C–H Activation

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$PdCl_2$ and *N*-Hydroxyphthalimide Cocatalyzed C_{sp^2}–H Hydroxylation by Dioxygen Activation**

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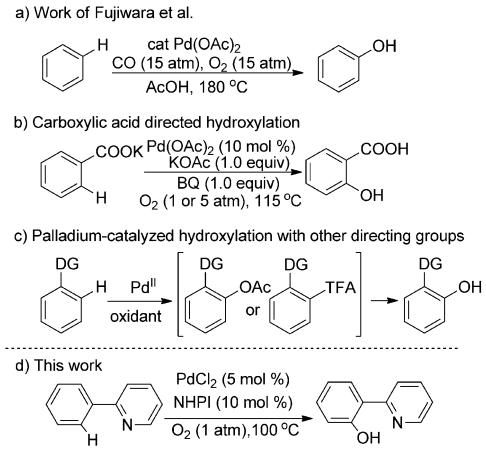
Direct functionalization of C–H bonds has been developed as a powerful strategy to form new chemical bonds.[1] Among them, transition-metal-catalyzed hydroxylation of C–H bonds has received considerable attention because of the industrially important alcohol or phenol products.[2,3] Despite the significant development in the past decades,[1,2] catalytic hydroxylation of C_{sp^2}–H bonds still remains a very challenging task.

With regard to green chemistry, molecular oxygen is regarded as an ideal oxidant because of its natural, inexpensive, and environmental friendly characteritics.[4] In 1990, Fujiwara and co-workers disclosed a $Pd(OAc)_2$-catalyzed hydroxylation of benzene with molecular oxygen (Scheme 1 a).[5] However, this reaction is limited by low efficiency (2.3 %), poor selectivity, and harsh reaction conditions (15 atm O_2, 15 atm CO, 180 °C). To control the selectivity and improve the efficiency, Yu and co-workers used a carboxyl group as the directing group and realized the direct hydroxylation of arenes with molecular oxygen (1 atm) in the presence of a benzoquinone oxidant (1.0 equiv) and base (1.0 equiv; Scheme 1 b).[6] Nevertheless, for substrates with other directing groups, the transition-metal-catalyzed direct hydroxylation is still difficult (Scheme 1 c). Alternatively, a hydrolysis process assisted by various stoichiometric oxidants (potassium persulfates or periodides) for substrates with carbonyl groups was disclosed by the groups of Rao,[7a] Dong,[7b] Kwong,[7c] and Ackermann[7d–e] (Scheme 1 c). Functionalized 2-(pyridin-2-yl)phenols are useful building blocks for preparing light-emitting materials[8] and bioactive molecules.[9] Recent development for the synthesis of these compounds was realized by this hydrolysis strategy through R-OAc intermediates.[10] Thus, it would be attractive to synthesize 2-(pyridin-2-yl)phenols by direct hydroxylation of a C–H bond with O_2 under neutral reaction conditions.



Scheme 1. Hydroxylation of C_{sp^2}–H bonds. BQ = benzoquinone, DG = directing group.

Herein, we disclose a novel $PdCl_2$ and NHPI (*N*-hydroxyphthalimide) cocatalyzed, direct C_{sp^2}–H hydroxylation of 2-phenylpyridines (Scheme 1 d). The significance of the present chemistry is threefold: 1) This process is a novel transition metal and organocatalyst cocatalyzed C_{sp^2}–H functionalization using a radical process.[11] A unique and reasonable mechanism is proposed for this reaction, which will probably promote the development of C_{sp^2}–H functionalization by the combination of a radical process with a transition-metal catalysis. 2) To the best of our knowledge, this reaction is a novel pyridyl group directed[12] hydroxylation with O_2, thus leading to useful products for preparing various biologically active molecules,[9] organic, and light-emitting materials.[8] 3) Molecular oxygen is employed as a reagent and the sole oxidant under neutral conditions without the addition of any other stoichiometric oxidant and base, thus making this protocol very green and practical.

