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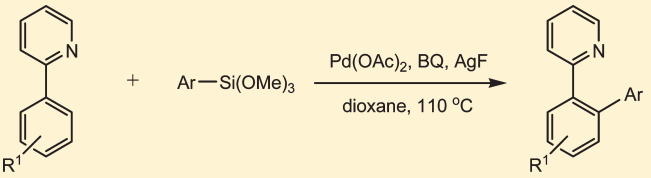
Palladium-Catalyzed Direct *Ortho* C−H Arylation of 2-Arylpyridine Derivatives with Aryltrimethoxysilane

Wu Li, Zhangwei Yin, Xiaoqing Jiang, and Peipei Sun*

College of Chemistry and Materials Science, Nanjing Normal University, Nanjing, 210097, China

Supporting Information

ABSTRACT: A $Pd(OAc)_2$-catalyzed cross-coupling reaction between 2-arylpyridine and aryltrimethoxysilane in the presence of AgF and BQ in 1,4-dioxane was studied. After various reaction parameters (catalyst, oxidant, additive, solvent and reaction temperature) were examined, the optimal conditions for the reaction were identified. The synthesis is compatible to aryltrimethoxysilane with both electron-withdrawing and electron-donating groups on the aryl moiety with moderate yields. The kinetic isotope effect (k_H/k_D) for the C−H bond activation was provided.



R^1 = H; *o*, *m*, *p*-Me; *p*-OMe; *p*-CN; *p*-COOEt; *m*, *p*-NO_2

Polyaromatic motifs are very often found in natural products and pharmaceuticals. Polyaromatics also possess some intrinsic physical properties and therefore have potential applications in research fields of dyes, organic semiconductors, and other advanced materials. Di- or triaromatic rings, especially phenyl heterocycles, are the backbone of some of the most efficient and selective ligands for asymmetric catalysis, especially when atropisomery is possible.[1] Thus, developing more efficient methods to construct these building blocks has received considerable attention in recent years.

Aryl−aryl bond formation is one of the most important tools to make up polyaromatic structures, thanks to its ability to couple two sophisticated moieties under mild conditions. Transition-metal-catalyzed biaryl cross-coupling reactions, which generally employ aryl halides and organometallics as coupling partners, have served as the most common methods for constructing biaryl unions.[2] As a potential green and efficient process to construct complicated structures from simple and commercially available chemicals, the development of methods for direct transformation of a C−H bond into a C−C bond continues to be an important challenge in organic synthesis and catalysis in recent years.[3] These reactions generally involve directing-group-assisted activation of sp^2 C−H bonds of *ortho* aromatic C−H bonds. Many directing groups, such as acetyl, acetamino, carboxylic acid, oxazolyl, pyridyl, hydroxyl, imino, and cyano moieties, have been used for C−H bond activation.[4] Mechanistic studies indicated that aromatic C−H bonds can be activated via a five-membered metallacycles. An attractive one among many approaches is cross-coupling of a C−H bond with an organometallic reagent under oxidative conditions.[5] Although many groups have reported palladium-catalyzed direct arylation or alkylation to aromatic C−H bond with organometallic compounds, especially organoboronic acids or organotin compounds,[6] there are still very few studies on the direct coupling using organosilanes by C−H functionalization even though this method possesses advantages such as environmental benignity, low toxicity, atomic efficiency, and safe handling.[7] Herein, we present the first direct cross-coupling reaction between 2-arylpyridine derivatives and trialkyloxyarylsilanes via C−H bond activation using a palladium catalyst.

As an initial experiment, we began our investigation by testing the reaction of 2-phenylpyridine (**1a**) with trimethoxyphenylsilane (**2a**) in the presence of a catalytic amount of Pd catalyst. The screening of the reaction conditions is summarized in Table 1. It was found that the nature of oxidant, additive, and solvent, as well as the catalyst, may play a critical role on the reaction efficiency. In the absence of Pd catalyst, the reaction cannot proceed at all. $Pd(OAc)_2$ showed evidently catalytic activity to the reaction, and the appropriate amount of the catalyst was 10 mol %. Decreasing the amount of $Pd(OAc)_2$ to 5 mol % might bring about a decrease of the yield (entry 2). Other palladium species such as $PdCl_2$ and $Pd(PPh_3)_4$ were substantially less effective (entries 15 and 16). Fluorine compound was beneficial to the reaction of trialkyloxyarylsilanes due to its activation to organosilane.[8] AgF was proved to be an efficient fluoride source, while the effects of tetra-n-butylammonium fluoride (TBAF) and NaF were poor (entries 3−6). We envisioned that AgF might play more roles than just a simple fluoride source; it may also serve as a co-oxidant with benzoquinone (BQ) to oxidize a Pd(0) species back to Pd(II) to fulfill the catalytic cycle. When 1 equiv of BQ was presented in the reaction mixture, the desired product was obtained in 62% yield. In the absence of BQ, almost no formation of the desired product was observed. We therefore conclude that BQ is also an essential reagent in the transmetalation−reductive elimination step, as the related reports suggest.[6a,b] And yet, other common oxidants such as Ag_2O and $Cu(OTf)_2$ were not efficient for this transformation (entries 8−10). The different solvents

