Pd(II)-Catalyzed Monoarylation of 2-Phenylpyridine *N*-Oxide with Iodobenzene in Water

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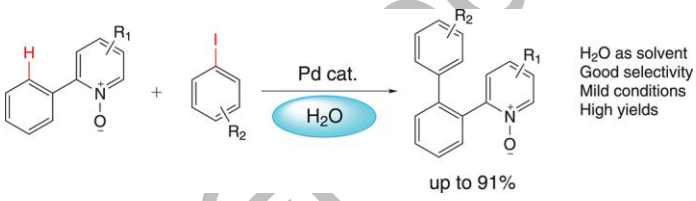
Abstract

A Pd(II)-catalyzed activation and arylation of C(sp^2)-H bond directed by pyridine *N*-oxide in water is achieved with high regioselectivity to form monoarylated products in yields up to 91%. The wide substrate scope highlights the flexibility of the catalyst. The reaction mechanism was proposed and the application of this method was taken example by the synthesis of COX-2 inhibitor analog.

Graphical Abstract



KEYWORDS: palladium; catalysis; pyridine *N*-oxide; aqueous; arylation

INTRODUCTION

The transition metal-catalyzed functionalization of C-H bonds has emerged as a powerful tool for the formation of C-C and C-heteroatom bonds in recent years.[1] Nickel,[2] palladium,[3] iron,[4] rhodium,[5] copper[6] and other metals have been appealing catalysts

for these transformations. Among them, palladium is now perhaps the most widely used for this type of reactions. Indeed, the past decade has witnessed the development of many Pd-catalyzed C-H arylation reactions employing various C(sp^2)-H electrophiles.[7] For example, the arylation of anilides[8] and benzoic acids[9] with aryl halides by Pd(II) catalysis has been studied by Daugulis and co-workers. The intramolecular arylation involving C(sp^2)-H activation to synthesize new polycyclic skeletons was then reported by Raboin and co-workers.[10] In 2015, Yu and co-workers reported Pd(II)-catalyzed *meta*-C(sp^2)-H arylation of amides with various aryl iodides as arylation reagents.[11] Recently, the groups of Shi,[12] Babu,[13] Hu[14] et al. also achieved the arylation in the presence of Pd(II) catalyst *via* C(sp^2)-H activation process.

On the other hand, 2-(2-arylphenyl)pyridine-containing heterocyclic molecules and their derivatives exist widely in natural products, functional materials and pharmaceuticals. For example, compound **A** was utilized as a cyclooxygenase-2 (COX-2) inhibitor;[15] compound **B** (GSK345931A), which demonstrated good metabolic stability in the rat and lower molecular weight, showed measurable CNS penetration in the mouse and rat and potent analgesic efficacy in acute and sub-chronic models of inflammatory pain;[16] compound **C** exhibited efficient activity to induce inhibition of 11β-HSD1;[17] while the supramolecular zinc ensemble of compound **D** exhibits 'ON-ON' response to Thr in the nanomolar range (Figure 1).[18]

The widespread applications of this kind of compounds have resulted in the development of synthetic methodology to construct them. For example, Studer et al. reported the

transition metal-catalyzed C(sp^2)-H arylation of 2-phenylpyridine with arylboronic acid, aryl halide, aryl acylperoxides etc., which were performed in organic solvents.[19] Then, Dixneuf, Gimeno and co-workers reported this reaction by using water as the reaction medium in the presence of ruthenium catalyst.[20,21] Considering the relatively high solubility of pyridine *N*-oxide in water as well as the certain coordination ability of oxygen atom of *N*-oxide,[22] we envisioned its potential application as ligand in aqueous catalysis. Actually, several groups have performed transition metal-catalyzed *ortho* C-H bond alkylation, alkenylation, and arylation of pyridine *N*-oxides in organic solvents.[23] Notably, Wu and co-workers revealed the copper-catalyzed direct C-H arylation of pyridine *N*-oxides with arylboronic esters for the synthesis of 2,6-diphenylpyridine and its derivatives (Scheme 1)[24], in which the copper catalyst coordinated and activated the *ortho*-position of pyridine ring[25].

