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C−H Arylation of Pyridines: High Regioselectivity as a Consequence of the Electronic Character of C−H Bonds and Heteroarene Ring

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Supporting Information

ABSTRACT: We report a new catalytic protocol for highly selective C−H arylation of pyridines containing common and synthetically versatile electron-withdrawing substituents (NO_2, CN, F and Cl). The new protocol expands the scope of catalytic azine functionalization as the excellent regioselectivity at the 3- and 4-positions well complements the existing methods for C−H arylation and Ir-catalyzed borylation, as well as classical functionalization of pyridines. Another important feature of the new method is its flexibility to adapt to challenging substrates by a simple modification of the carboxylic acid ligand or the use of silver salts. The regioselectivity can be rationalized on the basis of the key electronic effects (repulsion between the nitrogen lone pair and polarized C−Pd bond at C2-/C6-positions and acidity of the C−H bond) in combination with steric effects (sensitivity to bulky substituents).

Functionalized pyridines and related azines (quinolines, isoquinolines, and pyrimidines) are important heteroarenes frequently found in biologically active compounds, including natural products, synthetic biological probes, drug candidates, and clinically used drugs.[1] Azines are indispensable building blocks of medicinal chemistry as they enable tuning of protein binding affinity and selectivity, physical properties, and metabolism, all of which can be ascribed to the electronic properties of these rings and the ability to form hydrogen bonds.

In the context of a C−H functionalization program,[2] we have been interested in catalytic C−H arylation of heteroarenes.[3−5] Pyridines are particularly difficult substrates due to relatively low reactivity and high Lewis basicity. Several groups have recently made important contributions in this area, including C2-selective catalytic methods,[6,7] pyridine arylation dependent on carboxamide directing group,[8] and radical arylation methods.[9] Despite these advances, catalytic C−H arylation of pyridines remains a significant challenge as each of the existing methods has certain limitations, such as a narrow substrate scope or a low positional selectivity.

During our studies on the C−H arylation of imidazoles and pyrazoles, we observed that palladium-carboxylate catalytic systems avoided the position adjacent to the Lewis basic sp^2 nitrogen atom, and this was ascribed to the electronic repulsion between the nitrogen lone pair and polarized C−Pd bond (Figure 1A).[4] *In the context of pyridines, the same electronic effect should result in low reactivity at C-2 and C-6 positions, leading to C3- and C4-arylation* (Figure 1A). To increase the pyridine ring reactivity and to fine-tune the regioselectivity, we considered

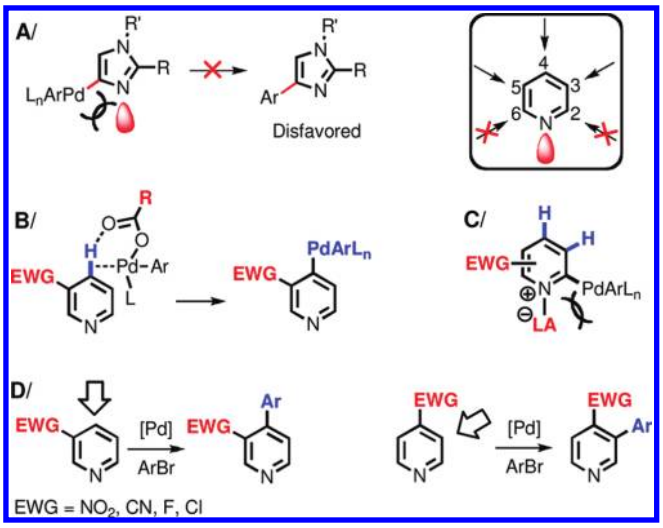

Figure 1. Direct and selective C−H arylation of pyridines—the mechanistic concepts underpinning the high regioselectivity. (A) Palladation at the C-4 position of 1,3-azoles is disfavored due to electronic repulsion between the nitrogen lone pair and polarized C−Pd bond. Similar electronic effect is operative with pyridines, inhibiting the C-2(6) arylation. (B) The electron-withdrawing group (EWG) in the 3-position facilitates C4-arylation by increasing the acidity of the corresponding C−H bond (and by reducing the Lewis basicity of the pyridine nitrogen). (C) The coordination of a Lewis acid further activates the C−H bonds of pyridines, diminishes deactivation of the palladium catalyst, and disfavors palladation at the C-2(6) positions due to steric repulsion between the Lewis acid and the Pd complex. (D) Catalytic C−H arylation of pyridines at C-3 and C-4 positions with haloarene donors. The chosen electron-withdrawing substituents are synthetically versatile.