Inspired by our previous work on aerobic oxidation by peroxide radical intermediates,[13] we started our model study by investigating the direct C–H hydroxylation of 2-phenylpyridine (**1a**). To our delight, when the reaction was conducted under O_2 using $PdBr_2$ and NHPI as cocatalysts at 100 °C in toluene, the desired *ortho*-hydroxylation product **2a** was obtained in 54 % yield (Table 1, entry 1). The screening on different palladium catalysts shows that $PdCl_2$ performed with high efficiency (entry 5). If TBHP (2.0 equiv) instead of NHPI was employed, the yield decreased slightly (entry 6), and the reaction did not work in the presence of TEMPO (10 mol %; entry 7). The additives such as base, Brønsted acids, Lewis acids, and ligands did not improve the efficiency

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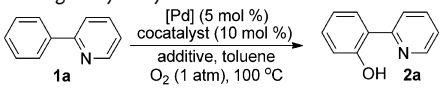
Table 1: Screening of hydroxylation conditions.[a]



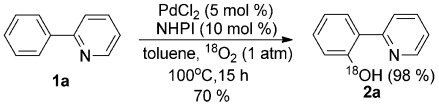
Entry	[Pd]	Cocatalyst	**2a** [%][b]
1	$PdBr_2$	NHPI	54
2	$Pd(OAc)_2$	NHPI	20
3	$PdTFA_2$	NHPI	44
4	$[Pd(dppf)Cl_2]$	NHPI	70 (55)
5	$PdCl_2$	NHPI	87 (72)
6	$PdCl_2$	TBHP (2.0 equiv)	80 (59)
7	$PdCl_2$	TEMPO	0
8[c]	$PdCl_2$	NHPI	0
9[d]	$PdCl_2$	NHPI	0
10[e]	$PdCl_2$	NHPI	76 (63)
11	–	NHPI	0
12	$PdCl_2$	–	0

[a] Reaction conditions: **1a** (0.2 mmol), [Pd] (0.01 mmol), NHPI (0.02 mmol), toluene (3 mL), O_2 (1 atm), 100 °C, 15 h. [b] Yield as determined by GC. The value within the parentheses is the yield of the isolated product. [c] Benzotrifluoride was used as solvent instead of toluene. [d] The reaction was carried out under Ar (1 atm). [e] The reaction was carried out under air (1 atm). dppf = 1,1′-bis-(diphenylphosphino) ferrocene, TBHP = *tert*-butyl hydroperoxide, TEMPO = 2,2,6,6-tetramethylpiperidin-*N*-oxyl, TFA = trifluoroacetate.

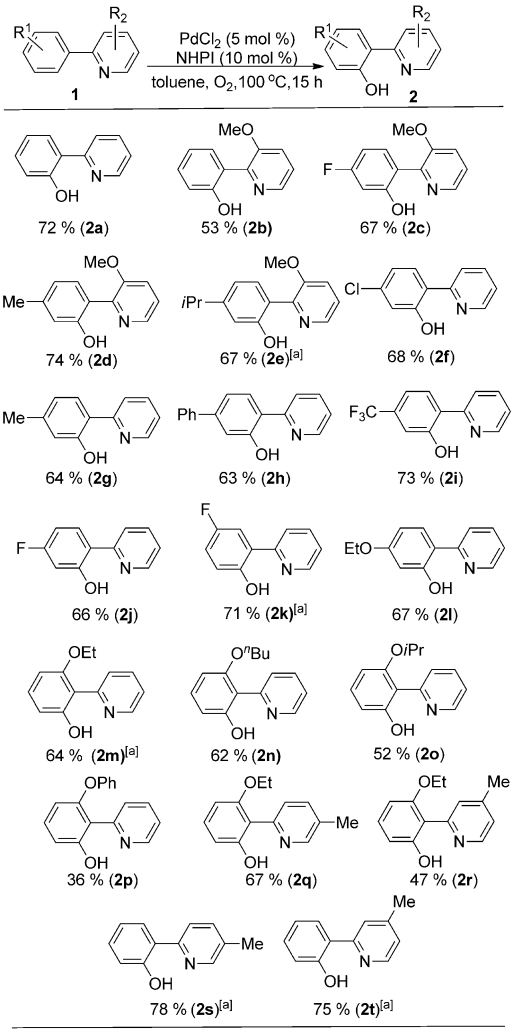
of this reaction (see the Supporting Information). The reaction in benzotrifluoride or under Ar did not work (entries 8 and 9), and in contrast, the reaction with air proceeded well but with a slightly lower yield (entry 10). Notably, the reaction in the absence of a palladium catalyst or NHPI did not work (entries 11 and 12). We additionally investigated the experiment with TBHP (2.0 equiv) in the absence of O_2, but no product was observed (see Scheme S1 in the Supporting Information). When TBHP (2.0 equiv) was employed instead of NHPI under $^{18}O_2$, the reaction afforded [^{18}O]-**2a** in 55% yield (Scheme S1). These results demonstrate that the combination of palladium and NHPI (or TBHP) catalysis, toluene, and O_2 were all essential for this reaction.

