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Efficient Synthesis of 2-Aryl-6-chloronicotinamides via PXPd2-Catalyzed Regioselective Suzuki Coupling

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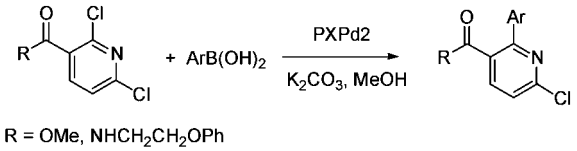
ABSTRACT



A short and convergent synthesis of 2-aryl-6-chloronicotinamides via regioselective Suzuki coupling of 2,6-dichloronicotinamide with aryl boronic acids is described. Regioselectivity was achieved by chelation of the palladium(0) species to an ester/amide group. The air-stable palladium catalyst PXPd2, when used in reagent-grade methanol with K_2CO_3 as the base, afforded the best regioselectivity and shortest reaction times among the catalysts screened.

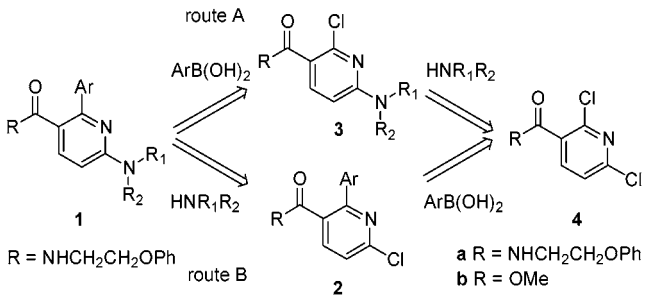
In the course of our investigations into suitable routes for the preparation of 6-amino-2-arylnicotinamide analogues **1**, we sought a convergent approach where a variety of 2-aryl and 6-amino groups could be installed late in the synthetic sequence. To our surprise, only a limited number of preparations of 6-amino-2-arylnicotinamides had been previously reported in the literature.[1] Moreover, these existing approaches were linear syntheses in which the aryl moieties were incorporated early in the synthesis, making it difficult to prepare a large number of analogues rapidly with variable substitution at the 2-position.

It was necessary for us to develop a new and more convergent method for the synthesis of 6-amino-2-arylnicotinamides. We envisioned two possible routes to nicotinamides **1** starting from readily available 2,6-dichloronicotinic acid derivatives **4a** or **4b** (Scheme 1).

Route A would incorporate the 6-amino group, via a nucleophilic aromatic substitution strategy and then employ a Suzuki coupling to install the 2-aryl moiety. Alternatively, the sequence could be reversed and route B would introduce the 2-aryl moiety through the Suzuki coupling and then subsequently incorporate the 6-amino group. The observed regioselectivity for reaction of **4a**/**4b** in either the S_NAr or Suzuki coupling would then be used to dictate which reaction sequence would be chosen.

Our initial efforts focused on the nucleophilic aromatic substitution sequence. Treating amide **4a** with phenylethyl-

Scheme 1. Two Possible Routes to Nicotinamide **1**



(1) (a) Gompper, V. R.; Helnemann, U. *Angew. Chem.* **1980**, *92*, 208−209. (b) Nuss, J. M.; Harrison, S. D.; Ring, D. B.; Boyce, R. S.; Johnson, K.; Pfister, K. B.; Ramurthy, S.; Seely, L.; Wagman, A. S.; Desai, M. Levine, B. H. WO 0220495.

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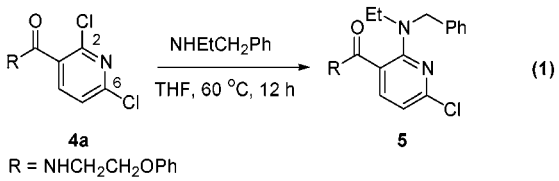
amine in THF at 60 °C gave 47% of the undesired, 2-amino pyridine **5**[2] as a single regioisomer along with 30% recovered starting material **4a** (eq 1).[3] Since the S_NAr strategy afforded the undesired regioisomer, we turned our attention to route B with Suzuki coupling.

