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Pd(0)/PR₃–Catalyzed Arylation of Nicotinic and Isonicotinic Acid Derivatives

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Abstract

The first example of C–H functionalizations of pyridine rings at the 3- and 4-positions is developed using Pd(0)/PR₃/ArBr. This reaction provides a powerful method for the preparation of structurally diverse nicotinic and isonicotinic acids that are of tremendous importance in drug discovery.

Due 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 reactions of amines and carbonyl compounds or cycloaddition reactions.³ Another important method for the decoration of pyridines is the utilization of transition–metal catalyzed cross–coupling reactions with their corresponding halogenated skeletons, however, these reactions pose significant challenges due to the substrates' instability and difficult preparation.⁴ Therefore, direct functionalization of pyridine C–H bonds catalyzed by transition metals is an attractive alternative to typical cross–coupling reactions. Pioneering works by a number of groups described the development of transition metal–catalyzed direct functionalization of pyridine or pyridine *N*–oxides (eq 1–6) at the 2-positions.⁵ Herein we report Pd(0)–catalyzed selective arylation at 3 or 4–positions of nicotinic and isonicotinic acid–derived amides (eq 7, 8). Notably, various approaches developed thus far have not been able to address these significant challenges that are frequently encountered in drug discovery.⁶

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Supporting Information Available: Experimental procedure and characterization of all new compounds (PDF). This material is available free of charge *via* the Internet at <http://pubs.acs.org>.

Arylated derivatives of nicotinic and isonicotinic acids are widely used building blocks in pharmaceuticals due to diverse biological activity.^{7a-c} For instance, studies have shown that compound **1**, **2** and **3** are a serine protease inhibitor,^{7a} a β -3 adrenoceptor agonist,^{7b} and a liver X receptor modulator for the treatment of LXR-mediated diseases,^{7c} respectively (Scheme 2). We envision that Pd-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 ring using directed C-H activation points to two inherent difficulties: first, Pd-catalyzed C-H functionalization of pyridines is hampered by the electronic deficiency of the ring; second, pyridyl compete favorably with directing groups in binding to Pd catalysts. We have recently reported a Pd(0)-catalyzed intermolecular arylation of sp^3 β -C-H bonds using a novel amide directing group.⁸ This new development, as well as Miura's pioneering report on amide-directed arylation⁹ and other related work¹⁰ prompted us to test whether intermolecular arylation of pyridine at 3- and 4-positions could be achieved using the amide directing group and the ArX/Pd(0)/PR₃ catalytic system by identifying a suitable ligand.

We were excited to find that 14 % of *mono*- and 8 % of *di*-arylated products were obtained using our previously established *N*-(perfluorophenyl) amide⁸ as a directing group for isonicotinic acid (Table 1). During our preliminary screening of directing group, it occurred to us that the strongly electron-withdrawing *N*-(perfluorophenyl) amide group could make the pyridine ring more electronically-deficient, thus retarding the reaction. We thus began to alter the substituent on the phenyl ring of the amide directing groups. Among the directing groups tested, the *N*-phenyl amide directing group gave excellent turnover number albeit in poor *mono*-selectivity. The *N*-(2,6-dimethylphenyl) amide group significantly improved the *mono*-selectivity but gave a lower product yield. Further screening showed that the *N*-(3,5-dimethylphenyl) amide significantly improved yield of the *mono*-arylated to 87%. This optimal auxiliary was then used for further ligand screening (Table 2). We found that PCy₂*t*-Bu-HBF₄¹¹ is a superior ligand giving the highest yield (entry 4, Table 2).