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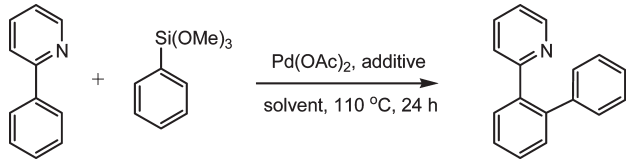
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst (mol %)	solvent	additive (equiv)	yield (%)
1	none	dioxane	AgF (2.0)/BQ (1.0)	0
2	$Pd(OAc)_2$ (5.0)	dioxane	AgF (2.0)/BQ (1.0)	29
3	**$Pd(OAc)_2$ (10.0)**	**dioxane**	**AgF (2.0)/BQ (1.0)**	**62** (25)[b]
4	$Pd(OAc)_2$ (10.0)	dioxane	TBAF (2.0)/BQ (1.0)	20
5	$Pd(OAc)_2$ (10.0)	dioxane	NaF (2.0)/BQ (1.0)	0
6	$Pd(OAc)_2$ (10.0)	dioxane	BQ (1.0)	0
7	$Pd(OAc)_2$ (10.0)	dioxane	AgF (2.0)	trace
8	$Pd(OAc)_2$ (10.0)	dioxane	Ag_2O (2.0)/BQ (1.0)	trace
9	$Pd(OAc)_2$ (10.0)	dioxane	AgF (2.0)/Ag_2O (1.0)	trace
10	$Pd(OAc)_2$ (10.0)	dioxane	AgF (2.0)/$Cu(OTf)_2$ (1.0)	23
11	$Pd(OAc)_2$ (10.0)	H_2O	AgF (2.0)/BQ (1.0)	0
12	$Pd(OAc)_2$ (10.0)	toluene	AgF (2.0)/BQ (1.0)	trace
13	$Pd(OAc)_2$ (10.0)	DMF	AgF (2.0)/BQ (1.0)	trace
14	$Pd(OAc)_2$ (10.0)	NMP	AgF (2.0)/BQ (1.0)	trace
15	$PdCl_2$ (10.0)	dioxane	AgF (2.0)/BQ (1.0)	trace
16	$Pd(PPh_3)_4$ (10.0)	dioxane	AgF (2.0)/BQ (1.0)	47

[a] Reaction conditions: 2-phenylpyridine (**1a**) (1.0 mmol), trimethoxyphenylsilane (**2a**) (2.0 mmol), catalyst (10 mol %), additive (2.0 mmol), oxidant (1.0 mmol), and solvent (4.0 mL) at 110 °C for 24 h. [b] Reaction proceeded at 80 °C.

were also screened, and dioxane was shown to be most suitable for this transformation, while no reactions occurred in H_2O, toluene, DMF, and NMP (entries 11−14). Low reaction temperature led to the low conversion (entry 3). When the reaction was carried out at 80 °C, a low yield of 25% was given, but a yield of 62% was obtained while the reaction proceeded at 110 °C. As the temperature was further increased to 120 °C, no obvious increase of the yield was observed. The reaction could finish in 24 h. Thus, the reaction efficiently proceeded when 10 mol % of $Pd(OAc)_2$ was used as a catalyst in combination with AgF (2 equiv) and BQ (1 equiv) in dioxane at 110 °C.