RESULTS AND DISCUSSION

Inspired by the above studies, it is reasonable to assume that the activation of C(sp^2)-H bonds might be achieved through palladium catalysis with the assistance of 2-phenylpyridine *N*-oxide. In continuation of our recent work on aqueous catalysis and C-H activation,[26] we commenced our studies by investigating the possibility of activation and arylation of 2-phenylpyridine *N*-oxide in water.

As shown in Table 1, 2-phenylpyridine *N*-oxide **1a** (0.25 mmol) was reacted with iodobenzene (1.5 equiv.) in the presence of $Pd(OAc)_2$ (10 mol%) in 1 mL H_2O at 100 ^oC for 12 h, affording the desired high regioselective *ortho*-monoarylated product **3a** in 23%

yield (Table 1, entry 1). Among different silver salt additives, AgOTf gave the best yield of 68% (Table 1, entries 2-11). Further experiments showed that other palladium sources such as $Pd(TFA)_2$ or $Pd(PPh_3)Cl_2$ gave lower yields (Table 1, entries 12-14). After addition of phase transfer reagent tetrabutylammonium bromide, the yield increased to 84% (Table 1, entry 15). Subsequently, other reaction parameters including the ratio of two substrates, reaction time, reaction temperature, and the amount of catalyst were also investigated (Table 1, entry 23-27). Finally, a combination of $Pd(OAc)_2$ (10 mol%), TBAB (20 mol%), 1.1 equiv. AgOTf, 1.5 equiv. iodobenzene, and 1 mL H_2O was established to be the best reaction conditions for this reaction. However, when chlorobenzene and bromobenzene were used as arylation reagents, the reaction didn't proceed well with only trace of product, which might be caused by the fact that the easier C-I cleavage than C-Cl and C-Br bonds.[27] More importantly, when the substrate 2-phenylpyridine *N*-oxides was replaced by 2-phenylpyridine, the reaction did not occur smoothly with only trace of product under the same reaction conditions, which indicated the necessity of *N*-oxide group in reaction.

With the optimized reaction conditions in hand, the scope of various iodobenzenes was then studied, and the results were listed in Table 2. A wide range of iodobenzenes with different functional groups, such as methyl (**2i**, **2k** and **2u**), methoxy (**2j** and **2l**), fluoro (**2b**, **2c** and **2s**), chloro (**2d**, **2m** and **2t**), bromo (**2e** and **2n**), nitro (**2h** and **2q**), trifluoromethyl (**2f** and **2o**), cyano (**2g** and **2p**), and ester (**2r**) groups, underwent efficient monoarylation to afford the corresponding substituted pyridine, 2-(1,1'-biphenyl)-2-yl-*N*-oxides in good to excellent yields ranging from 62% to 91%. Substrates bearing either

electron-donating (**2i**-**2l**, **2u**) or electron-withdrawing groups (**2b**-**2h, 2m**-**2t**) could also be coupled with **1a** in high isolated yields. Meanwhile, *ortho*-substituted substrates (**2w**) gave lower yield except fluoro group (**2b**), which might be ascribed to the less steric hindrance of the fluoro atom. Moreover, non-*ortho*- disubstituted aryl iodides could also be coupled under the standard conditions to afford the desired products in moderate to good yields (**3s**-**3u**). The reaction also proceeded well with heterocyclic coupling partner, such as 2-iodothiophene (**2v**). The structure of the arylated products (**3t**) was unambiguously established by X-ray crystallographic analysis (Figure 2).

Next, substituted 2-phenylpyridine *N*-oxides were applied for this reaction with iodobenzene as substrate. As summarized in Table 3, in general, substrates bearing electron-donating substituents resulted in better yields than those bearing electron-withdrawing groups (**4d**-**4e**).[28] The position (*ortho*, *meta*, *para*) of the substituents, on the other hand, appeared to have few effects on the results.

