C–H Activation

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Pd^0/PR_3-Catalyzed Arylation of Nicotinic and Isonicotinic Acid Derivatives**

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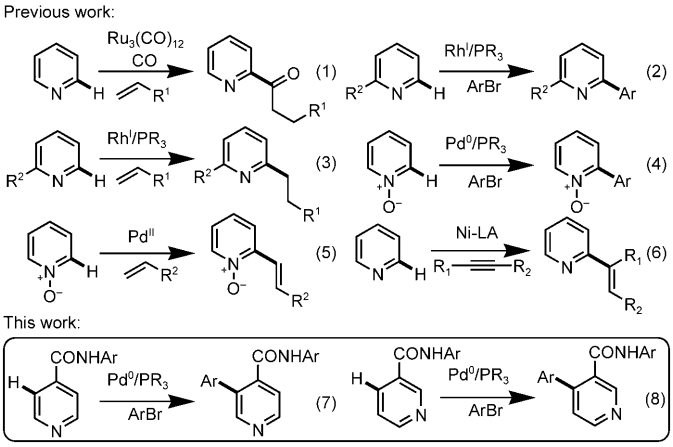
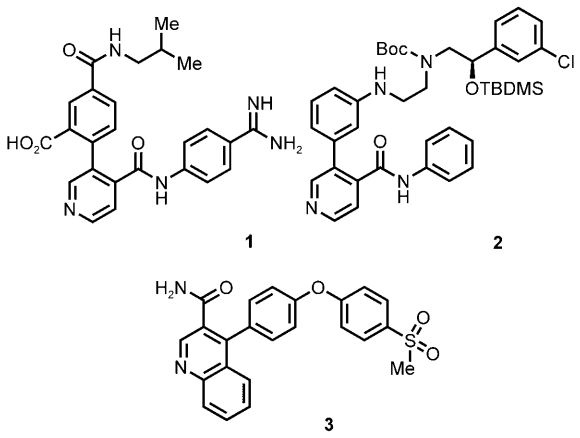
Owing to the prominence of azaheterocycles in natural products and pharmaceuticals,[1,2] diverse synthetic methods have been developed to construct substituted pyridines and quinolines.[3] Most syntheses of pyridine rings rely upon one of two approaches: condensation of amines and carbonyl compounds or cycloaddition reactions.[3] Further decoration of pyridine rings often involves transition-metal-catalyzed cross-coupling reactions of their halogenated analogues.[4] Therefore, the direct functionalization of pyridine C–H bonds using transition metal catalysis is an attractive alternative to typical cross-coupling reactions. A number of groups have reported the selective transition-metal-catalyzed direct functionalization at the 2-position of pyridine or pyridine *N*-oxides [Scheme 1, Eq. (1)–(6)],[5] and the intramolecular arylation at the 3- or 4-position of substituted pyridines.[6] The palladium-catalyzed intermolecular arylation of 2,3,5,6-tetrafluoropyridine[7] at the 4-position and the copper(I)-catalyzed arylation of 3-fluoropyridine at the 4-position have also been achieved.[8] Herein, we report the selective palladium(0)-catalyzed arylation reactions at the 3- or 4-positions of nicotinic and isonicotinic acids using a simple amide directing group [Scheme 1, Eq. (7), (8)]. Notably, this is the first example of a directing group activating the pyridine ring.[9]

Arylated derivatives of nicotinic and isonicotinic acids are widely used as building blocks for pharmaceuticals owing to their diverse biological activity.[10a–c] For instance, studies have shown that compounds **1**, **2**, and **3** are a serine protease inhibitor,[10a] an α,β-3-adrenoceptor agonist,[10b] and a liver X-receptor modulator for the treatment of LXR-mediated diseases,[10c] respectively (Scheme 2). We envision that the palladium-catalyzed functionalization of nicotinic and isonicotinic acids will be a powerful method for accessing a large family of biologically useful compounds. Our previous failed attempts to functionalize pyridine rings using directed C–H activation point to two inherent difficulties: first, the palladium-catalyzed C–H functionalization of pyridines is hampered by the poor electron density of the ring; second, the pyridyl group favorably competes with the directing groups for binding to the palladium catalysts. We recently reported the palladium(0)-catalyzed intermolecular arylation of sp^3 β-C–H bonds using a novel amide directing group.[11] This development, with the pioneering report on amide-directed arylation by Miura and co-workers[12] and other related work[13] prompted us to investigate the intermolecular arylation of pyridine at the 3- and 4-positions using an amide directing group and a suitable ligand via the $ArX/Pd^0/PR_3$ catalytic system.