With the optimized reaction conditions in hand, different trialkyloxyarylsilanes were surveyed (Table 2). In general, the reactions of arylsilanes with electron-donating groups in the aromatic ring gave higher yields than those with the electron-deficient groups. But when the polycyclic arylsilane such as trimethoxy(naphthalen-1-yl)silane was used, only trace corresponding product was obtained, which may be attributed to the steric hindrance of the polycyclic group (entry 23). It is worth pointing out that the chloro group on the aromatic ring could remain in the product. The tolerance of the reaction for C−Cl bond in arylsilanes ensures that it could be further transformed into different functionalities (entries 6 and 18). The reactions of 2-arylpyridine derivatives with several substituents on the phenyl ring were also studied. In the presence of *o*-, *m*-, and *p*-methyl, as well as *p*-methoxyl on the phenyl ring, the reaction gave the desired products with moderate yields. Unfortunately, almost no targeted products were isolated as a strong electron-withdrawing group nitro was substituted on the phenyl ring (entries 24 and 25), while the reaction of 2-arylpyridines with moderate electron-withdrawing group such as cyano or ester group gave the desired products, though the yields were not very high (entries 19−22). This palladium-catalyzed arylation had very good regioselectivity, and no diarylated products or other byproducts were isolated.

A possible mechanism for the present palladium(II)-catalyzed *ortho* arylation of 2-phenylpyridine (**1a**) via C−H bond activation is proposed, as shown in Scheme 1. First, the reaction of $Pd(OAc)_2$ with 2-phenylpyridine (**1a**) afforded a cyclopalladated intermediate **4**, which was actually confirmed by many related reports.[6b,9] This intermediate reacted with the in situ generated pentavalent silicate to form the (aryl)(2-phenylpyridine)palladium(II) species **5** in which benzoquinone could act as a ligand to coordinate with palladium.[9a,10] The subsequent reductive elimination liberated the arylated 2-phenylpyridine, and the released palladium(0) was reoxidized by Ag(I) and *p*-benzoquinone to regenerate palladium(II), which would continue the catalytic cycle. The high regioselectivity could also provide strong evidence to support this step.

The kinetic isotope effect was investigated by using 2-(*o*-deuteriophenyl)pyridine (**1a-D**) to react with **2a** to form **3aa** and **3aa-D** (Scheme 2). The k_H/k_D ratio for the C−H bond activation when (trimethoxy) phenylsilane (**2a**) was used was determined to be 1.02 (compared with the standard ^{1}H NMR spectrum of **3aa**). This indicated that the palladium(II)-catalyzed C−H bond cleavage of 2-phenylpyridine (**1a**) did not occur in the rate determining step. Thus, the reaction of the palladacycle with trialkyloxyarylsilanes was still a viable option for the rate-determining step, similar to the reaction of 2-phenylpyridine with arylboronic compound.[9a]

In conclusion, we have developed a new catalytic system for the arylation of pyridine derivatives with arylsiloxanes through the C−H functionalization reaction, which allows efficient synthesis of a variety of pyridine derivatives. It was also a new example of the direct coupling using organosilanes by C−H functionalization.

EXPERIMENTAL SECTION

General Methods. All reactions were run in oven-dried flasks under nitrogen. Unless otherwise noted, reagents were commercially available and were used without purification. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ [using $(CH_3)_4Si$ (for ^{1}H, δ = 0.00; for ^{13}C, δ = 77.00) as internal standard]. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet. Melting points are uncorrected.

General Experimental Procedures and Characterizations. A seal tube (15 mL) initially fitted with a septum containing $Pd(OAc)_2$ (22 mg, 0.10 mmol), silver(I) fluoride (253 mg, 2.00 mmol), and BQ (108 mg, 1.00 mmol) was evacuated and purged with nitrogen gas three times. 1,4-Dioxane (4 mL), arylpyrimidines (1.00 mmol), and trimethyloxyarylsilanes (2.0 mmol) were added to the system, and the reaction mixture was stirred at 110 °C for 24 h. The mixture was filtered through a short Celite pad and washed with dichloromethane several times. The filtrate was concentrated by vacuum and separated on a silica gel column using hexane/EtOAc as eluent to give the corresponding pure *ortho*-arylated 2-phenylpyridine derivatives.

*2-(Biphenyl-2-yl)pyridine (**3aa**).*[9b] Light yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.67 (d, J = 2.4 Hz, 1H), 7.73−7.74 (m, 1H), 7.49−7.50 (m, 3H), 7.42 (t, J = 7.3 Hz, 1H), 7.26−7.29 (m, 3H), 7.19−7.20 (m, 2H), 7.12 (t, J = 5.6 Hz, 1H), 6.91 (d, J = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.3, 149.4, 148.5, 141.8, 141.3, 140.6, 139.5, 135.2, 134.9, 128.2, 127.6, 126.7, 125.4, 121.4, 120.9.