With the optimized reaction conditions in hand, the scope of substituted 2-phenylpyridines was investigated (Scheme 2). The benzene ring with electron-donating and electron-withdrawing groups proceeded well. Notably, the substrates containing a halogen group were also compatible under the standard reaction conditions (**2c**, **2f**, **2j** and **2k**), and allows additional substrate modification. Substituents at *ortho*, *meta,* or *para* positions did not affect the efficiency of this transformation (**2j**–**2k**, **2l**–**2p**). Moreover, substrates with substituents on the pyridine ring (at the 3-,4-, or 5-position) also reacted well (**2b**–**2e, 2q**–**2t**).

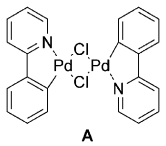
To further probe the mechanism, some control experiments were investigated. The ^{18}O-labeling results proved that the oxygen atom in the hydroxy group originates from molecular oxygen [Eq. (1); determined by HRMS. See the Supporting Information]. Furthermore, the proposed Pd^{II} complex **A** was prepared and employed in the reaction instead of a $PdCl_2$ catalyst. Interestingly, the desired product **2a** was obtained in 74% yield [Eq. (2)]. However the reaction of the **A** alone did not produce the desired product **2a** [Eq. (3)].

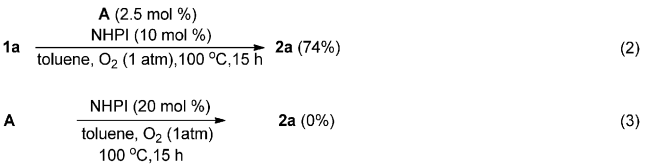


(1)

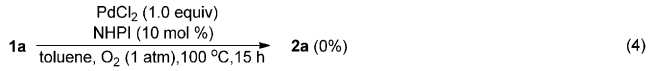


Scheme 2. Palladium-catalyzed hydroxylation of 2-phenylpyridine with O_2. Standard reaction conditions: **1** (0.4 mmol), $PdCl_2$ (0.02 mmol), NHPI (0.04 mmol), toluene (6 mL), 100 °C, O_2 (1 atm), 15 h. Yields of isolated products given. [a] PhCHO (0.8 mmol) was added.



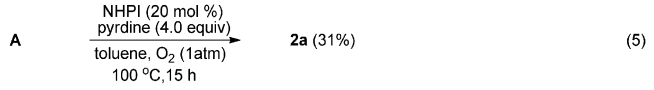


We had hypothesized that the very low solubility of **A** in toluene shuts down the reaction, and investigated by running control experiments. When a stoichiometric amount of $PdCl_2$ was employed in the reaction of 2-phenylpyridine (**1a**), none



(4)

of the desired product **2a** formed [Eq. (4)], thus indicating that the strong chelation between the palladium catalyst and substrate may prevent the further hydroxylation of **1a**. Interestingly, a similar reaction of **A** in the presence of 4.0 equivalents of pyridine produced **2a** in 31% yield [Eq. (5)]. Moreover, when **A** was used as both the catalyst and substrate, **2a** and **2j** were obtained in 26 and 28% yield, respectively [Eq. (6)]. These results suggest that free pyridine



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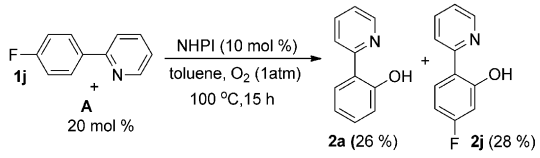
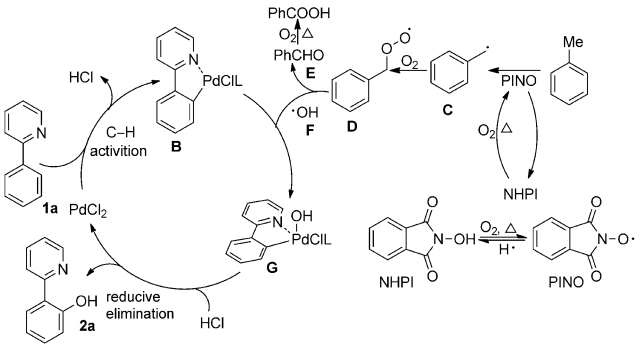


(6)

or 2-arylpyridine may be necessary to break up the Pd^{II} complex **A** to form a monomeric Pd^{II} intermediate.[12p,14]