Scheme 1. Direct arylation, alkylation or vinylation reactions of pyridine or pyridine *N*-oxide. LA = Lewis acid.



Scheme 2. Pharmaceutical drugs containing nicotinic or isonicotinic acid frameworks.

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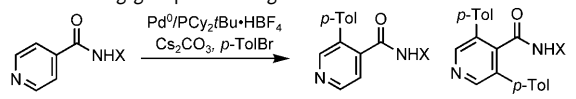
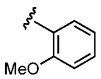
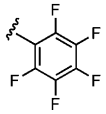
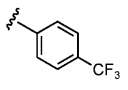
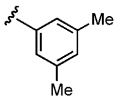
We were pleased to find that using our previously reported *N*-perfluorophenyl amide[11] as a directing group afforded monoarylated (14%) and diarylated (8%) products for isonicotinic acid (Table 1). During our preliminary screening of different directing groups, it occurred to us that the strongly electron-withdrawing *N*-perfluorophenyl amide group would render the pyridine ring more electronically deficient, thus retarding the reaction. Therefore, we investigated the effect that the different substituents on the phenyl ring of the amide directing group have on the arylation reaction. Of the directing groups tested, *N*-phenyl amide gave an excellent overall yield, albeit with poor selectivity for the monoarylated product. The *N*-2,6-dimethylphenyl amide group significantly improved the mono selectivity, but in lower yield. The *N*-3,5-dimethylphenyl amide protecting group significantly improved the yield of the monoarylated product to 87% (Table 1). This auxiliary was then used for further ligand screening (Table 2). We found that the PCy_2tBu-HBF_4 ligand reported by Fu and Netherton[14] was the most effective, giving the highest yield of 87% (Table 2, entry 4). It is worth noting that the use of freshly prepared phosphonium salts gave better yields.

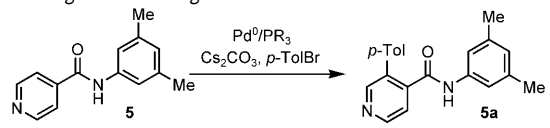
Table 1: Directing group screening.[a,b]



X =	OMe		
	a 0%	**a** 34%	**a** 38%
	b 0%	**b** 52%	**b** 2%
X =			
	a 2%	**a** 24%	**a** 12%
	b 0%	**b** 21%	**b** 11%
X =			
	a 14%	**a** 24%	**a** 87%
	b 8%	**b** 26%	**b** 4%

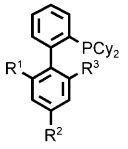
[a] Conditions: 0.2 mmol of substrate, 10 mol% $Pd(OAc)_2$, 10 mol% ligand, 3.0 equiv of Cs_2CO_3, 1.5 equiv of aryl bromide, 100 mg 3 Å M.S., 1 mL toluene, 130°C, N_2, 48 h. [b] Yield was determined by ^1H NMR analysis of the crude product using CH_2Br_2 as an internal standard.

Table 2: Ligand screening.[a,b]