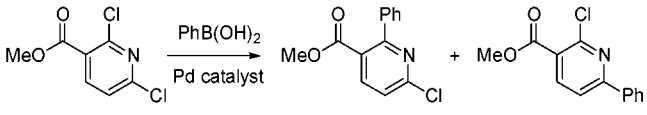


(1)

Methyl ester **4b** and phenyl boronic acid were initially chosen as a model system to examine the regioselectivity in the Suzuki coupling (Table 1). Refluxing **4b**, phenyl boronic acid, anhydrous K_2CO_3, and $Pd(Ph_3P)_4$ in THF for 16 h gave a 1:5 mixture of **2b**:**6b**, with the undesired 6-aryl isomer predominating (entry a). Similar results were observed when bidentate ligands[4] were employed (entries b and c). Presumably, the regioselectivity for the Suzuki coupling is dictated by the relative rates in oxidative addition for the two carbon−chloride bonds.[5] The undesired 6-aryl isomer predominated since oxidative addition of the catalytically active phosphine Pd(0) complex to the C6 carbon−chloride bond is less sterically encumbered and thus favored. We sought to improve the regioselectivity for the Suzuki coupling by taking advantage of the adjacent ester group to chelate the catalytically active Pd(0) species and direct its insertion into the C2 carbon−chloride bond.[6] Though Overman and Hallberg have taken advantage of coordinating functional groups to chelate transient Pd(II) complexes and direct the regioselectivity in a variety of Heck reactions,[7] chelation of the Pd(0) species to direct the oxidative addition step in a palladium-catalyzed process has not been previously reported. To promote chelation of the ester and the Pd(0) species, we reasoned that reduction of the ratio of ligand to palladium, thereby making the palladium more coordinatively unsaturated, might prove to be successful. Hartwig's mechanistic studies[8] on Pd/P(*t*-Bu)$_3$-catalyzed aminations revealed that a 1:1 ratio of Pd:P(*t*-Bu)$_3$ was optimal, thus invoking a monophosphine Pd(0) complex as the catalytically active species. Indeed, treatment of **4b**, phenyl boronic acid, and KF, with $Pd_2(dba)_3$/[HP(*t*-Bu)$_3$]BF_4[9] in THF at 50 °C, afforded a 1.7:1 mixture of **2b**:**6b**, favoring the desired 2-aryl regioisomer (entry d). Use of $Pd(PCy_3)_2Cl_2$ as the catalyst gave results almost identical to those seen with $Pd_2(dba)_3$/[HP(*t*-Bu)$_3$]BF_4, suggesting the active species was most likely also a 1:1 ratio of Pd:PCy_3 complex (entry e). Even though the bulky, electron-rich trialkylphosphines provided the desired C2 aryl regioisomer as the major product, we sought a catalyst system that did not require vigorous degassing and therefore would be more amenable to parallel synthesis. Recently, Li[10] demonstrated that air-stable 1:1 Pd/phosphinous acid complexes such as POPd2[11] and PXPd2[12] are efficient precatalysts for the Suzuki coupling of aryl chlorides. Though the Suzuki coupling with POPd2 (entry f) led to only a trace amount of product, PXPd2 in refluxing methanol[13] (entry g) gave a 2.5:1 mixture of **2b**:**6b**. In addition to providing the best regioselectivity in the Suzuki coupling reactions, the PXPd2 system provided an additional advantage in that the coupling reactions could be run open to the air without degassing the reaction mixture.

Encouraged by the preliminary results for the PXPd2-catalyzed reaction, we chose to examine the effect of solvent and base on the regioselectivity and reactivity of the coupling (Table 2). In fact, the Suzuki coupling proceeded rapidly even at room temperature, completely consuming the phenyl boronic acid within 1 h (entry a). When anhydrous methanol was used, the reaction was more sluggish, though the

Table 1. Regioselectivity for Suzuki Coupling with Different Palladium Catalysts[a]



entry	Pd source (mol %)	solvent	**2b**:**6b**[b]
a	$Pd(PPh_3)_4$ (5)	THF	1:5[c]
b	$Pd(dppf)Cl_2$ (5)	THF	1:2.9
c	$Pd(OAc)_2$ (3)/(*o*-biphenyl)PCy_2 (4.5)[d]	THF	1:1.8
d	$Pd_2(dba)_3$ (1.5)/[HP(*t*-Bu)$_3$]BF_4 (3)[e]	THF	1.7:1
e	$Pd(PCy_3)_2Cl_2$ (5)	THF	1.7:1
f	POPd2 (1)	MeOH	trace
g	PXPd2 (1)[f]	MeOH	2.5:1