electron-withdrawing groups (EWG) that are readily available, synthetically versatile, and frequently used in molecular design (NO_2, F, Cl, and CN). For example, the substrates bearing the EWG in the 3-position should afford C4-arylation as the major process (Figure 1B). Also, we considered the use of a suitable azophilic Lewis acid to increase pyridine reactivity (and diminish the catalyst deactivation); in this case, C2- and C6-arylation is also disfavored most probably due to steric hindrance (Figure 1C).[10−12]

Following these mechanistic concepts, we developed the direct C−H arylation of electron-deficient pyridines with predictable regioselectivity; 3-substituted pyridines undergo C4-arylation while 4-subsituted pyridines undergo C3-arylation, in both series with high positional selectivity (Figure 1D).

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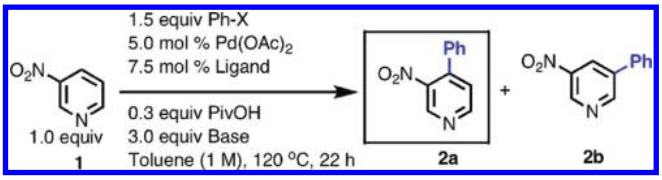
Table 1. C−H Arylation of 3-Nitropyridine: Protocol Optimization[a]



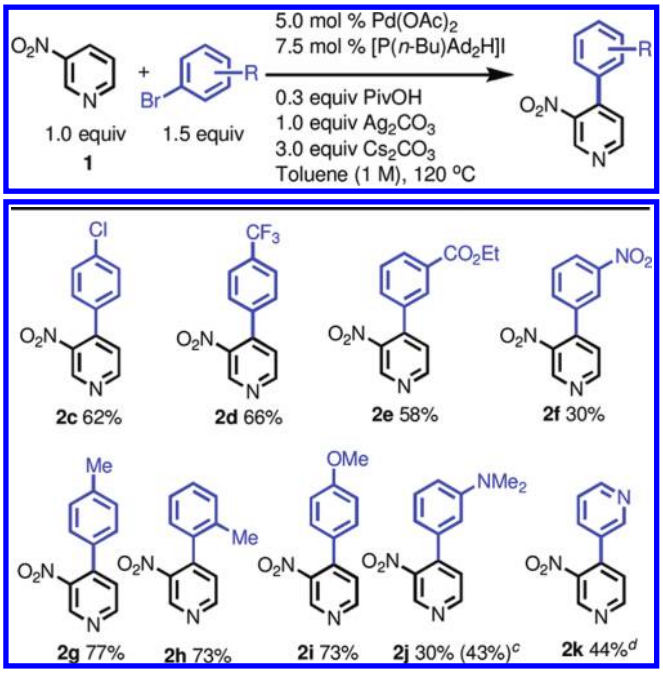
Entry	X	Ligand	Base	Ag_2CO_3 (equiv)	1 (%)	2a (%)	2b (%)
1	Br	[P(*n*-Bu)Ad$_2$H]BF$_4$	Cs_2CO_3	none	63	19	6
2	Br	[P(*n*-Bu)Ad$_2$H]I	Cs_2CO_3	0.3	29	55	<1
3	Br	[P(*n*-Bu)Ad$_2$H]I	Cs_2CO_3	0.5	12	66	<1
4	Br	[P(*n*-Bu)Ad$_2$H]I	Cs_2CO_3	1.0	<1	78	<1
5	Br	[P(*n*-Bu)Ad$_2$H]I	Cs_2CO_3	1.5	<1	80	<1
6	Br	[P(*n*-Bu)Ad$_2$H]I	K_2CO_3	1.5	1	66	<1
7	I	[P(*n*-Bu)Ad$_2$H]I	Cs_2CO_3	1.5	<1	71	<1
8	Cl	[P(*n*-Bu)Ad$_2$H]I	Cs_2CO_3	1.5	83	<1	<1
9	Br	none	Cs_2CO_3	1.5	90	<1	<1

[a] All reactions were performed on a 0.5 mmol scale. Yield was determined by ^{1}H NMR analysis of the crude product using $(CHCl_2)_2$ as the standard. Small amounts of 2,4-diarylated products were generated (<5%).