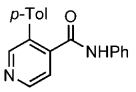
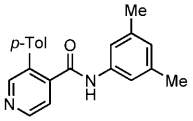
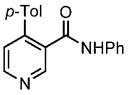
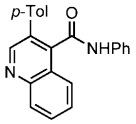
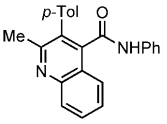
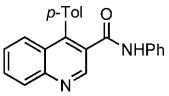
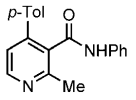
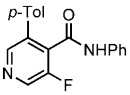
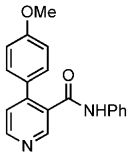
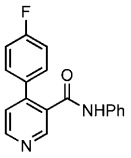
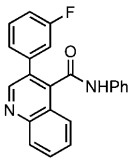
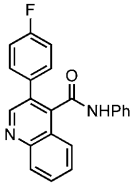
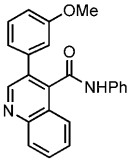
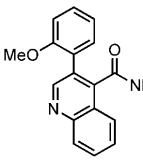
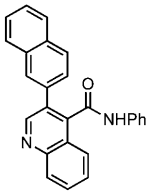
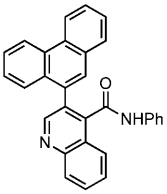
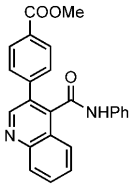
Entry	PR_3	Yield [%]	Entry	PR_3	Yield [%]
1	PPh_3	3	8	PCy_2(o-Tol)•BF_4	0
2	$PiPr_3$•BF_4	51	9	Cy-JohnPhos•BF_4	12
3	PCy_3•BF_4	71	10	MePhos•BF_4	10
4	PCy_2tBu•BF_4	87	11	DavePhos•BF_4	19
5	$PtBu_3$•BF_4	50	12	SPhos•BF_4	9
6	$PtBu_2Me$•BF_4	60	13	RuPhos•BF_4	15
7	PAd_2nBu•BF_4	64	14	XPhos•BF_4	8

[a] For reaction conditions, see: Table 1, footnote [a]. [b] Yield was determined by ^1H NMR analysis of the crude product using CH_2Br_2 as an internal standard.



Cy-JohnPhos: $R^1=R^2=R^3=H$
MePhos: $R^1=R^2=H$, $R^3=Me$
DavePhos: $R^1=R^2=H$, $R^3=NMe_2$
SPhos: $R^1=R^3=OMe$, $R^2=H$
RuPhos: $R^1=R^3=O$*i*Pr, $R^2=H$
XPhos: $R^1=R^2=R^3=$*i*Pr

Table 3: Arylation of nicotinic and isonicotinic derivatives.[a,b]

		
4a 27% mono **4b** 51% di	**5a** 86% mono trace di	**6a** 58% *para* **6b** 5% *ortho*
		
7a 89%	**8a** 63%	**9a** 50% *para* **9b** 14% *ortho*
		
10a 58%		**11a** 62%
		
6c 44% *para* trace *ortho*	**6d** 60% *para* **6e** 9% *ortho*	**7b** 82%
		
7c 88%	**7d** 94%	**7e** 71%
		
7f 92%	**7g** 68%	**7h** 83%

[a] Conditions: 0.2 mmol of substrate, 10 mol% $Pd(OAc)_2$, 10 mol% PCy_2tBu•HBF_4, 3.0 equiv of Cs_2CO_3, 1.5 equiv of aryl bromide, 100 mg 3 Å M.S., 1 mL toluene, 130°C, N_2, 48 h. [b] Yield of isolated product.

With these optimized conditions in hand, we began to test this reaction with commercially available nicotinic and isonicotinic acids (Table 3). Mono selective arylation of isonicotinic acid was successfully performed using the bulky *N*-3,5-dimethylphenyl amide as the directing group, whilst the simple *N*-phenyl amide give a mixture of monoarylated and diarylated products (**4a**, **4b**, and **5a**). This reaction provides a potentially efficient route to structurally diverse nicotinic acids that are highly desirable in medicinal chemistry. At present, a commercial route typically involves a lengthy amide-directed lithiation/iodination/cross-coupling reaction sequence.[15]

Interestingly, other substrates are also mono selectively arylated, even using only the simple *N*-phenyl amide directing group (**6a, 6c, 6d, 9a**), presumably because the two available *ortho*-C–H bonds have drastically different reactivities. Arylation of the more-hindered fluorinated substrates afforded lower yields (**8a, 11a**). Importantly, the aryl bromides could tolerate substituents such as fluorine atoms (**6d, 7b, 7c**), methoxy groups (**7d, 7e**), and ester groups (**7h**). Following completion of the reaction, the amide group could be converted to the corresponding acid by treatment with 4 M HCl (see the Supporting Information).[15]

In summary, we have developed a Pd^0/PR_3-catalyzed arylation procedure for nicotinic and isonicotinic acid derivatives, the first example of directed transition-metal-catalyzed C–H functionalizations of a pyridine ring at the 3- or 4-positions. This procedure allows us to rapidly generate a library of arylated nicotinic and isonicotinic acid derivatives that are of tremendous importance in medicinal chemistry.

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