[a] General reaction conditions: 1.0 equiv of **4b**, 1.0 equiv of phenyl boronic acid, 3.0 equiv of K_2CO_3, reflux, 16 h. [b] Ratio determined by reverse-phase analytical HPLC. [c] Ratio determined by ^{1}H NMR, since **2b** and Ph_3PO overlapped in the HPLC. [d] KF. [e] KF, 50 °C. [f] Reaction time: 30 min.

(2) Regiochemistry was confirmed by NOE experiments. The amide proton gave NOE when the peaks for CH_2CH_3 or CH_2Ph were irradiated.

(3) Hirokawa, Y.; Horikawa, T.; Kato, S. *Chem. Pharm. Bull*. **2000**, *12*, 1847. Hirokawa obtained a mixture of regioisomers upon addition of amines to 2,6-dichloronicotinic acid methyl ester, with the 2-amino regioisomer predominating.

(4) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158. The (*o*-biphenyl)PCy_2 ligand can be thought of as a bidentate ligand since Buchwald proposed participation of the π-system of the ortho aromatic with the unoccupied d-orbital on palladium.

(5) However, Hartwig has shown that the oxidative addition can be reversible. Roy, A. H.; Hartwig, J. F. J. *J. Am. Chem. Soc*. **2001**, *123*, 1232.

(6) Precoordination of Pd(0) species to the π-system of sp^2 carbon-halide bonds has been proposed.

(7) (a) Madin, A.; Overman, L. E. *Tetrahedron Lett*. **1992**, *33*, 4859. (b) Nilsson, P.; Larhed, M.; Hallberg, A. *J. Am. Chem. Soc*. **2003**, *125*, 3430. (c) Olofsson, K.; Sahlin, H.; Larhed, M.; Hallberg, A. *J. Org. Chem*. **2001**, *66*, 544.

(8) (a) Alcazar-Roman, L. M.; Hartwig, J. F. *J. Am. Chem. Soc*. **2001**, *123*, 12905. (b) Hartwig, J. F.; Kawatsura, M.; Haack, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem*. **1999**, *64*, 5575.

(9) Netherton, M. R.; Fu, G. C. *Org. Lett*. **2001**, *3*, 4295.

(10) (a) Li, G. Y.; Zheng, G.; Noonan, A. F. *J. Org. Chem*. **2001**, *66*, 8677. (b) Li, G. Y. *Angew. Chem., Int. Ed*. **2001**, *40*, 1513. (c) Li, G. Y. *J. Org. Chem*. **2002**, *67*, 3643.

(11) POPd2, CAS #386706-32-7, was commercially available from CombiPhos Catalysts, Inc. http://www.combiphos.com.

(12) PXPd2, CAS 386706-33-8, was available exclusively from CombiPhos Catalysts, Inc. http://www.combiphos.com.

(13) Methanol and ethanol are preferred solvents with the Pd/phosphinous acid complexes. Li, G. Y. Personal communication.

Table 2. Solvent and Base Effects on PXPd2-Catalyzed Suzuki Coupling[a]

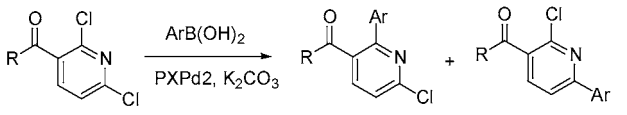
entry	solvent	base	**2b**:**6b**[c]
a	MeOH (reagent)[b]	K_2CO_3	1.8:1
b	MeOH (anhydrous)	K_2CO_3	2.7:1
c	MeOH (reagent)	KF	1.4:1
d	MeOH (reagent)	Cs_2CO_3	hydrolysis of ester
e	THF, 65 °C	K_2CO_3	1.8:1
f	toluene	K_2CO_3	1.8:1
g	DMF, 65 °C	K_2CO_3	1.1:1