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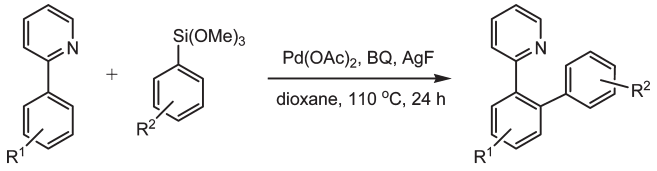
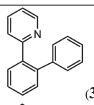
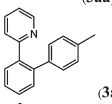
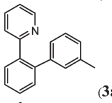
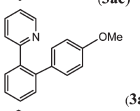
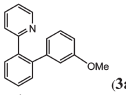
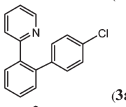
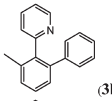
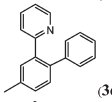
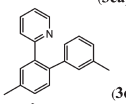
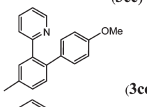
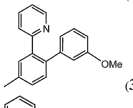
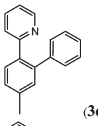
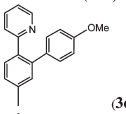
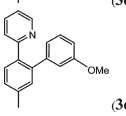
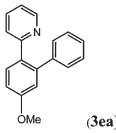
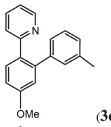
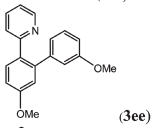
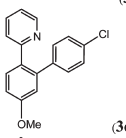
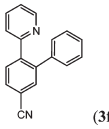
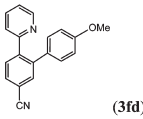
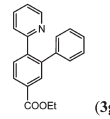
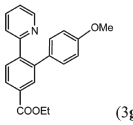
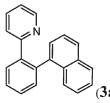
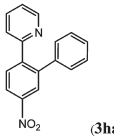
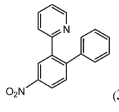
Table 2. Reaction Results of 2-Arylpyridine Derivatives with Trialkyloxyarylsilanes[a]



1 (a~g) **2 (a~g)** **3**

entry	R^1	R^2	product	yield (%)
1	H (**1a**)	H (**2a**)	 (**3aa**)	62
2	H (**1a**)	*p*-Me (**2b**)	 (**3ab**)	63
3	H (**1a**)	*m*-Me (**2c**)	 (**3ac**)	61
4	H (**1a**)	*p*-OMe (**2d**)	 (**3ad**)	67
5	H (**1a**)	*m*-OMe (**2e**)	 (**3ae**)	60
6	H (**1a**)	*p*-Cl (**2f**)	 (**3af**)	43
7	*o*-Me (**1b**)	H (**2a**)	 (**3ba**)	52
8	*m*-Me (**1c**)	H (**2a**)	 (**3ca**)	61
9	*m*-Me (**1c**)	*m*-Me (**2c**)	 (**3cc**)	56
10	*m*-Me (**1c**)	*p*-OMe (**2d**)	 (**3cd**)	58
11	*m*-Me (**1c**)	*m*-OMe (**2e**)	 (**3ce**)	41
12	*p*-Me (**1d**)	H (**2a**)	 (**3da**)	59
13	*p*-Me (**1d**)	*p*-OMe (**2d**)	 (**3dd**)	56
14	*p*-Me (**1d**)	*m*-OMe (**2e**)	 (**3de**)	53
15	*p*-OMe (**1e**)	H (**2a**)	 (**3ea**)	61
16	*p*-OMe (**1e**)	*m*-Me (**2c**)	 (**3ec**)	57
17	*p*-OMe (**1e**)	*m*-OMe (**2e**)	 (**3ee**)	70
18	*p*-OMe (**1e**)	*p*-Cl (**2f**)	 (**3ef**)	48
19	*p*-CN (**1f**)	H (**2a**)	 (**3fa**)	51
20	*p*-CN (**1f**)	*p*-OMe (**2d**)	 (**3fd**)	57
21	*p*-COOEt (**1g**)	H (**2a**)	 (**3ga**)	48
22	*p*-COOEt (**1g**)	*p*-OMe (**2d**)	 (3**gd**)	55
23	H (**1a**)	1-naphthyl (**2g**)	 (**3ag**)	trace
24	*p*-NO_2 (**1h**)	H (**2a**)	 (**3ha**)	trace
25	*m*-NO_2 (**1i**)	H (**2a**)	 (**3ia**)	trace

[a] All of the reactions were carried out using pyridine derivatives **1** (1.0 mmol), trialkyloxyarylsilanes **2** (2.0 mmol), $Pd(OAc)_2$ (10 mol %), AgF (2.0 mmol), and BQ (1.0 mmol) in dioxane (4.0 mL) at 110 °C for 24 h.