We first examined the coupling of 3-nitropyridine **1** and bromobenzene. Our systematic study found that Pd(OAc)$_2$/P(*n*-Bu)Ad$_2$/Cs_2CO_3/PivOH/toluene system gave C-4 arylated product **2a** in 19% yield, in conjunction with C-5 arylated product **2b** in 6% yield (Table 1, entry 1). Importantly, addition of Ag_2CO_3, as a Lewis acid and a scavenger of halide, significantly improved not only the yield of **2a** (entries 2−5), but also the selectivity—the arylation takes place at the C-4 position of 3-nitropyridine with high selectivity. Only traces of the C5-product were detected along with a small amount of the 2,4-diarylated product (<5%). Presumably, this is due to the greater activation of the C-4 position (versus C-5) by Lewis acid complexation. The hypothesis that silver carbonate may act as a Lewis acid is supported by the H/D exchange study (Supporting Information).[13] A substoichiometric amount of Ag_2CO_3 gave inferior results (entries 2 and 3), whereas an excess amount provided no significant improvement, revealing 1.0 equiv of Ag_2CO_3 as the optimal amount with respect to the yield of product **2a** (entry 4). Other silver salts showed similar trends; however, they were not as efficient as Ag_2CO_3. In terms of the base, Cs_2CO_3 is superior to K_2CO_3 (entry 6). Both iodobenzene and bromobenzene are competent haloarene donors, while chlorobenzene is unreactive (entries 7 and 8). This chemoselectivity allows for regioselective C−H arylation of chloropyridines (see below). Also, it is noteworthy that the phosphine ligand is required for the C−H arylation of pyridines (entry 9);[3d] P(*n*-Bu)Ad$_2$ is significantly superior to other readily available phosphines.

The scope of haloarene donors was investigated by subjecting 3-nitropyridine and a range of commercially available bromoarenes to the optimized reaction conditions (Table 2). Both electron-deficient (**2c**−**2f**) and electron-rich (**2g**−**2j**) bromoarenes coupled with 3-nitropyridine to give good isolated yields of C4-arylated products. A variety of functional groups are tolerated, such as chloride (**2c**), carboxylic acid ester (**2e**), *ortho*-methyl (**2h**), dimethylamino (**2j**), as well as pyridyl (**2k**) groups. The low yield of products **2f** or **2j** is most likely due to the catalyst decomposition as significant amounts of the starting material was not consumed (40−45%, Supporting Information).

Table 2. C4-Selective Arylation of 3-Nitropyridine: Bromoarene Scope[a,b]

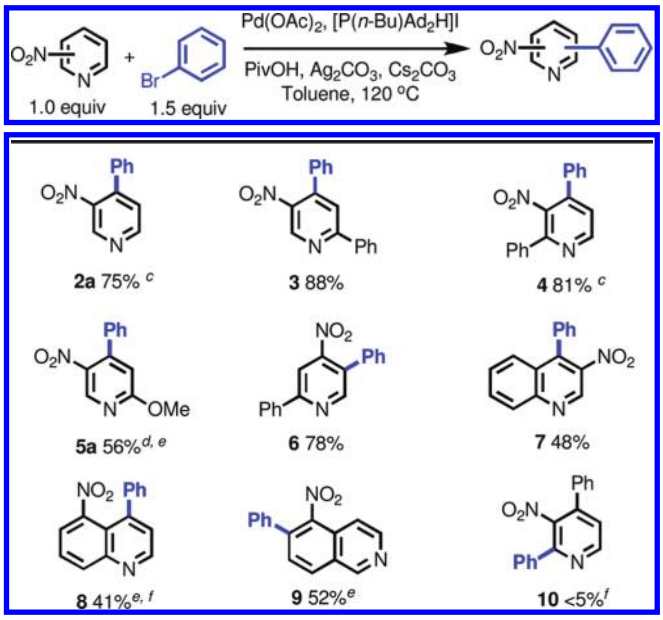


[a] All reactions were performed on a 0.5 mmol scale. [b] Yield of isolated product, otherwise noted. [c] 2,2-Dimethylhexanoic acid was used instead of pivalic acid (see Scheme 1). [d] A total of 15 mol % [P(*n*-Bu)Ad$_2$H]I and 1.2 equiv of 3-iodopyridine were used.

With a good range of haloarene donors established, we examined the scope of nitropyridines (Table 3). For 3-nitropyridines, C-4 arylated products were obtained in high yields when a phenyl substituent was present at either of α-positions (**3**, **4**). In the presence of a methoxy substituent at C-2 position, both C-4 and C-3 arylated products were produced in 56% and 18% yield, respectively (**5a**). The lower selectivity with this substrate can be ascribed to the activation of the 3-position by the adjacent methoxy group. Interestingly, 4-nitro-2-phenylpyridine afforded the corresponding C5-arylation product **6** in 78% yield, indicating sensitivity of the C−H arylation reaction to bulky substituents. The C−H arylation of nitroquinolines and isoquinolines is also highly regioselective and the observed products can readily be explained via combination of the electronic effects (see above) and the sterics. The arylation of 3-nitro- and 5-nitro-quinolines (**7**, **8**) occurs in the pyridine ring, whereas 5-nitro-isoquinoline gives C6-arylation (**9**). As a control, we show that 3-nitro-4-phenylpyridine only provides a small amount of the C-2 arylated product (**10**), which confirms the low reactivity of the C-2 position under the palladium-carboxylate catalyzed conditions.