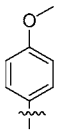
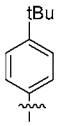
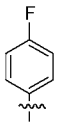
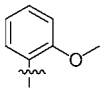
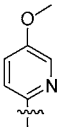
[a] General reaction conditions: 1.0 equiv of **4b**, 1.0 equiv of phenyl boronic acid, 3.0 equiv of base, room temperature, 16 h, 1% catalyst. [b] Reaction time: 30 min. [c] Ratio determined by reverse-phase analytical HPLC.

regioselectivity was improved compared with results obtained in the identical reaction carried out in reagent-grade methanol (entry b). This observation suggested that trace amounts of water present in standard reagent-grade methanol might play a role in accelerating the reaction. This acceleration might possibly be a result of solvolytic transformation of PXPd2 to a more active catalyst such as that seen in the examples reported by Bedford[14] or due to more efficient solubilization of the inorganic base. Switching the base to potassium fluoride afforded a similar ratio of regioisomers, though the reaction proceeded at a slower rate (entry c). Replacement of potassium carbonate with cesium carbonate resulted in rapid hydrolysis of the methyl ester to the corresponding acid, and only a trace amount of product was observed by HPLC (entry d). Finally, with other solvents such as THF, DMF, and toluene, the reactions proceeded more slowly than those with methanol and therefore required elevated temperatures and/or prolonged reaction times (entries e−g).

Having identified a catalyst system that provided the desired regioselectivity, we turned our attention to the target substrate **4a** for the Suzuki coupling. If the observed improvement in regioselectivity is in fact attributable to chelation of the ester group to the Pd(0) species, then amide **4a** with enhanced coordinating ability relative to the ester should lead to even greater regioselectivity. Indeed, subjecting amide **4a** to the optimized Suzuki conditions[15] led to a

Table 3. Suzuki Coupling of 2,6-Dichloronicotinamide Catalyzed by PXPd2[a]



entry	Ar	**2a** : **6a**	yield of **2a**[b]
a		9 : 1	61%
b		8 : 1	58%
c		15 : 1	60%
d		5 : 1	51%[c]
e		**6a** not observed	19%[d]
f		4 : 1	53%[c]

[a] General reaction conditions: 1.0 equiv of **4b**, 1.2 equiv of phenyl boronic acid, 3.0 equiv of K_2CO_3, 55 °C, 1 h, 2% catalyst. [b] Isolated yields after purification. [c] Based on 10−20% recovered starting material. [d] EtOH was used as solvent.

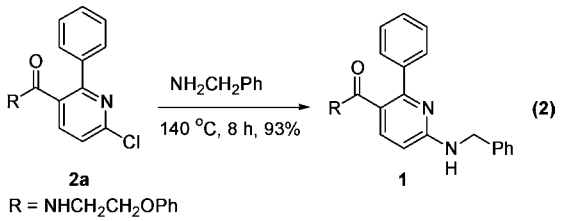
9:1 mixture of 2-aryl:6-aryl isomer (Table 3, entry a). Amide **4a** was also found to be less reactive toward Suzuki coupling than ester **4b** but at the same time more prone to nucleophilic substitution by methanol or water at the 2-position. As a result, the coupling reactions generally gave greater yields with heating and higher catalyst loading (2%). This method was subsequently applied to the preparation of a variety of 2-aryl-6-chloronicotinamides **2a** (Table 3). This optimized combination of directing group, catalyst, and reaction conditions worked consistently well with both electron-rich (entries b and c) and electron-deficient (entries d and f) boronic acids,

(14) Bedford, R. B.; Hazelwood, S. L.; Limmert, M. E.; Brown, J. M.; Ramdeehul, S.; Cowley, A. R.; Coles, S. J.; Hursthouse, M. B. *Organometallics* **2003**, *22*, 1364.