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*2-[2-(4-Methylphenyl)]phenylpyridine (**3ab**).*[11] Light yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.67 (d, J = 3.2 Hz, 1H), 7.70−7.71 (m, 1H), 7.40−7.47 (m, 4H), 7.13 (t, J = 5.6 Hz, 1H), 7.06−7.07 (m, 4H), 6.92 (d, J = 7.8 Hz, 1H), 2.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.9, 149.1, 141.1, 140.3, 139.2, 134.9, 130.2, 129.4, 128.2, 127.7, 126.4, 125.1, 121.0, 22.4.

*2-[2-(3-Methylphenyl)]phenylpyridine (**3ac**).*[12] White solid. Mp = 88−89 °C (lit.[12] mp 90−91 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.66 (d, J = 4.5 Hz, 1H), 7.70−7.71 (m, 1H), 7.41−7.49 (m, 4H), 7.10−7.15 (m, 2H), 7.03−7.05 (m, 2H), 6.92 (d, J = 8.0 Hz, 2H), 2.27 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.7, 149.1, 141.2, 137.8, 131.9, 130.3, 127.9, 127.6, 126.8, 125.5, 120.9, 115.7, 113.2, 22.7.

*2-[2-(4-Methoxyphenyl)]phenylpyridine (**3ad**).*[11] Light yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.65 (d, J = 4.8 Hz, 1H), 7.68−7.70 (m, 1H), 7.43−7.46 (m, 4H), 7.08−7.13 (m, 3H), 6.91 (d, J = 8.0 Hz, 1H), 6.78 (d, J = 8.0 Hz, 2H), 3.79 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.4, 158.3, 149.4, 140.2, 139.3, 135.3, 133.7, 130.8, 130.5, 130.4, 128.5, 127.3, 125.4, 121.3, 113.5, 55.2.

*2-[2-(3-Methoxyphenyl)]phenylpyridine (**3ae**).*[11] Light yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.66 (d, J = 4.6 Hz, 1H), 7.71−7.73 (m, 1H), 7.48−7.50 (m, 3H), 7.42−7.44 (m, 1H), 7.12−7.19 (m, 2H), 6.95 (d, J = 8.0 Hz, 1H), 6.79 (d, J = 8.0 Hz, 2H), 6.70 (s, 1H), 3.65 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.0, 158.9, 149.1, 142.4, 140.2, 139.2, 135.0, 130.0, 130.1, 128.8, 128.2, 127.4, 125.1, 121.9, 121.1, 114.6, 112.6, 54.8.

*2-[2-(4-Chlorophenyl)]phenylpyridine (**3af**).*[9b] Light yellow solid. Mp: 95−96 °C (lit.[9b] mp 96.1−97.6 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.65 (d, J = 4.4 Hz, 1H), 7.69−7.71 (m, 1H), 7.51−7.48 (m, 3H), 7.41−7.43 (m, 1H), 7.22 (d, J = 8.0 Hz, 2H), 7.15−7.16 (m, 1H), 7.10 (d, J = 8.0 Hz, 2H), 6.94 (d, J = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.0, 149.5, 139.8, 139.4, 139.3, 135.6, 132.8, 131.0, 128.3, 127.9, 126.8, 125.3, 121.6.

*2-(3-Methylbiphenyl-2-yl)pyridine (**3ba**).*[13] Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.61 (d, J = 4.8 Hz, 1H), 7.43−7.45 (m, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.24−7.26 (m, 2H), 7.09−7.12 (m, 3H), 7.04−7.08 (m, 3H), 6.86 (d, J = 8.0 Hz, 1H), 2.17 (s, 3H) ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.6, 148.8, 141.7, 141.3, 139.3, 136.7, 135.7, 129.6, 129.4, 128.0, 127.6, 127.5, 126.2, 125.6, 121.3, 20.5.

