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Catalytic Amination of 2-Substituted Pyridines with Hydrazine Derivatives

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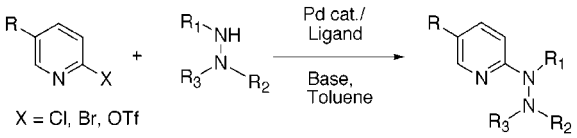
ABSTRACT



Protected pyridylhydrazine derivatives were prepared in a one-step palladium-catalyzed amination reaction using chelating phosphine ligands. 2-Pyridyl chlorides, bromides, and triflates were effective electrophiles in these reactions. Di-*tert*-butyl hydrazodiformate was an excellent hydrazine substrate, and the resulting products were deprotected under mild conditions. Catalytic amination provides a direct route to protected bifunctional hydrazinopyridine linkers that are suitable for metal-bioconjugate syntheses.

Hydrazinopyridines are important compounds for the synthesis of triazines and substituted pyridines as agrochemicals and pharmaceuticals.[1−4] 2-Pyridylhydrazines are particularly interesting synthetic targets as a result of their efficiency as ligands for a variety of metal complexes and potential applications in nuclear medicine.[5−9] Direct displacement of 2-chloropyridines with hydrazine hydrate has been used for the synthesis of 2-pyridylhydrazine derivatives, and typical reaction conditions involve heating in highly corrosive, concentrated 85% hydrazine hydrate.[10,11] These conditions also generate the powerful reducing agent diimide, which rapidly reduces alkenes and alkynes.[12] Our interest in rhenium- and technetium-labeled biomolecules as potential radiopharmaceuticals[13−15] led us to investigate metal-catalyzed amination as a possible alternative method for preparing protected 2-pyridylhydrazine derivatives that would be compatible with multistep syntheses. Catalytic amination of aryl halides and sulfonates has become an important method for preparing anilines and other arylamines.[16−23]

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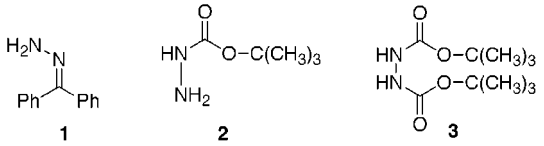
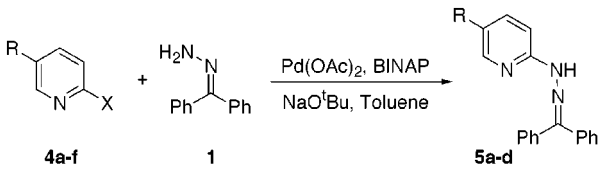
Chelating phosphine ligands enable Pd-catalyzed C−N bond formation of bromopyridines with alkyl and arylamines,[24] and sterically hindered monodentate biphenylphosphine ligands are useful for coupling chloropyridines.[20] Other examples of halopyridyl aminations catalyzed by Pd[25−31] and Ni[32−37] have been reported. There are relatively few examples of catalytic amination reactions with hydrazine derivatives. The palladium-catalyzed amination of aryl halides with benzophenone hydrazone **1** has recently been reported.[20,38−40] The protected hydrazine *tert*-butylcarbazate **2** has also been used as a substrate for Pd-catalyzed aminations.[41] Herein, we present the results of a comprehensive investigation of the catalytic amination of 2-pyridyl chlorides, bromides, and triflates with hydrazine substrates, **1**−**3**, and provide a convenient general methodology for the synthesis of protected 2-hydrazinopyridine derivatives.



The standard conditions[38−40] for the N-arylation of **1** using 2 mol % $Pd(OAc)_2$, 2 mol % of the chelating ligand 2,2′-bis(diphenylphosphandanyl)-1,1′-binaphthyl (BINAP), and sodium *tert*-butoxide base in toluene were used for the pyridyl substrates **4a**−**f** as shown in Table 1. The hydrazone **1** was used as the limiting reagent to facilitate chromatographic purification of the products **5a**−**d**. 2-Chloropyridine **4a** was an effective substrate under these conditions. The reaction with 2-bromopyridine **4b** was faster and gave improved yields, paralleling the normal relative reactivity of aryl halides. Changing the chelating ligand from BINAP to 1,1′-bis(diphenylphosphanyl) ferrocene (DPPF) in these cases resulted in significantly lower yields. The yields were also lower when $Pd_2(dba)_3$ was used as catalyst precursor. No reaction occurred using the catalytic system $Ni(COD)_2$/DPPF/NaO^{t}Bu.[32] Selective amination of the 2-position was observed for the Pd/BINAP-catalyzed reaction of 2,5-dibromopyridine **4c** with **1** in very good yield.

