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Pd(II)-Catalyzed C3-Selective Arylation of Pyridine with (Hetero)arenes

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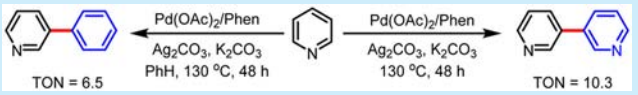
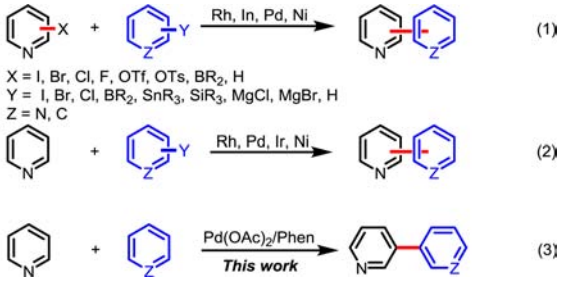
Supporting Information

ABSTRACT: Palladium catalyzed, nondirected 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.



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 transition-metal-catalyzed cross-coupling reactions, such as Stille,[2] Suzuki,[3] Grignard,[4] Negishi,[5] Kumada,[6] Hiyama,[7] 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 efficiency in synthesis (eq 2). Several reports have described progress in the development of C−H arylation of pyridine with activated arenes.[9,10] Arylations 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 in 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 ourknowledge, there are no examples of direct C3-selective arylation of unactivated pyridines with simple (hetero)arenes. Herein, we report a Pd-catalyzed C3-selective arylation of pyridine with pyridines or simple arenes.

We started our investigation utilizing pyridine as the limiting reagent (5 mmol) in various solvents and observed very low TONs 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: $Pd(OAc)_2$

Table 1. Optimization of Conditions[a]

entry	1a (mL)	Ag_2CO_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_2CO_3 (1.0)	120	24	1.5 (0.8)
3	1	0.5	K_2CO_3 (1.0)	120	24	3.0 (1.0)
4[c]	1	0.5	K_2CO_3 (1.0)	120	24	0.5 (0.3)
5	1	0.5	K_2CO_3 (1.0)	120	48	4.3 (1.3)
6	1	0.5	K_2CO_3 (1.0)	130	48	4.8 (1.3)
7	1	0.5	K_2CO_3 (1.0)	140	48	4.4 (0.8)
8	1	0.5	K_2CO_3 (1.0)	130	72	5.0 (1.1)
9	1	1.0	K_2CO_3 (1.0)	130	48	6.8 (2.0)
10	1	1.5	K_2CO_3 (1.0)	130	48	7.0 (1.5)
11	2	1.0	K_2CO_3 (1.0)	130	48	9.5 (2.8)
12[d]	**3**	**1.0**	**K_2CO_3 (1.0)**	**130**	**48**	**11.2 (2.8)**
13	4	1.0	K_2CO_3 (1.0)	130	48	9.5 (2.5)

[a]Reaction conditions: $Pd(OAc)_2$ (0.05 mmol, 10 mol %), 1,10-phenanthroline (0.05 mmol, 10 mol %), 1.0 mL of pyridine is 12 mmol of pyridine (12 equiv). [b]TON (based on Pd) was determined by ^1H NMR using CH_2Br_2 as an internal standard. [c]$AgBF_4$ used instead of Ag_2CO_3. [d]Isolated TONs was 10.3 (2.2).

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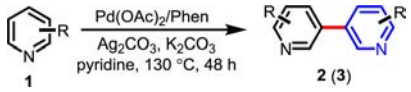
Table 2. Synthesis of C3 Bipyridines[a]

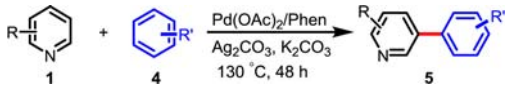


entry	substrate	product	TON[b]
1	1a	2a	10.3 (2.2)
2	1b	2b	9.3 (0)
3	1c	2c	6.5 (0.7)
4	1d	2d	6.0 (0)
5	1e	2e	5.6 (0.6)
6	1f	2f	4.8 (0.5)
7	1g	2g	8.3 (1.0)
8	1h	2h	7.3[c] (2.0)

[a]Reaction conditions: **1** (2.7 mL, 20−32 equiv, dependent on density and formula weight of **1**), $Pd(OAc)_2$ (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 °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.