*2-(4-Methylbiphenyl-2-yl)pyridine (**3ca**).*[9b] Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.62 (d, J = 4.4 Hz, 1H), 7.51 (s, 1H), 7.28−7.36 (m, 2H), 7.24−7.25 (m, 1H), 7.19−7.21 (m, 3H), 7.07−7.13 (m, 3H), 6.84 (d, J = 8.0 Hz, 1H), 2.43 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.1, 149.1, 141.0, 138.9, 137.5, 137.1, 134.8, 130.8, 130.2, 129.4, 129.0, 127.7, 126.2, 125.2, 121.0, 20.8.

*2-(3′-Methyl-4-methylbiphenyl-2-yl)pyridine (**3cc**).* Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.66 (d, J = 4.4 Hz, 1H), 7.55 (s, 1H), 7.35−7.41 (m, 2H), 7.28 (d, J = 8.5 Hz, 1H), 7.10 (t, J = 7.2 Hz, 2H), 7.03 (d, J = 8.8 Hz, 2H), 6.90 (t, J = 7.2 Hz, 2H), 2.47 (s, 3H), 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.2, 149.1, 141.2, 140.8, 139.1, 137.7, 135.3, 130.5, 130.4, 128.6, 127.9, 127.6, 127.5, 126.9, 125.5, 121.4, 22.7, 21.4. HRMS (ESI): calcd for $C_{19}H_{17}N$[H] 260.1439, found 260.1440.

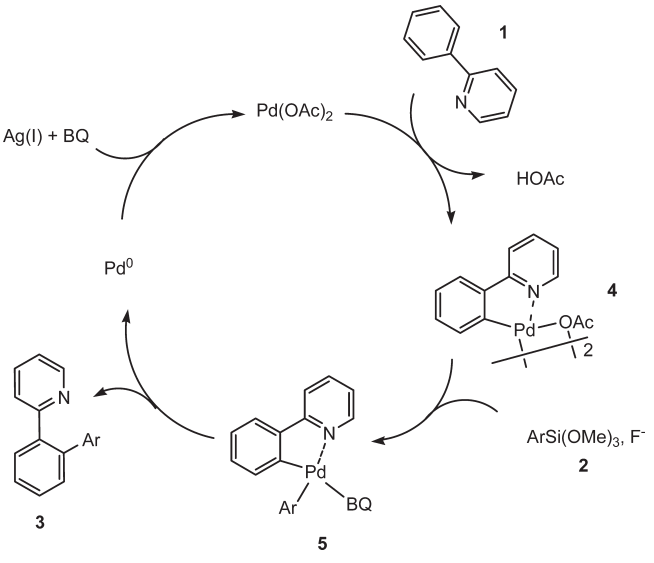
*2-(4′-Methoxy-4-methylbiphenyl-2-yl)pyridine (**3 cd**).*[13] Colorless solid. Mp: 86−87 °C (lit.[13] mp 88−89 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.66 (d, J = 4.8 Hz, 1H), 7.53 (s, 1H), 7.39 (t, J = 6.4 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.27 −7.29 (m, 1H), 7.12−7.14 (m, 1H), 7.06 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 7.8 Hz, 1H), 6.77 (d, J = 8.4 Hz, 2H), 3.80 (s, 3H), 2.46 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.5, 158.4, 149.4, 139.1, 137.4, 137.1, 135.2, 133.7, 131.1, 130.7, 130.4, 129.3, 125.5, 121.3, 113.5, 55.2, 21.1.

*2-(3′-Methoxy-4-methylbiphenyl-2-yl)pyridine (**3ce**).* Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.67 (d, J = 4.4 Hz, 1H), 7.55 (s, 1H), 7.42 (t, J = 8.0 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.12 (t, J = 7.6 Hz, 2H), 6.92 (d, J = 8.0 Hz, 1H), 6.75−6.78 (m, 2H), 6.68 (s, 1H), 3.56 (s, 3H), 2.47 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.1, 158.9, 149.0, 142.3, 138.9, 137.4, 137.2, 134.9, 130.7, 130.0, 129.0, 128.7, 125.1, 121.9, 121.0, 114.7, 112.4, 54.8, 22.4. HRMS (ESI): calcd for $C_{19}H_{17}NO$[H] 276.1388, found 276.1396.