In addition, a kinetic isotopic effect (KIE) study was also conducted, and the KIE values ($K_H/K_D = 1.86$ for intramolecular study and $K_H/K_D = 2.85$ forintermolecular study; see the Supporting Information) suggest that the cleavage of a C–H bond might be involved in the rate-limiting step.[15] Similar reactions in the presence of 1.1 equivalents of *m*CPBA (3-chloroperbenzoic acid) or NHPI under Ar did not work [see Eq. (S6) and (S7) in the Supporting Information], and may exclude the possibility of a peroxybenzoic acid as an intermediate. Furthermore, considering that pyridines can be oxidized to pyridine N-oxides in the presence of peroxides, 2.0 equivalents of pyridine N-oxide[16] was employed in the reaction of **1a** under Ar and under O_2. However, **2a** was not observed under either of these reaction conditions [Eq. (S8) and (S9) in the Supporting Information]. These results may exclude pyridine N-oxides as a key intermediate in this transformation.

On the basis of the mechanistic studies, a proposed reaction pathway is illustrated in Scheme 3. Initially, the palladium(II) intermediate **B**[14] is generated by chelate-directed C–H activation. Meanwhile, homolysis of NHPI affords the PINO radical, which triggers the formation of the benzyl radical **C**. The benzyl radical **C** is then trapped by O_2 to produce the peroxide radical **D**, which subsequently forms the hydroxyl radical **F** and benzaldehyde (**E**; benzaldehyde can be oxidized to benzoic acid under O_2. Both benzaldehyde and benzoic acid are detected by GC/MS and TLC; see the Supporting Information). Then, the reaction of radical **F** and **B** may produce the reactive Pd^{III} **G** (the palladium complex is not completely clear yet, and a Pd^{IV} intermediate cannot be excluded).[14a,17] The last step involves carbon–oxygen bond formation by reductive elimination of **G** to afford the



Scheme 3. Proposed mechanism.

hydroxylation product **2a** and regeneration of the catalyst (Scheme 3).

To further prove the proposed mechanism, the reaction was monitored by EPR (electron paramagnetic resonance spectroscopy) with DMPO (5,5-dimethyl-1-pyrroline *N*-oxide) as the radical trap. Interestingly, when the reaction was recorded under the standard reaction conditions (Figure 1 A), the signals corresponding to DMPO-OH could be

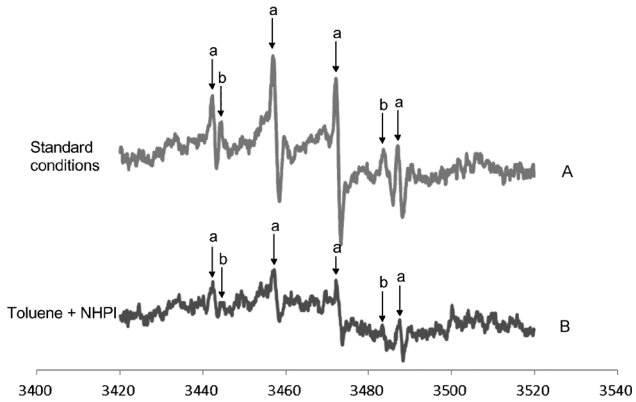
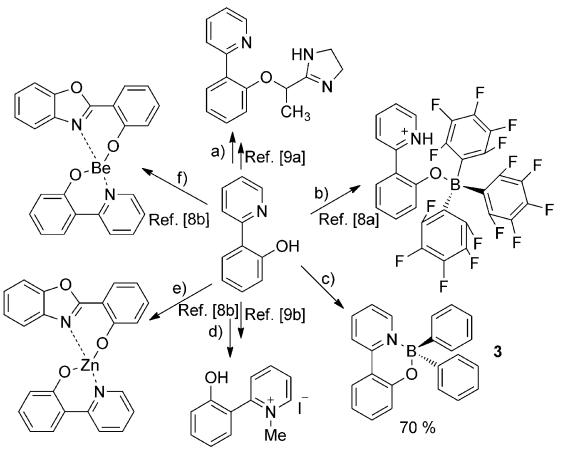


Figure 1. The EPR spectra (X band, 9.7 GHz, RT): A) A reaction mixture (**1a**, $PdCl_2$, NHPI, toluene and O_2) in the presence of the radical trap DMPO (3×10^{-2} M). B) A reaction mixture (NHPI and toluene) in the presence of radical trap DMPO (3×10^{-2} M).

assigned. The four corresponding peaks are labeled a in Figure 1). The calculated hyperfine splittings are g_0 (2.0053) and $\alpha_N = \alpha^{\beta}_H = 1.49$ mT,[18] which indicates the presence of hydroxyl radicals during the transformation. Although there was some overlap, peaks labeled b in this spectrum were identified as signals corresponding to DMPO-OO(H), and they disappeared with the addition of superoxide dismutase (SOD; see the Supporting Information).[18,19] When NHPI was employed alone in toluene (0.0067 M), the hydroxyl radical and superoxide radical signals were present, though weak (Figure 1 B). These EPR studies (for more details see the Supporting Information) strongly indicate that hydroxyl radical **F** is involved in the NHPI catalytic process in this transformation.