To gain insight into the reaction pathway, the deuteration experiments were performed. At first, a hydrogen/deuterium exchange experiment showed that the hydrogen atom of *ortho* C-H bond was almost replaced by deuterium (eq. 1). Next, a primary kinetic isotopic effect (KIE) of 1.0 was observed in the parallel reaction between **1a** and **[D_2]-1a** with aryl iodide (**2a**) (eq. 2), which revealed that the C-H bond cleavage might not be involved in the rate-determining step.[29]

On the basis of our experiments and reported literatures,[30] which suggested the Pd(II)-catalyzed arylation reactions with ArI in the presence of Ag(I) salt would involve a Pd(II/IV) mechanism. A plausible reaction pathway for the present process was proposed as shown in Figure 3. Firstly, Pd(II) catalyst coordinates with 2-phenylpyridine *N*-oxides **1a** and attacks C(sp^2)-H bond to produce complex **E**. Then **E** is transformed to be Pd(IV) **F** after oxidative addition with iodobenzene. At last, the product is formed by reductive elimination from the high valent Pd(IV) species, while the Pd(IV) species is reduced to be Pd(II) to fulfil the catalytic cycle.

Additionally, 2-(2-phenylphenyl)pyridine *N*-oxide could be easily deoxygenated by reaction with zinc powder in THF at room temperature,[31] making the present route an attractive approach to form 2-(2-phenylphenyl)pyridine (Scheme 2).

Attracted by the medicinal value of compound **A**, we then tried to synthesize its analogue 2-(4,5-difluoro-4'-methoxy-biphenyl-2-yl)-5-methyl-pyridine **6**. As shown in Scheme 3, **6** could be synthesized by the sequential arylation of 2-chloro-5-methylpyridine, oxidation by H_2O_2, catalysis under standard condition, and at last reduction in a 48% total yield, which could shorten two-steps compared with the reported synthetic method.[15] The structure of **6** was also confirmed by X-ray crystallographic analysis (Figure 4), and as expected, the only arylated position is the less steric *ortho* position of pyridine ring.

EXPERIMENTAL

Typical Procedure For The Synthesis Of Compound 3a

A Schlenk tube with a magnetic stir bar was charged with catalyst (10 mol%), silver salt (1.1 equiv.), additive (20 mol%), 2-phenylpyridine *N*-oxide 1a (0.25 mmol, 0.0388 g), iodobenzene 2a (1.5 equiv.) and H_2O (1 mL). The resulting solution was stirred at the indicated temperature. The resulting organic layer was extracted with trichloromethane, treated with Na_2SO_4 and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (EtOAc/CH_3OH = 100/1, v/v) to provide **3a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (d, J = 7.8 Hz, 1H), 7.02 (t, J = 7.7 Hz, 1H), 7.11 (t, J = 6.0 Hz, 1H), 7.16-7.30 (m, 5H), 7.40-7.58 (m, 4H), 8.24 (d, J = 6.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.53, 123.94, 126.11, 126.24, 127.08, 127.38, 127.52, 128.48, 128.97, 129.00, 130.71, 138.79, 139.44, 140.66, 149.03. HRMS (ESI): calcd for $C_{17}H_{13}NO$ $[M+H]^+$ 248.0997, found 248.1067.

CONCLUSION

In summary, we have disclosed an efficient and practical protocol for the C-H monoarylation of 2-phenylpyridine *N*-oxide by using water as an environmentally benign solvent. This reaction enables highly selective installation of aryl scaffolds into the *ortho* site of benzene ring with the assistance of 2-phenylpyridine *N*-oxides auxiliary. Good structural versatility in both aryl iodides and 2-phenylpyridine *N*-oxides and high functional group tolerance provide an efficient protocol for the synthesis of COX-2 inhibitor derivatives. Further investigations of this system for use in other reactions is currently ongoing in our laboratory.

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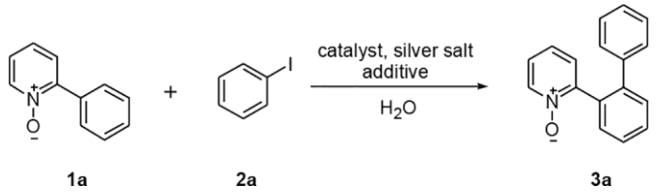
Table 1. Optimization of reaction conditions[a]