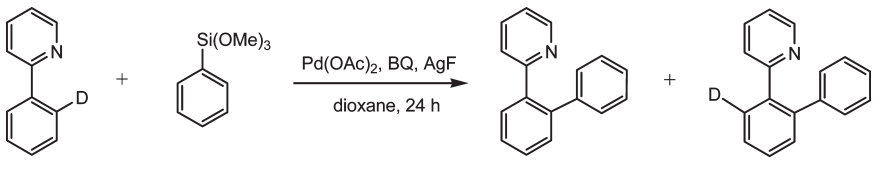
*2-(5-Methylbiphenyl-2-yl)pyridine (**3da**).*[9b] Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.64 (d, J = 4.4 Hz, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.36−7.40 (m, 2H), 7.24−7.32 (m, 4H), 7.16−7.19 (m, 2H), 7.11−7.12 (m, 1H), 6.87 (d, J = 7.8 Hz, 1H), 2.47 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.1, 149.0, 141.2, 140.2, 138.1, 134.9, 130.9, 130.2, 129.4, 128.2, 127.7, 127.3, 126.3, 125.1, 120.9, 20.9.

*2-(4′-Methoxy-5-methylbiphenyl-2-yl)pyridine (**3dd**).*[11] Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.64 (d, J = 3.8 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.38 (t, J = 8.8 Hz, 2H), 7.25 (s, 1H), 7.12−7.07 (m, 3H), 6.88 (d, J = 7.8 Hz, 1H), 6.78 (d, J = 8.6 Hz, 2H), 3.81 (s, 3H), 2.46 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.0, 156.3, 141.3, 140.5, 130.6, 130.5, 129.9, 129.6, 127.0, 119.7, 116.0, 115.9, 113.1, 55.2, 21.2.

Scheme 1. Proposed Reaction Mechanism



Scheme 2. Kinetic Isotope Effect



k_H/k_D = 1.02

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*2-(3′-Methoxy-5-methylbiphenyl-2-yl)pyridine (**3de**).* Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.64 (d, J = 4.0 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.36 (t, J = 7.8 Hz, 1H), 7.07−7.10 (m, 5H), 7.00−7.03 (m, 1H), 6.85 (s, 1H), 6.72 (d, J = 8.0 Hz, 1H), 3.90 (s, 3H), 2.35 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.3, 158.8, 149.0, 141.7, 138.1, 136.3, 134.8, 131.9, 131.6, 129.2, 128.6, 125.1, 120.6, 115.4, 112.8, 55.1, 20.5. HRMS (ESI): calcd for $C_{19}H_{17}NO[H]$ 276.1388, found 276.1392.

*2-(5-Methoxybiphenyl-2-yl)pyridine (**3ea**).*[13] Colorless solid. Mp: 66−67 °C (lit.[13] mp 68.5−69.5 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.60 (d, J = 4.8 Hz, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.33−7.35 (m, 1H), 7.23−7.25 (m, 3H), 7.16−7.18 (m, 2H), 7.06−7.07 (m, 1H), 7.00 (d, J = 8.5 Hz, 1H), 6.95 (s, 1H), 6.80 (d, J = 7.8 Hz, 1H), 3.88 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.6, 157.8, 148.2, 141.0, 140.3, 134.2, 130.9, 128.6, 127.1, 125.9, 124.4, 119.9, 114.7, 112.3, 54.4.

*2-(3′-Methyl-5-methoxybiphenyl-2-yl)pyridine (**3ec**).* Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.62 (d, J = 4.5 Hz, 1H), 7.67 (d, J = 8.5 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 7.01−7.12 (m, 5H), 6.92−6.96 (m, 2H), 6.84 (d, J = 8.0 Hz, 1H), 3.90 (s, 3H), 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.2, 149.1, 141.2, 140.8, 139.1, 137.7, 135.4, 130.5, 130.4, 128.6, 127.9, 127.6, 127.5, 126.9, 125.5, 121.4, 55.4, 22.7. HRMS (ESI): calcd for $C_{19}H_{17}NO[H]$ 276.1388, found 276.1390.