(15) Representative experimental procedures for the preparation of compounds **2a** and **6a** are as follows: amide **4a** (228 mg, 0.73 mmol), boronic acid (107 mg, 0.88 mmol), and K_2CO_3 (302 mg, 2.19 mmol) were mixed in MeOH (1.5 mL), and PXPd2 (10.5 mg, 0.015 mmol) was added. The reaction mixture was heated at 55 °C for 1 h, after which the reaction mixture was concentrated and partitioned between water (10 mL) and EtOAc (10 mL). The aqueous layer was extracted again with EtOAc (2 × 10 mL), the combined EtOAc layers were dried over $MgSO_4$, filtered, and condensed to yield a yellow semisolid. Reverse-phase HPLC purification provided compounds **2a** (158 mg, 61%), **6a** (18 mg, 7%), and bis-phenyl product (55 mg, 19%), all as a white solid. The structures of these three compounds were confirmed by HMQC experiments. **Compound 2a.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.53 (dd, J = 5.4, 10.4 Hz, 2H), 3.73 (t, J = 5.0 Hz, 2H), 5.81 (brs, 1H), 6.61 (d, J = 7.9 Hz, 2H), 6.88 (t, J = 7.4 Hz, 1H), 7.12−7.22 (m, 5H), 7.26 (d, J = 8.1 Hz, 1H), 7.53 (d, J = 7.1 Hz, 2H), 7.88 (d, J = 8.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.8, 66.2, 114.8, 121.6, 123.0, 129.0, 129.2, 129.8, 130.1, 130.2, 137.9, 140.4, 152.4, 157.2, 158.6, 167.8. **Compound 6a.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.84 (dd, J = 5.5, 10.4 Hz, 2H), 4.12 (t, J = 5.2 Hz, 2H), 6.86 (dd, J = 0.9, 8.7 Hz, 2H), 6.91 (t, J = 7.4 Hz, 1H), 7.11 (brs, 1H), 7.18−7.25 (m, 2H), 7.36−7.43 (m, 3H), 7.53 (d, J = 8.0 Hz, 1H), 7.93−7.96 (m, 2H), 8.13 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.2, 66.8, 115.0, 119.2, 121.7, 127.6, 128.9, 129.3, 130.0, 130.7, 137.1, 141.3, 147.3, 158.8, 159.6, 165.1. **Bis-phenyl Compound.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.59 (dd, J = 5.4, 10.4 Hz, 2H), 3.74 (t, J = 5.0 Hz, 2H), 5.99 (brs, 1H), 6.63 (d, J = 7.9 Hz, 2H), 6.90 (t, J = 7.4 Hz, 1H), 7.18−7.27 (m, 5H), 7.41−7.45 (m, 3H), 7.61 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.1 Hz, 1H), 7.94−7.96 (m, 2H), 8.18 (d, J = 8.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.0, 66.0, 114.8, 119.9, 121.6, 127.9, 129.0, 129.3, 129.4, 129.8, 130.1, 130.6, 137.4, 137.8, 139.7, 156.1, 158.4, 158.5, 168.8.

with isolated yields all above 50%. When a sterically hindered boronic acid such as 2-methoxyphenyl boronic acid was used (entry e), the reaction was sluggish even in refluxing reagent-grade ethanol and the yield was lower due to competing reaction of the 2-chloro group with water.

The synthesis of target 6-amino-2-arylnicotinamide **1** was accomplished by treatment of **2a** with amines at 140 °C as exemplified in eq 2.



2a **1** (2)

In summary, a novel method using the ester/amide moiety to direct the insertion of the catalytically active Pd(0) species to the C2 carbon−chloride bond to control the regioselectivity in Suzuki couplings of 2,6-dichloronicotinamides was discovered. The air-stable palladium catalyst PXPd2 was found to catalyze the Suzuki coupling of 2,6-dichloronicotinamide with aryl boronic acids to give the 2-aryl-6-chloronicotinamides **2a** in moderate to good yields. This methodology offers a short (three steps) and convergent synthesis 6-amino-2-arylnicotinamides from commercially available 2,6-dichloronicotinic acid. Furthermore, this method could be easily adapted to high-throughput parallel synthesis.

Acknowledgment. We thank Ms. Yixin Li for performing NMR experiments on compounds **2b** and **6b**. We are thankful to Dr. Lawrence Hamann for valuable suggestions and Drs. Ruth Wexler and Karnail Atwal for helpful comments.

Supporting Information Available: Experimental procedure and characterization for compounds **1**, **2b**, **6b**, and **5**, entries a−f in Table 3. This material is available free of charge via the Internet at http://pubs.acs.org.

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