1a 2a 3a

entry	catalyst	silver salt	additive	Yield[b] of 3a(%)	Conv.[c] of 1a (%)
1	$Pd(OAc)_2$			23	30
2	$Pd(OAc)_2$	AgOAc		37	43
3	$Pd(OAc)_2$	AgTFA		51	61
4	$Pd(OAc)_2$	Ag_2O		18	27
5	$Pd(OAc)_2$	Ag_2CO_3		trace	10
6	$Pd(OAc)_2$	$AgSbF_6$		36	45
7	$Pd(OAc)_2$	$AgBF_4$		48	56
8	$Pd(OAc)_2$	$CH_3(CH_2)_2COOAg$		20	27
9	$Pd(OAc)_2$	$CH_3(CH_2)_3COOAg$		23	29
10	$Pd(OAc)_2$	$AgNO_3$		59	67
11	$Pd(OAc)_2$	AgOTf		68	79
12	$Pd(TFA)_2$	AgOTf		64	77
13	$Pd(PPh_3)_2Cl_2$	AgOTf		39	48
14	$Pd(PPh_3)_4$	AgOTf		28	36
15	$Pd(OAc)_2$	AgOTf	TBAB	84	90
16	$Pd(OAc)_2$	AgOTf	TPPTS	73	84
17	$Pd(OAc)_2$	AgOTf	TBAI	72	79
18	$Pd(OAc)_2$	AgOTf	SDS	70	78

19	$Pd(OAc)_2$	AgOTf	SDBS	75	83
20	$Pd(OAc)_2$	AgOTf	TsOH	74	85
21	$Pd(OAc)_2$	AgOTf	PPh_3	30	41
22	$Pd(OAc)_2$	AgOTf	Phen	NR	0
23[d]	$Pd(OAc)_2$	AgOTf	TBAB	75	91
24[e]	$Pd(OAc)_2$	AgOTf	TBAB	70	85
25[f]	$Pd(OAc)_2$	AgOTf	TBAB	84	92
26[g]	$Pd(OAc)_2$	AgOTf	TBAB	61	90
27[h]	$Pd(OAc)_2$	AgOTf	TBAB	74	82

[a]The reactions were conducted with 0.25 mmol **1a**, 0.375 mmol **2a**, 10 mol% of catalyst, 1.1 equiv. silver salt, 20 mol% additive, 1 mL H_2O at 100 ^oC for 12 h unless otherwise noted.

[b]Isolated yields.

[c]Consideration determined by GC/MS based on 2-phenylpyridine *N*-oxides (internal standard: tetradecane).

[d]110 ^oC.

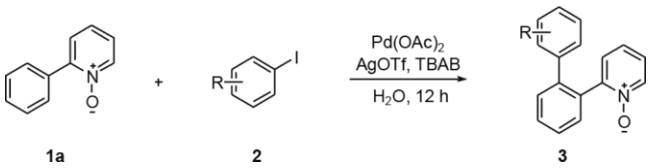
[e]90 ^oC.

[f]4 equiv. **2a**.

[g]24 h.

[h]5 mol% $Pd(OAc)_2$ TBAB: tetrabutylammonium bromide; TPPTS: triphenylphosphine-3,3',3''-trisulfonicacidtrisodium salt; TBAI: tetrabutylammonium iodide; SDS: sodium dodecyl sulfonate; SDBS: sodium dodecyl benzene sulfonate; TsOH: 4-methylbenzenesulfonic acid; Phen: 1,10-phenanthroline.

Table 2. Scope of aryl iodides[a,b,c]



1a 2 3

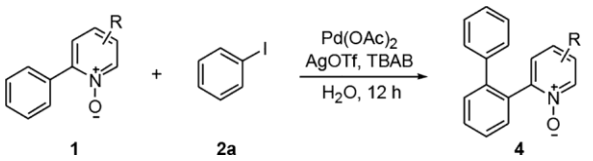
3a, 84% (90%)	**3b**, 65% (73%)	**3c**, 77% (86%)	**3d**, 71% (83%)
3e, 91% (96%)	**3f**, 75% (82%)	**3g**, 62% (74%)	**3h**, 67% (75%)
3i, 80% (87%[c])	**3j**, 73% (80%)	**3k**, 86% (91%)	**3l**, 82% (87%)
3m, 84% (93%)	**3n**, 82% (90%)	**3o**, 75% (84%)	**3p**, 73% (80%)
3q, 71% (82%)	**3r**, 72% (78%)	**3s**, 75% (84%)	**3t**, 72% (80%)
3u, 67% (75%)	**3v**, 57% (65%)	**3w**, NR (0%)	

[a] The reactions were conducted with 0.25 mmol **1**, 0.375 mmol **2a**, 10 mol% $Pd(OAc)_2$, 1.1 equiv. AgOTf, 20 mol% TBAB, 1 mL H_2O and stirred for 12 h unless otherwise noted.