*2-(3′-Methoxy-5-methoxybiphenyl-2-yl)pyridine (**3ee**).* Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.63 (d, J = 4.7 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.39 (t, J = 7.8 Hz, 1H), 7.18 (t, J = 7.8 Hz, 1H), 7.09 (t, J = 7.8 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H), 7.00 (s, 1H), 6.87 (d, J = 8.0, 1H), 6.79−6.82 (m, 2H), 6.72 (s, 1H), 3.91 (s, 3H), 3.67 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.4, 158.9, 158.6, 148.9, 142.4, 141.5, 134.9, 131.9, 131.6, 128.8, 125.1, 121.8, 120.7, 115.3, 114.6, 113.1, 112.7, 55.2, 54.8. HRMS (ESI): calcd for $C_{19}H_{17}NO_2[H]$ 292.1338, found 292.1329.

*2-(4′-Chloro-5-methoxybiphenyl-2-yl)pyridine (**3ef**).* Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.59 (d, J = 4.2 Hz, 1H), 7.62 (d, J = 8.5 Hz, 1H), 7.34−7.42 (m, 2H), 7.19 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 8.0 Hz, 2H), 6.99−7.01 (m, 1H), 6.89 (s, 1H), 6.82 (d, J = 8.0 Hz, 1H), 3.87 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.8, 158.6, 149.3, 140.7, 139.8, 135.6, 133.0, 132.0, 130.9, 128.3, 125.3, 121.2, 115.8, 113.4, 55.5. HRMS (ESI): calcd for $C_{18}H_{14}ClNO[H]$ 296.0842, found 296.0844.

*2-(5-Cyanobiphenyl-2-yl)pyridine (**3fa**).* Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.67 (d, J = 4.4 Hz, 1H), 7.81 (d, J = 7.6 Hz, 1H), 7.73−7.75 (m, 2H), 7.41 (t, J = 8.0 Hz, 1H), 7.27−7.28 (m, 3H), 7.13−7.18 (m, 3H), 6.88 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.3, 149.8, 143.7, 141.8, 139.1, 135.6, 134.1, 131.4, 130.9, 129.4, 128.5, 127.7, 125.2, 122.3, 118.6, 112.3. HRMS (ESI): calcd for $C_{18}H_{12}N_2[H]$ 257.1079, found 257.1079.

*2-(4′-Methoxy-5-cyanobiphenyl-2-yl)pyridine (**3fd**).* Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.66 (d, J = 4.4 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.70−7.71 (m, 2H), 7.45 (t, J = 7.8 Hz, 1H), 7.16 −7.20 (m, 1H), 7.04 (d, J = 7.8 Hz, 2H), 6.90 (d, J = 8.0 Hz, 1H), 6.80 (d, J = 8.4 Hz, 2H), 3.80 (s,3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.2, 157.5, 149.8, 143.5, 141.4, 135.6, 134.0, 131.4, 130.6, 128.6, 125.4, 122.2, 118.7, 113.9, 113.6, 112.3, 55.2; HRMS (ESI): calcd for $C_{19}H_{14}N_2O[H]$ 287.1168, found 287.1184.

*2-(5-Ethoxycarbonylbiphenyl-2-yl)pyridine (**3ga**).*[13] Brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (d, J = 4.4 Hz, 1H), 8.12−8.14 (m, 2H), 7.78 (d, J = 8.4 Hz, 1H), 7.41 (t, J = 8.0 Hz, 1H), 7.25−7.27 (m, 3H), 7.13−7.18 (m, 3H), 6.91 (d, J = 8.0 Hz, 1H), 4.42 (q, J = 7.2 Hz, 2H), 1.42 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.4, 158.2, 149.5, 143.4, 140.4, 135.4, 131.7, 130.7, 130.4, 129.6, 128.6, 128.2, 127.6, 127.1, 125.4, 121.9, 61.2, 14.3.

*2-(4′-Methoxy-5-ethoxycarbonylbiphenyl-2-yl)pyridine (**3gd**).* Brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.66 (d, J = 4.4 Hz, 1H), 8.09−8.10 (m, 2H), 7.75 (d, J = 8.0 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.15−7.17 (m, 1H), 7.09 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 8.0 Hz, 1H), 6.79 (d, J = 8.4 Hz, 2H), 4.42 (q, J = 7.2 Hz, 2H), 3.83 (s, 3H), 1.42 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.5, 159.2, 159.0, 149.6, 143.4, 142.6, 135.4, 132.8, 131.6, 130.8, 130.7, 130.4, 128.2, 125.4, 121.8, 113.7, 61.1, 55.2, 14.3; HRMS (ESI): calcd for $C_{21}H_{19}NO_3[H]$ 334.1430, found 334.1443.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H NMR and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: sunpeipei@njnu.edu.cn.

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