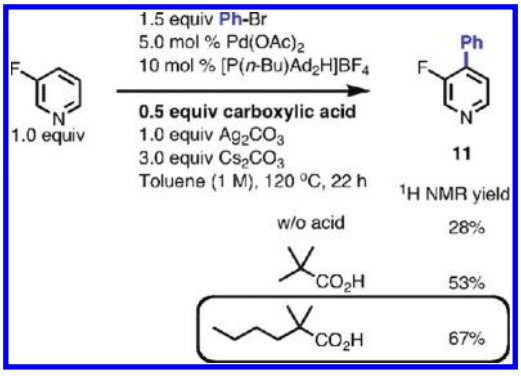
Next, we examined C−H arylation of pyridines containing other important electron-withdrawing groups. Fluorine is a frequently used substituent in both medicinal chemistry and organic materials design, owing to its unique electronic properties and relatively small size. 3-Fluoropyridine was examined first under the C−H arylation conditions, yielding 3-fluoro-4-phenylpyridine in 53% yield, where no other regioisomers were detected (Scheme 1).[14] The moderate yield is consistent with a lower electron-withdrawing effect of the fluoro substituent in comparison to the nitro group. The ongoing mechanistic studies in our group focused on C−H arylation of heteroarenes suggested the use of bulkier and more soluble carboxylates. This led

Table 3. Selective C−H Arylation: Nitropyridine Scope[a,b]



[a] Reaction conditions (0.5 mmol scale): 5.0 mol % $Pd(OAc)_2$, 7.5 mol % $[P(n\text{-}Bu)Ad_2H]I$, 1.5 equiv PhBr, 0.3 equiv pivalic acid, 1.0 equiv Ag_2CO_3, 3.0 equiv Cs_2CO_3, toluene (1.0 M), 120 °C, 22−24 h. [b] Yield of isolated product, otherwise noted. [c] The corresponding diarylation product was formed (in 5% yield along with the major product **2a**; 7% yield along with the product **4**). [d] The corresponding C-3 arylation product **5b** was also produced in 18% yield. [e] A total of 10 mol % $[P(n\text{-}Bu)Ad_2H]I$ was used. [f] Yield was determined by ^1H NMR.

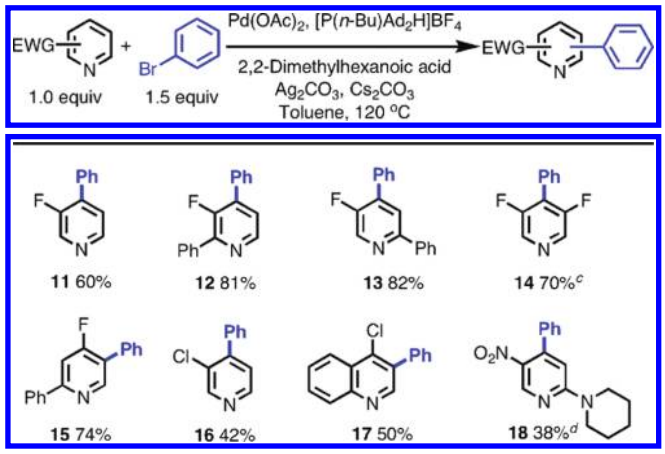
Scheme 1. Effect of Carboxylates on Selective C−H Arylation of 3-Fluoropyridine



to identification of 2,2-dimethylhexanoic acid as a superior ligand in comparison to pivalic acid; a significant improvement was achieved (67% NMR yield, Scheme 1, also see Supporting Information).