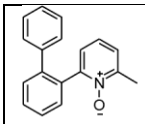
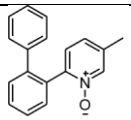
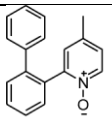
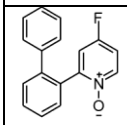
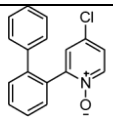
[b] Isolated yields.

[c] Conversion in parenthesis.

Table 3. Scope of 2-phenylpyridine *N*-oxide[a,b,c]



1 **2a** **4**

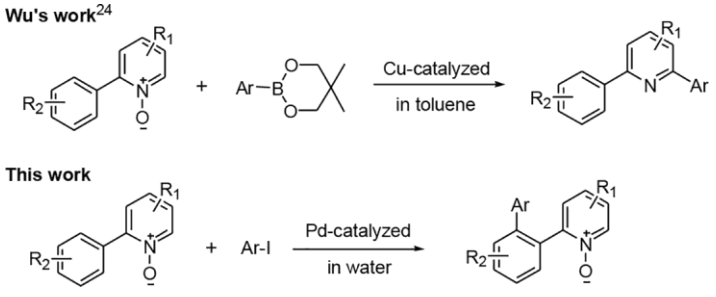
 **4a**, 72% (80%)	 **4b**, 74% (85%)	 **4c**, 70% (81%)
 **4d**, 45% (56%)	 **4e**, 48% (57%)	

[a] The reactions were conducted with 0.25 mmol of **1**, 0.375 mmol of **2a**, 10 mol% of $Pd(OAc)_2$, 1.1 equiv. of AgOTf, 20 mol% of TBAB, and 1 mL of H_2O for 12 h unless otherwise noted.

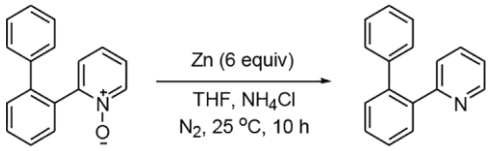
[b] Isolated yields.

[c] Conversion in parenthesis.

Scheme 1. The catalyzed-arylation of 2-phenylpyridine *N*-oxides



Scheme 2. Deoxygenation of 2-(2-phenylphenyl)pyridine-*N*-oxide by zinc powder.



3a **5**

Scheme 3. Synthesis of compound **6**. a. $Pd(PPh_3)_4$, K_2CO_3, toluene/CH_3CH_2OH (7.5:1), 80 ^oC, 48 h, 81% yield; b. H_2O_2; c. $Pd(OAc)_2$, AgOTf, TBAB, H_2O, 100 ^oC, 12 h, 78% yield; d. zinc powder, THF, NH_4Cl, 10 h, 92% yield.

