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Pd(II)–Catalyzed C3-selective arylation of pyridine with (hetero)arenes

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Abstract

Palladium catalyzed, non-directed C3-selective arylation of pyridines with arenes and heteroarenes in the presence of 1,10-phenanthroline as the ligand has been developed. The optimized conditions allow for a highly C3-selective arylation of pyridines, affording various 3,3'-bipyridines and 3-arylpyridines.

Graphical Abstract

Arylated pyridines are important structural motifs in many natural products, pharmaceuticals, functional materials, ligands, and biologically active compounds.¹ The construction of C-C bonds linking pyridine with arenes and heteroarenes commonly utilizes the transition-metal-catalyzed cross-coupling reactions, such as Stille,² Suzuki,³ Grignard,⁴ Negishi,⁵ Kumada,⁶ Hiyama⁷ and Ullmann reductive coupling.⁸ While these methods using arylboronic acids, aryl halides or other aryl organometallic compounds are remarkably efficient (eq 1), the development of direct arylation of unactivated pyridine with activated or unactivated arenes has received growing attention due to their potential for further improving the efficiency in synthesis (eq 2). Several reports have described the progress in the development of C-H arylation of pyridine with activated arenes.^{9, 10} Arylation of pyridine with unactivated arenes or heteroarenes are less explored (eq 3). The absence of activating groups on both of the coupling partners presents a challenge for controlling regioselectivity. Recently, You *et al.* reported the direct dehydrogenative C2 coupling of pyridine with electron rich arenes such as thiophenes and benzothiophenes.¹¹ To the best of our knowledge, there are no examples of direct C3-selective arylation of unactivated pyridines

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Supporting Information Available

Experimental procedures and ¹H and ¹³C NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

with simple (hetero)arenes. Herein, we report a Pd-catalyzed C3-selective arylation of pyridine with pyridines or simple arenes.

(1)

(2)

(3)

We started our investigation utilizing pyridine as the limiting reagent (5mmol) in various solvents and observed very low TON's for the bipyridine products (see the Supporting Information for details). Through extensive screening of ligands and conditions, we found that 3,3'-bipyridine (**2a**) was formed under the following reaction conditions: Pd(OAc)₂ (0.05 mmol), 1,10-phenanthroline (Phen) (0.05 mmol) and Ag₂CO₃ (0.5 mmol) in 1.0 mL pyridine (**1a**) in a sealed pressure tube at 120 °C for 24 h. However, the turnover number (TON) of the product **2a** was only 1.0. Along with the desired product **2a**, 2,3'-bipyridine (**3a**) was also obtained with 0.5 TON (Table 1, entry 1). Further optimization of reaction conditions showed that the use of K₂CO₃ and Ag₂CO₃ improved the TON of **2a** to 3.0, however, the formation of **3a** was also increased (Table 1, entries 2 – 4). When the reaction time was prolonged to 48 hours, the TON of **2a** was improved to 4.3 (Table 1, entry 5). Increasing the temperature from 120 °C to 130 °C gave a slight improvement in the TON (Table 1, entry 6). Further raising the reaction temperature or increasing the reaction time did not show any obvious enhancement in the reactivity (Table 1, entry 7 and 8). Increasing loading of Ag₂CO₃ to 1.0 mmol resulted in the apparent boost in the TON of **2a** to 6.8 (Table 1, entry 9). Further increase in the loading of Ag₂CO₃ showed minimal effects in reactivity (Table 1, entry 10). The amount of pyridine was found to be crucial for the product TON (Table 1, entries 10 – 13). When the amount of pyridine was increased from 1.0 mL to 3.0 mL, the TON of **2a** was significantly improved to 11.2 (Table 1, entry 12).

With these optimized conditions in hand, we explored the substrate scope with various pyridines (Table 2). Unfortunately, under the standard reaction conditions, 2,6-dimethoxypyridine (**1b**) only provided 1.7 TON of desired product **2b**. Further investigation

into the reaction conditions revealed that the addition of 0.3 mL of pyridine as an additive along with 2.7 mL of **1b** (see Supporting Information, 2,6-dimethoxy-3,3'-bipyridine (**2i**) was found as the byproduct), significantly enhanced the TON of **2b** to 9.3. Similarly, other pyridine substrates gave efficient TONs when pyridine was used as an additive. We assume that pyridine might act as a complementary ligand to improve the reactivity of the catalyst. The reaction worked efficiently for both electron-rich (**1b**, **1e**) and electron-deficient (**1c**, **1d**, **1f**, **1g**) pyridine substrates, giving the corresponding 3,3'-bipyridines with good TONs, and 2,3'-bipyridines (**3e**, **3g**) were isolated as minor products, respectively. Surprisingly, when 2,5-difluoropyridine (**1h**) was used as substrate, 4,4'-bipyridine, instead of 3,3'-bipyridine was isolated as main product with high TON. The possible explanation for the C4-coupling is that C-H activation occurs through a CMD (Concerted Metalation–Deprotonation) pathway,¹² where the C3 fluoro atom enhances the acidity of the already acidic C4 proton. Quinoline and isoquinoline substrates provided trace amount of products when subjected to these reaction conditions.