Table 1. Coupling of 2-Pyridyl Systems with **1**[a]



4a-f **1** **5a-d**

entry	R	X	product[b]	time (h)	yield (%)
1	H	Cl, **4a**	**5a**	16	70
2	H	Br, **4b**	**5a**	8	95
3	Br	Br, **4c**	**5b**	6	80
4	$CO_2C_6Cl_5$	Cl, **4d**	**5c**	14	42
5	H	OTf, **4e**	**5a**	16	62
6	$CO_2C_2H_5$	OTf, **4f**	**5d**	16	72

[a] All reactions were run with 2 mol % of $Pd(OAc)_2$, 2 mol % of BINAP, 0.8 equiv of **1**, 1.4 equiv of Na O^{t}Bu, and 1 equiv of pyridine derivative, at 100 °C with 2 mL of toluene for 1 mM substrate. [b] All products were characterized by ^{1}H and ^{13}C NMR and HRMS spectroscopy methods. [c] Yields of isolated product.

Activated ester derivatives of 6-hydrazidonicotinic acid are used as bifunctional labeling agents and are important synthetic compounds.[5−8] The Pd/BINAP-catalyzed amination of pentachlorophenyl ester analogue **4d** with **1** gave a moderate yield of the desired compound **5c**. We were interested in the possible catalytic amination of pyridyl triflates, since these compounds can be easily prepared from the hydroxypyridines[42] and aryl triflates have been shown to be effective substrates for Pd-catalyzed amination with anilines and alkylamines.[43−46] The direct coupling of pyridyl triflates with amines is known;[47,48] however, we observed no direct reaction between **1** and **4e** after heating a toluene solution at 100 °C for 24 h. The pyridyl triflate **4e** was converted to the hydrazone **5a** by the Pd/BINAP catalyst. The yield of **5a** from the triflate **4e** was lower than that of the halogenated substrates but comparable to the amination of aryl triflates catalyzed by $Pd(OAc)_2$/BINAP.[43] The 2-pyridyl triflates were stable under the basic reaction conditions, no competing cleavage to hydroxypyridine was

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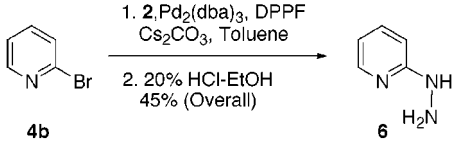
observed, and excess starting material was recovered at the end of the reaction. The presence of an ethyl ester substituent in the 5-postion **4f** resulted in a mild activation and improved the yield of the hydrazone product **5d**. The proposed mechanistic model for N-arylation involves oxidative addition as the rate-determining step.[49] Coordination of pyridine has been shown to inhibit the Pd(0)/P(*o*-tolyl)$_3$-catalyzed amination of aryl bromides but does not displace bisphosphines.[24] The electron-withdrawing ester substituent decreases the ligating ability of the pyridine further to enhance the rate of oxidative addition and also is expected to facilitate the subsequent reductive elimination that produces the C−N bond.

Scheme 1. Coupling of 2-Bromopyridine **4b** with **2**



4b **6**

Electron-deficient aryl bromides and 4-nitro-2-bromopyridine have been shown to undergo Pd/DPPF amination with the protected hydrazine derivative *tert*-butylcarbazate **2**.[41] We observed that 2-bromopyridine was coupled with **2** using 8 mol % Pd$_2$(dba)$_3$, 12 mol % DPPF, and Cs_2CO_3 in toluene. The N-pyridyl products underwent decomposition during attempted purification by silica gel chromatography. 2-Hydrazinopyridine **6** was obtained in an overall yield of 45% from 2-bromopyridine **4b** by hydrolysis of the crude reaction mixture using 20% HCl/EtOH, followed by neutralization and extraction with ether. No reaction of **2** with 2-bromopyridine was observed using the catalytic system Pd(OAc)$_2$/BINAP/NaO^{t}Bu that was effective with the hydrazone **1**, and no reaction occurred using Ni catalysts with various chelating ligands.[32−37]

The limited success we observed for coupling pyridyl substrates with **2** led us to investigate the possibility of Pd-catalyzed amination using the symmetrical hydrazine derivative di-*tert*-butyl hydrazodiformate **3**, Table 2.

Catalytic N-arylations with protected amines such as carbamates have generally been difficult,[46,50] and no examples of catalytic C−N bond formation using **3** have been reported. Using 2 mol % Pd$_2$(dba)$_3$/3 mol % DPPF/Cs_2CO_3 in toluene, the reaction of 2-chloropyridine was very slow (entry 1). Increasing the catalyst to 8% decreased the reaction time and improved the yield significantly (entry 2). The more reactive 2-bromopyridine gave good yields using 2−4 mol % Pd; however, the optimum results were obtained using 8 mol % of Pd (entry 5). 2,5-Dibromopyridine **4c** underwent selective coupling at the 2-position to produce **7b** in high yield. The Pd/BINAP catalyst used for the synthesis of hydrazones **5a**−**d** was not successful with **3**.