To illustrate the synthetic utility of this direct C–H hydroxylation reaction, a variety of transformations of 2-



Scheme 4. Transformations of 2-(pyridin-2-yl)phenol.

(pyridin-2-yl)phenols are displayed in Scheme 4. A series of biologically active molecules can be prepared form 2-(pyridin-2-yl)phenols (Schemes 4a and d).[9] In addition, 2-(pyridin-2-yl)phenols are widely used in organic light-emitting materials as a ligand because of their two strong chelating groups (the hydroxy group and the pyridine ring; Schemes 4b,c,e, and f).[8] For example, the four-coordinate boron compound **3** is a novel hole-blocking material for phosphorescent OLEDs,[8a] and was easily prepared in 70% yield from our product **2a** (Scheme 4c). According to the literature, the ligand has an important influence on these materials' properties.[8a] However, it is not easy to prepare 2-(pyridin-2-yl)phenols with different substituents. Therefore, the present protocol provides a practical approach to various substituted 2-(pyridin-2-yl)phenols for the discovery of new organic light-emitting materials.

In summary, we have demonstrated a novel $PdCl_2$ and NHPI cocatalyzed, direct C_{sp^2}–H hydroxylation of 2-phenylpyridines. Molecular oxygen is employed as a reagent and the sole oxidant under neutral conditions without the addition of any other stoichiometric oxidant and base. A novel combination of transition-metal-catalyzed C–H activation and a NHPI-initiated radical process is proposed as the mechanism based on a series of mechanistic studies. This chemistry provides a green and practical method to synthetize a variety of substituted 2-(pyridin-2-yl)phenols. Additional studies focused on understanding the reaction mechanism and the synthetic applications are ongoing in our laboratory.

Experimental Section

NHPI (6.6 mg, 0.04 mmol), $PdCl_2$ (3.6 mg, 0.02 mmol) 2-phenylpyridine (**1a**, 62.0 mg, 0.4 mmol) toluene (6.0 mL), and a stir bar were added to a 50 mL Schlenk tube under O_2. The mixture was stirred at 100 °C under O_2 (1 atm) for 15 h as monitored by TLC. The solution was then diluted with ethyl acetate (15 mL), and evaporated under vaccum. The crude reaction mixture was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 40:1) to get product **2a** (49.4 mg, 72%). **2a**:[10] yellow solid, ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 14.4$ (s, 1H), 8.47 (d, $J = 4.4$ Hz, 1H), 7.88 (d, $J = 8.4$ Hz, 1H), 7.80–7.76 (m, 2H), 7.32–7.28 (m, 1H), 7.22–7.19 (m, 1H), 7.03 (d, $J = 8.0$ Hz, 1H), 6.89 ppm (t, $J = 7.4$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 159.9$, 157.8, 145.7, 137.7, 131.4, 126.0, 121.4, 119.0, 118.7, 118.5 ppm; IR (neat): $\tilde{\nu}$ =3433.8, 1588.6, 1503.2, 1473.6, 1430.3, 1392.3, 1303.6, 1264.8, 1244.5, 795.6, 753.8, 725.8, 640.9, 626.5 cm^{-1}; MS (*m*/*z*, %): 171.10.

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Communications

C–H Activation

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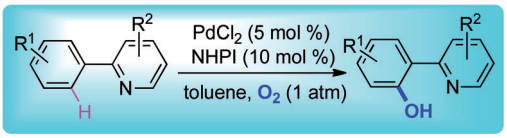

PdCl$_2$ and *N*-Hydroxyphthalimide Cocatalyzed C$_{sp^2}$–H Hydroxylation by Dioxygen Activation

Rad transition: The combination of transition-metal-catalyzed C–H activation and a NHPI-initiated radical process is essential for the title transformation. The neutral conditions and the ideal oxidant, molecular oxygen, make this hydroxylation environmentally friendly and practical. NHPI = *N*-hydroxyphthalimide.