Next, we investigated the use of simple arenes as arylation reagents for pyridine. Under the reaction conditions that were used for pyridine-pyridine coupling, we screened the effect of different ratios of arene and pyridine (see Supporting Information, biphenyl (**5a**) was detected as byproduct). When 1.5 mL of benzene (**4a**) and 1.5 mL of pyridine (**1a**) were used, 3-phenylpyridine (**5a**) was obtained as the major product with the TON of 6.5. Both electron-rich (**1e**) and electron-deficient (**1c**, **1f**) pyridines were well tolerated. *para*-Xylene also proved to be good arylation reagent for pyridine, and gave the desired product **5b** with TON of 5.6. However, when toluene was used as the substrate, the products were formed in low TON with no regioselectivity.

On the basis of our previous study,^{9b} a plausible mechanism is proposed for this reaction in Scheme 1. After the formation of intermediate A, with the assistance of the ligand pyridine dissociates from Pd(OAc)₂ and subsequently adjusts itself to coordinate to Pd through its π system, thus facilitating the C3-H activation of pyridine (**B**). Then a similar C-H activation process occurs to give bi(hetero)arene-Pd(II) **C**, which undergoes reductive elimination to give the desired product. Finally the Pd is oxidized by Ag⁺ to regenerate Pd(OAc)₂.

In summary, a C3-selective arylation of pyridines with simple (hetero)arenes has been developed for the first time using Pd(OAc)₂ catalyst and phenanthroline ligand. These reactions, upon further development, could potentially provide an efficient route to 3,3'-bipyridines and 3-arylpyridines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.
Plausible mechanism

Table 1

Optimization of conditions^a

entry	1a (mL)	Ag ₂ CO ₃ (mmol)	base (mmol)	temp (°C)	time (h)	TON 2a (3a) ^b
1	1	0.5	None	120	24	1.0 (0.5)
2	1	0.5	Na ₂ CO ₃ (1.0)	120	24	1.5 (0.8)
3	1	0.5	K ₂ CO ₃ (1.0)	120	24	3.0 (1.0)
4	1	0.5	K ₂ CO ₃ (1.0)	120	24	0.5 (0.3)
5	1	0.5	K ₂ CO ₃ (1.0)	120	48	4.3 (1.3)
6	1	0.5	K ₂ CO ₃ (1.0)	130	48	4.8 (1.3)
7	1	0.5	K ₂ CO ₃ (1.0)	140	48	4.4 (0.8)
8	1	0.5	K ₂ CO ₃ (1.0)	130	72	5.0 (1.1)
9	1	1.0	K ₂ CO ₃ (1.0)	130	48	6.8 (2.0)
10	1	1.5	K ₂ CO ₃ (1.0)	130	48	7.0 (1.5)
11	2	1.0	K ₂ CO ₃ (1.0)	130	48	9.5 (2.8)
12 ^c	3	1.0	K ₂ CO ₃ (1.0)	130	48	11.2 (2.8)
13	4	1.0	K ₂ CO ₃ (1.0)	130	48	9.5 (2.5)

^aReaction conditions: Pd(OAc)₂ (0.05 mmol, 10 mol %), 1,10-phenanthroline (0.05 mmol, 10 mol %), 1.0 mL pyridine is 12 mmol pyridine (12 equiv).^bTON (based on Pd) was determined by ¹H NMR using CH₂Br₂ as an internal standard.^cIsolated TON were 10.3 (2.2).

Table 2The synthesis of C3 bipyridines^a

entry	substrate	product	TON ^b
1	1a	2a	10.3 (2.2)
2	1b	2b	9.3 (0)
3	1c	2c	6.5 (0.7)
4	1d	2d	6.0 (0)
5	1e	2e	5.6 (0.6)
6	1f	2f	4.8 (0.5)

entry	substrate	product	TON ^b
7	1g 	2g 	8.3 (1.0)
8	1h 	2h 	7.3 ^c (2.0)

^a Reaction conditions: **1** (2.7 mL, 20 – 32 equiv, depends on density and formula weight of **1**), $\text{Pd}(\text{OAc})_2$ (0.05 mmol, 10 mol %), 1,10-phenanthroline (0.05 mmol, 10 mol %), Ag_2CO_3 (1.0 mmol, 2 equiv), K_2CO_3 (1.0 mmol, 2 equiv), pyridine (0.3 mL, 4 equiv) at $130\text{ }^\circ\text{C}$ for 48 h.

^b TON (based on isolated product) for 3,3'-bipyridine (2,3'-bipyridine).

^c 2,2',5,5'-Tetrafluoro-4,4'-bipyridine was isolated as the major product, 2,2',5,5'-tetrafluoro-3,3'-bipyridine was also observed by ^1H NMR as minor product.

Table 3

The synthesis of C3 arylpyridines^a

entry	pyridine	arene	product	TON ^b
1		4a	5a	6.5 (0.6, 0.3)
		5b	
2	1a		5b	5.6 (0.5, 0.2)
3	1c	4a	5c	5.7 (0.4, 0.2)
4	1e	4a	5d	4.5 (0.4, 0.2)
5	1f	4a	5e	6.5 (0.5, 0.3)

^aReaction conditions: pyridine substrate **1** (1.5 mL, 26 – 32 equiv, based on density and formula weight of **1**), arene **4** (1.5 mL, benzene 30 equiv, *p*-xylene 22 equiv), Pd(OAc)₂ (0.05 mmol, 10 mol %), 1,10-phenanthroline (0.05 mmol, 10 mol %), Ag₂CO₃ (1.0 mmol, 2 equiv), K₂CO₃ (1.0 mmol, 2 equiv) at 130 °C for 48 h.

^bTONs for 3-Arylpyridine (2-Arylpyridine, 4-Arylpyridine).