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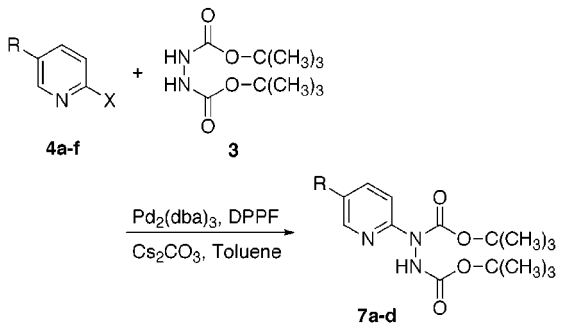
Table 2. Coupling of 2-Pyridyl Systems with **3**[a]



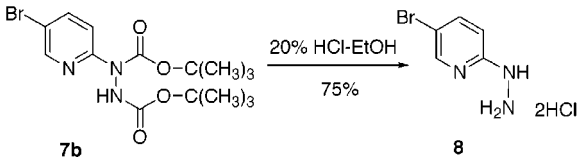
4a-f **3** **7a-d**

entry	R	X	Pd/DPPF (mol %)	time (h)	yield[b,c] (%)
1	H	Cl, **4a**	2/3	16	**7a**, 30
2	H	Cl, **4a**	8/12	16	**7a**, 70
3	H	Br, **4b**	2/3	16	**7a**, 61
4	H	Br, **4b**	4/6	8	**7a**, 61
5	H	Br,**4b**	8/12	8	**7a**, 85
6	Br	Br, **4c**	2/3	10	**7b**, 73
7	Br	Br, **4c**	8/12	6	**7b**, 85
8	$CO_2C_6Cl_5$	Cl, **4d**	8/12	14	**7c**, 45
9	H	OTf, **4e**	8/12	16	**7a**, 0
10	$CO_2C_2H_5$	OTf, **4f**	8/12	16	**7d**, 57

[a] All reactions were run with specified mol % Pd/DPPF, 0.8 equiv of **3**, 1 equiv of Cs_2CO_3, and 1 equiv of pyridine derivative at 100 °C with 2 mL of toluene for 1 mM substrate. [b] All products were characterized by ^{1}H and ^{13}C NMR and HRMS spectroscopy methods. [c] Yields of isolated product.

The pentachlorophenyl ester derivative of 2-chloropyridine **4d** was coupled with **3** by Pd/DPPF to produce **7c** in moderate yield. The unactivated pyridyl triflate **4e** did not react under these conditions. Efforts to couple this substrate using the catalyst ligand combination Pd(OAc)$_2$/(*o*-biphenyl)-PCy$_2$, which is effective for aryl triflates,[20] were also unsuccessful. The introduction of an ethyl ester improved the reactivity of the pyridyl triflate **4f**, such that **7d** was formed in moderate yield using Pd/DPPF.

Scheme 2. Hydrolysis of the ^{t}BOC-Protected Hydrazine **7b**



7b **8**

These results demonstrate that Pd-catalyzed aminations with **1** and **3** are efficient methods for the preparation of protected hydrazone and *tert*-butyl carbamate (^{t}BOC) protected hydrazine derivatives. To determine the relative ease of deprotection, we treated **5b** and **7b** with 20% HCl/EtOH. Under these conditions, the ^{t}BOC protecting groups of **7b** were completely hydrolyzed to furnish hydrazine dihydrochloride salt **8** in 75% yield. In contrast, the hydrazone **5b** was stable under these conditions.

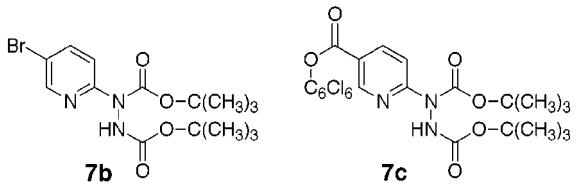


Figure 1. Protected bifunctional hydrazinopyridines.

These results illustrate the reactivity of 2-pyridyl electrophiles in Pd-catalyzed amination reactions and provide convenient methods for the synthesis of protected 2-pyridyl hydrazines. The reactions were successful using 2-pyridyl chlorides and triflates, although the best results were obtained with the bromides. The optimum reaction conditions for the pyridyl substrates with the hydrazine derivative **3** required a relatively high catalyst loading. The protected hydrazine derivative **3** was an excellent substrate for C−N bond formation and should be useful for the synthesis of a wide variety of hydrazines via catalytic amination. The hydrolysis of the ^{t}BOC protecting groups in **7a**−**d** is considerably easier than for the hydrazone derivatives **5a**−**d**. The catalytic amination of pyridyl electrophiles with **3** provides a direct route to protected bifunctional hydrazinopyridine linkers **7b** and **7c**, which are suitable for metal-bioconjugate syntheses. Efforts to further utilize these derivatives for the synthesis of radiopharmaceuticals are currently in progress.

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Supporting Information Available: Experimental procedures for **5a**−**d** and **7a**−**d** and analytical data for the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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