.88, 22.23, 38.48, 122.67, 125.43, 126.41, 127.07, 128.07, 128.63, 128.71, 128.77, 129.06, 132.03, 132.75, 133.11, 134.43, 138.93, 139.14, 139.19, 148.29, 151.04, 155.51, 168.53; ESIMS m/z 394 (M^++1).

Compound **5a**: 11%; Pale yellow oil; IR (film) 1600, 1493, 1426, 1246 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.59 (s, 3 H), 3.23 (s, 3H), 4.06 (s, 2H), 6.63 (dd, J = 8.4 and 0.9 Hz, 1H), 6.99 (td, J = 7.5 and 0.9 Hz, 1H), 7.06–7.10 (m, 2H), 7.13–7.17 (m, 3H), 7.21–7.27 (m, 4H), 7.29–7.34 (m, 2H), 7.40 (s, 1H), 7.44 (dd, J = 7.2 and 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.41, 38.57, 54.72, 110.77, 120.80, 126.35, 126.54, 127.58, 128.57, 128.61, 128.91, 129.32, 129.87, 131.45, 132.74, 135.07, 138.42, 139.15, 140.32, 152.43, 155.59, 156.15; ESIMS m/z 366 (M^++1).

11. The use of $Pd(PPh_3)_4$ instead of $Pd(OAc)_2$ caused less reactivity in the reaction of **3a**, as an example. The use of H_2O_2 (30% solution) instead of Oxone produced **7a** in trace amounts (<10%).
12. The reaction of acetophenone oxime methyl ether afforded the corresponding 2-hydroxy product in 47%.[4c] Whereas the reaction of 2-phenylpyridine gave 2-hydroxy compound in only 5% (2-phenylpyridine was recovered in 16% and dimeric compound[2b] was isolated in 20%).
13. Recently, Cu(II)-catalyzed *ortho*-hydroxylation of 2-phenylpyridine has been reported using O_2 as an oxidant and they used water as an anion (OH) source in the reaction.[5i] Sanford and coworkers also observed $Pd(OAc)_2$-catalyzed C–H bond methoxylation with MeOH/Oxone and they proposed the mechanism involving Pd^{IV} intermediate.[4c]