With these optimized conditions in hand, we began to test this reaction with commercially available nicotinic and isonicotinic acids. *mono*-Selective arylation of isonicotinic acid was successfully performed using the bulky *N*-(3,5-dimethylphenyl) amide as the directing group, although the remaining C-H bonds at the 3-position display similar reactivity to the already arylated ones (**4a**, **4b**, and **5a**). This reaction provides a potentially efficient route for preparation of structurally diverse isonicotinic acids that are highly sought after in medicinal chemistry. Currently, a commercial route typically involves amide-directed lithiation/iodination/cross-coupling sequence.¹¹

Interestingly, other substrates are *mono*-selectively arylated with simple *N*-phenyl amide directing group (**6a**, **7a**, **8a**, **9a**), presumably because the two available *ortho*-C-H bonds are drastically different in reactivity. Arylation of the more hindered and fluorinated substrates afforded lower yields (**8a**, **11a**). We were pleased to find that the aryl bromides could tolerate substitutions such as fluorine, methoxy, and ester. After the reaction is completed, the directing group can be reconverted to the corresponding acids by treatment with 4N HCl under reflux.¹²

In summary, we have developed a Pd(0)/PR₃-catalyzed arylation protocol for nicotinic and isonicotinic acid derivatives, the first example of transition metal-catalyzed C-H functionalizations of pyridine ring at the 3- and 4-positions. This reaction protocol allows us to rapidly generate a library of arylated nicotinic and isonicotinic acid derivatives which are of tremendous importance in medicinal chemistry.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1. Direct arylation, alkylation and vinylation of pyridine and pyridine *N*-oxide

Scheme 2.
Drugs arising from nicotinic and isonicotinic acids.

Table 1

Directing group screening^{a,b}

X =	
OMe
a 0%	a 34%
b 0%	b 52%

	a 38%
	b 2%

	a 2%
	b 0%

	a 24%
	b 21%
X =

	a 12%
	b 11%

	a 14%
	b 8%

	a 24%
	b 26%

	a 87%
	b 4%

^a Conditions: 0.2 mmol of substrate, 10 mol% Pd(OAc)₂, 10 mol% ligand, 3.0 equiv of Cs₂CO₃, 1.5 equiv of aryl bromide, 100 mg 3 Å MS, 1 mL toluene, 130 °C, N₂, 48 h.

^b Yield was determined by ¹H NMR analysis of crude product using CH₂Br₂ as the internal standard.

Table 2

Ligand screening^a

entry	PR ₃	¹ H NMR yield (%)	entry	PR ₃	¹ H NMR yield (%)
1	PPh ₃	3	8	PCy ₂ (<i>o</i> -Tol)•HBF ₄	0
2	P ^{<i>i</i>} Pr ₃ •HBF ₄	51	9	Cy-JohnPhos•HBF ₄	12
3	PCy ₃ •HBF ₄	71	10	MePhos•HBF ₄	10
4	PCy ₂ ^{<i>i</i>} Bu•HBF ₄	87	11	DavePhos•HBF ₄	19
5	P ^{<i>t</i>} Bu ₃ •HBF ₄	50	12	SPhos•HBF ₄	9
6	P ^{<i>t</i>} Bu ₂ Me•HBF ₄	60	13	RuPhos•HBF ₄	15
7	PAd ₂ ^{<i>n</i>} Bu•HBF ₄	64	14	XPhos•HBF ₄	8

Cy-JohnPhos:
R¹=R²=R³=H

MePhos:
R¹=R²=H, R³=Me

DavePhos:
R¹=R²=H, R³=NMe₂

SPhos:
R¹=R³=OMe, R²=H

RuPhos:
R¹=R³=O^{*i*}Pr, R²=H

XPhos:
R¹=R²=R³=^{*i*}Pr

^aThe reaction conditions are identical to those described in Table 1.

Table 3

Arylation of Nicotinic and Isonicotinic Derivatives^{a,b}

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

^a Conditions: 0.2 mmol of substrate, 10 mol% Pd(OAc)₂, 10 mol% PCy₂t-Bu-HBF₄, 3.0 equiv of Cs₂CO₃, 1.5 equiv of aryl bromide, 100 mg 3Å MS, 1 mL toluene, 130 °C, N₂, 48 h.

^b Isolated yield.