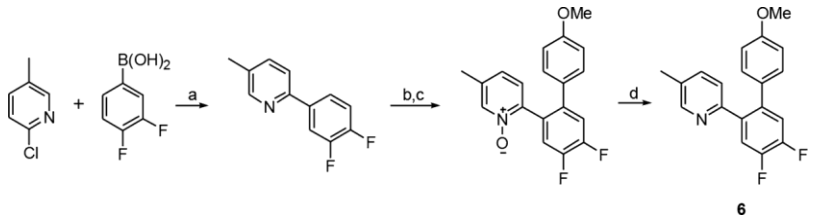


Figure 1. Examples of bioactive 2-(2-phenylphenyl)pyridine

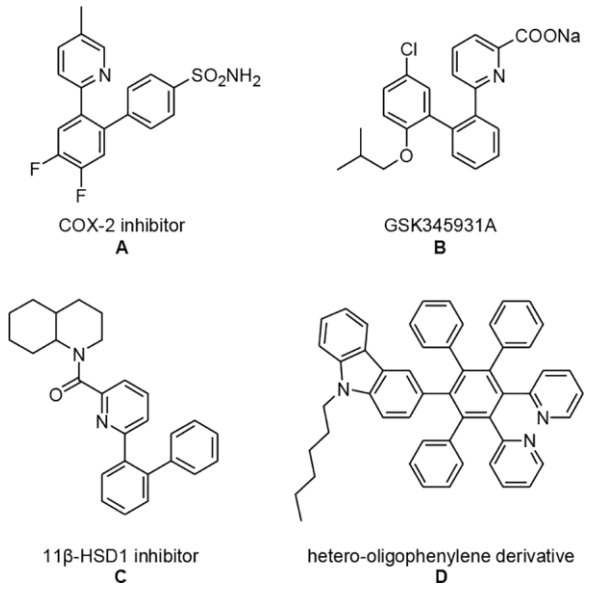


Figure 2. The crystal structure of compound **3t**

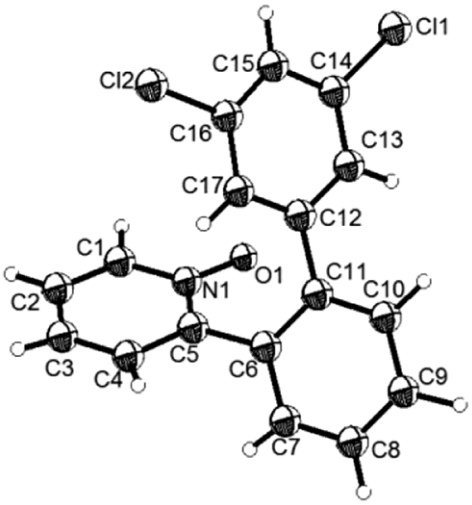


Figure 3. Proposed plausible catalytic pathway

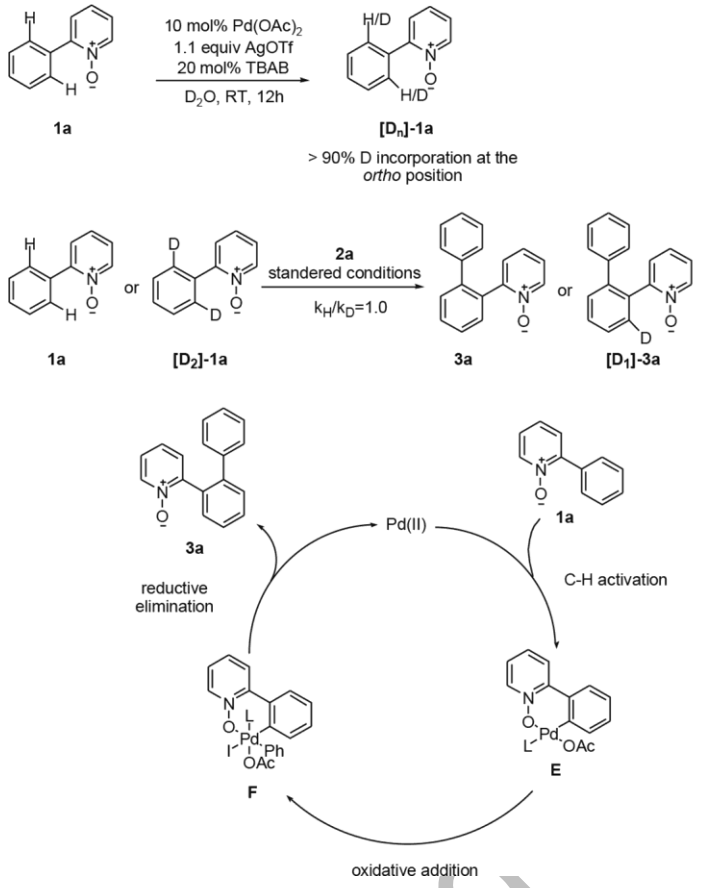


Figure 4. The crystal structure of compound **6**