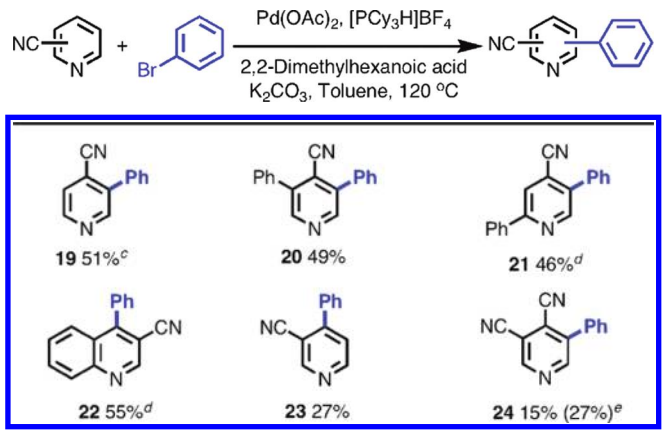
With the improved catalytic system in hand, we investigated less reactive pyridine substrates (than nitropyridines) of considerable synthetic potential (Table 4). For 3-fluoropyridines, C-4 arylated products were prepared with good yields and excellent regioselectivities (**11**−**14**). In addition, a 4-fluoropyridine substrate was arylated to give the 5-phenylpyridine product **15** in 74% yield and high regioselectivity. Importantly, the selective arylation can be extended to chloro derivatives, exemplified by 3-chloropyridine and 4-chloroquinoline (**16**, **17**).

Table 4. C−H Arylation of Relatively Unreactive Pyridines[a,b]



[a] Reaction conditions (0.5 mmol scale): 1.5 equiv PhBr, 5.0 mol % $Pd(OAc)_2$, 10 mol % $[P(n\text{-}Bu)Ad_2H]BF_4$, 1.0 equiv Ag_2CO_3, 3.0 equiv Cs_2CO_3, 0.5 equiv 2,2-dimethylhexanoic acid, toluene (1.0 M), 120 °C, 22−24 h. [b] Yield of isolated product, otherwise noted. [c] Acetic acid was used instead of 2,2-dimethylhexanoic acid (see Scheme 1). [d] Yield was determined by ^1H NMR; the product was inseparable from the corresponding starting material.

Table 5. C−H Arylation of Cyanopyridines[a,b]



[a] Reaction conditions (0.5 mmol scale): 5 mol % $Pd(OAc)_2$, 1.5 equiv PhBr, 10 mol % $[PCy_3H]BF_4$, 0.3 equiv 2,2-dimethylhexanoic acid, 3.0 equiv K_2CO_3, toluene (1.0 M), 120 °C, 22−24 h. [b] Yield of isolated product, otherwise noted. [c] A total of 1.5 equiv of the pyridine and 1.0 equiv of bromobenzene were used. The corresponding 3,5-diarylated product was also formed in 19% yield. [d] Yield was determined by ^1H NMR; the product was inseparable from the corresponding starting material. [e] PCy_3 was used instead of $[PCy_3H]BF_4$.

The adaptability of this catalytic system is illustrated by the following substrates. For example, 5-nitro-2-piperidinopyridine is a much less reactive substrate due to the amino substituent (electron-donating and catalyst-coordinating group). The effect of the carboxylate is dramatic in this case; the yield of C-4 arylated pyridine **18** was increased from 8% to 38% by replacing pivalic acid with 2,2-dimethylhexanoic acid (Table 4). Also, 3,5-difluoropyridine is a less reactive substrate than 3-fluoropyridine, which we ascribe to an increased steric hindrance at the position C-4 caused by two flanking fluorines (relative to the other substrates containing only one fluorine next to C-4). Exclusive C4-arylation was accomplished in a good yield (**14**,

Table 4) by using a smaller acetic acid co-catalyst (converted in situ to acetate ligand) instead of bulky 2,2-dimethylhexanoic or pivalic acid (from 50% to 70% yield improvement).

Furthermore, we found that the presence of a cyano group is not compatible with the catalytic protocol using silver carbonate, most likely due to the coordination of the cyano group with the silver salts. We overcame this limitation by reoptimizing the catalytic protocol in the absence of Ag_2CO_3 (Table 5). The silver-free conditions enabled C−H arylation of cyanopyridines with predictable regioselectivity. In particular, 4-cyanopyridine was a better substrate than the 3-cyano isomer (**19** versus **23**). The method is not effective for pyridines bearing ester or ketone functionality at C-3/C-4 positions.

In conclusion, we have developed a new catalytic protocol for highly selective C−H arylation of pyridines containing common and versatile electron-withdrawing substituents. The new protocol significantly expands the scope of catalytic azine functionalization as the excellent regioselectivity at the 3- and 4-positions well complements the existing methods for C−H arylation as well as the Ir-catalyzed borylation of pyridines. Another important feature of the new method is its flexibility to adapt to challenging substrates by a modification of the carboxylic acid ligand or the use of silver salts. The regioselectivity can be rationalized on the basis of the key electronic effects (repulsion between the nitrogen lone pair and polarized C−Pd bond and acidity of the C−H bond) in combination with steric effects (sensitivity to bulky substituents). Further exploration of new methods for C−H arylation of complex azines is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

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