(0.05 mmol), 1,10-phenanthroline (Phen) (0.05 mmol), and Ag_2CO_3 (0.5 mmol) in 1.0 mL of 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 a 0.5 TON (Table 1, entry 1). Further optimization of reaction conditions showed that the use of K_2CO_3 and Ag_2CO_3 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 h, the TON of **2a** was improved to 4.3 (Table 1, entry 5). Increasing the temperature from 120 to 130 °C gave a slight impovement 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, entries 7 and 8). Increasing the loading of Ag_2CO_3 to 1.0 mmol resulted in the apparent boost in the TON of **2a** to 6.8 (Table 1, entry 9). A further increase in the loading of Ag_2CO_3 showed minimal effects in reactivity (Table 1, entry 10). The amount of pyridine

Table 3. Synthesis of C3 Arylpyridines[a]



entry	pyridine	arene	product	TON[b]
1	1a	4a	5a	6.5 (0.6, 0.3)
2	1a	4b	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)

[a]Reaction 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 %), Ag_2CO_3 (1.0 mmol, 2 equiv), K_2CO_3 (1.0 mmol, 2 equiv) at 130 °C for 48 h. [b]TONs for 3-arylpyridine (2-arylpyridine, 4-arylpyridine).

was found to be crucial for the product TON (Table 1, entries 10−13). When the amount of pyridine was increased from 1.0 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 a TON of 1.7 for 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 a substrate, 4,4′-bipyridine, instead of 3,3′-bipyridine, was isolated as the main product with a high TON. A 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 a 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

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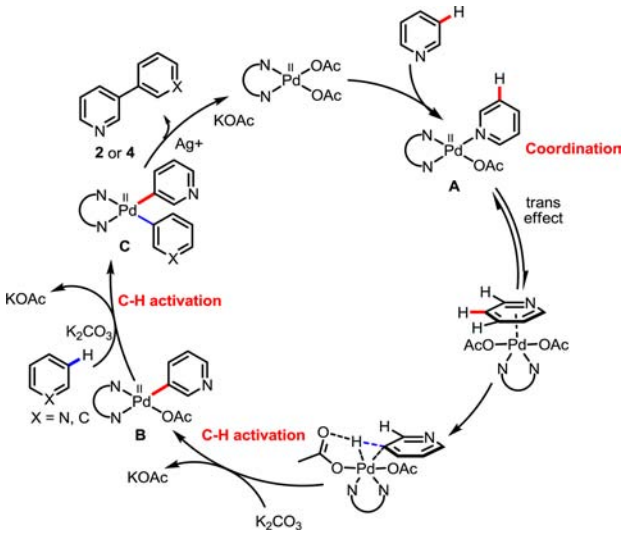
different ratios of arene and pyridine (see Supporting Information; biphenyl (**6a**) was detected as a byproduct). When 1.5 mL of benzene (**4a**) and 1.5 mL of pyridine (**1a**) were used, 3-phenylpyridine (**5a**) was obtained as the major product with a TON of 6.5 (Table 3). Both electron-rich (**1e**) and electron-deficient (**1c**, **1f**) pyridines were well tolerated. *para*-Xylene also proved to be a good arylation reagent for pyridine and gave the desired product **5b** with a 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

Scheme 1. Plausible Mechanism



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 a $Pd(OAc)_2$ catalyst and phenanthroline ligand. These reactions, upon further development, could potentially provide an efficient route to 3,3′-bipyridines and 3-arylpyridines.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03712.

Experimental procedures and ^1H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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