The Synthesis of Aminopyridines: A Method Employing Palladium-Catalyzed Carbon−Nitrogen Bond Formation

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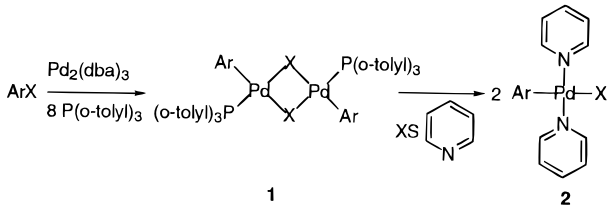
Aminopyridines are important in various fields of chemistry. They have been used as acyl transfer reagents in organic chemistry[1,2] and as ligands in inorganic and organometallic chemistry.[3−7] Additionally, aminopyridine derivatives have been used as fluorescent dyes[8,9] and are biologically important as central nervous system stimulants.[10] Current methods for the preparation of aminopyridines generally involve nucleophilic aromatic substitution of a pyridine substrate. However, these methods typically produce only modest yields of the desired aminopyridine, require activated substrates, and often require harsh reaction conditions.[11−15]

Palladium(0)/P(*o*-tolyl)$_3$ complexes are effective catalysts for the cross-coupling of aryl bromides and aminostannanes and for the cross-coupling of aryl halides and amines in the presence of sodium *tert*-butoxide.[16−18] Unfortunately, attempts to extend this protocol to the amination of bromopyridines were unsuccessful. It has been shown that pyridine inhibits the Pd(0)/P(*o*-tolyl)$_3$-catalyzed amination of aryl bromides[19] and also displaces a P(*o*-tolyl)$_3$ ligand from key catalytic intermediates such as the oxidative addition product **1** to form complexes such as bis(pyridyl) derivative **2** (Scheme 1).[20]

We have recently reported a palladium-catalyzed procedure for the cross-coupling of aryl bromides and primary amines that employed chelating bis-(phosphine) ligands.[21] The efficiency of this system is presumably due to the ability of the chelating phosphine ligand to inhibit side reactions such as β-hydride elimination from an amidopalladium intermediate and the formation of bis-(amine) complexes that lead to products of hydrodebromination. We have found that this catalyst system is also effective with pyridine-containing substrates *for a different reason*. We have found that the chelating bis-(phosphine) does not undergo ligand exchange with excess pyridine, and consequently, the formation of bis-(pyridine) complexes, which terminate the catalytic cycle, is prevented.[22a] Here, we report the use of these chelating bis(phosphine)/Pd complexes as catalysts for the amination of halopyridines to form 2-, 3-, or 4-substituted aminopyridines under mild conditions and in good to excellent yields. This work constitutes the first example of a palladium-mediated amination of haloheteroaromatic substrates.

Scheme 1



1 **2**

Mixtures of the chelating bis-(phosphine) ligand 1,3-bis(diphenylphosphino)propane (dppp) and $Pd_2(dba)_3$ generated an effective catalyst for coupling 2-bromopyridine with primary amines that do not contain α-hydrogens and with secondary amines (Table 1, entries 1−3). For example, the reaction of 2-bromopyridine with *N*-benzylmethylamine (1.2 equiv) and sodium *tert*-butoxide (1.4 equiv) employing a catalytic mixture of $Pd_2(dba)_3$ (2 mol %) and dppp (4 mol %) in toluene at 70 °C for 3 h gave, after workup and purification, 2-(*N*-benzyl-*N*-methylamino)pyridine in 86% yield (Table 1, entry 1). However, this catalyst system was not completely general. Neither 3-bromopyridine nor primary amines that contained α-hydrogen atoms were effectively cross-coupled.[23] In contrast to the dppp-derived catalyst, the catalyst generated from $Pd_2(dba)_3$ and (±)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl [(±)−BINAP] was generally effective for the cross-coupling of a wide variety of substrates including that of 3-bromopyridine with both primary and secondary amines (Table 1, entries 5−9). In the case of unbranched primary amines such as *n*-hexylamine, both the mono- or diarylated amine could be obtained selectively. For example, the procedure employing a 3:1 ratio of *n*-hexylamine:2-bromopyridine produced the monoarylated product in 74% yield (Table 2, entry 1). In contrast, the procedure which used a 2-fold excess of 2-bromopyridine relative to amine, gave the diarylated compound in 71% yield (Table 2, entry 2). Additionally, *trans*-1,2-diaminocyclohexane, upon treatment with excess 2-bromopyridine (3 equiv) gives the triarylated diamine (Table 2, entry 3), without formation of the corresponding tetrapyridyl derivative. Clean formation of 2,2′-dianilinopyridine occurred when 2,2′-dibromopyridine was heated with excess aniline. In thiscase the initial coupling step is considerably more facile than the second addition (Table 2, entry 5).

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(22) (a) In an NMR tube pyridine (2.1 μL, 0.26 mmol) was added to a solution of [(*R*)-Tol-BINAP]Pd(4-benzonitrile)(Br)[22b] (10 mg, 1×10^{-3} mmol) in $CDCl_3$. The ^{1}H NMR spectrum of the [(*R*)-tol-BINAP]Pd(4-benzonitrile)(Br) complex remained unchanged. (b) Widenhoefer, R. A.; Buchwald S. L. Unpublished results.

(23) These substrates instead afforded predominantly imine and pyridine, presumably formed from β-hydride elimination of the corresponding palladium-amido intermediate.

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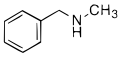
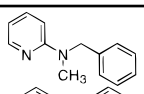
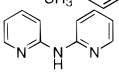
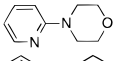
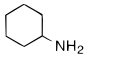
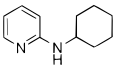
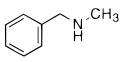
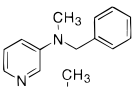
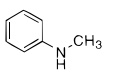
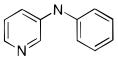
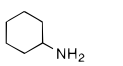
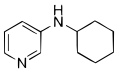
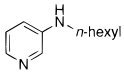
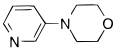
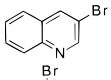
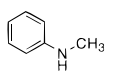
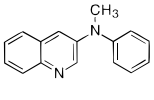
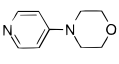
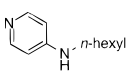
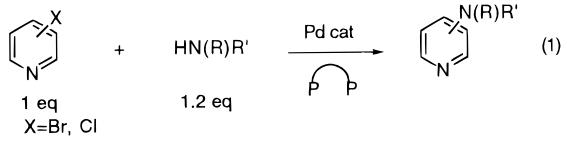
Table 1. Palladium-Catalyzed Formation of Aminopyridines

entry	halopyridine	amine	product	reaction condns	reaction time (h)	yield(%)[i]
1				A	3	86
2				A	4	87
3				A	2	87
4				D	22	73
5				B	4	77
6				B	12	86
7				B	2	82
8[ii]		H_2N-(*n*-hexyl)		B	2	67
9				B	2	75
10				B	4	84
11	 •HCl			C	2	91
12	 •HCl	H_2N-(*n*-hexyl)		D	1	67

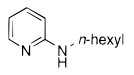
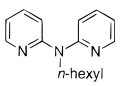
[i] Yields refer to the average of two isolated yields of >95% purity as determined by GC, ^{1}H NMR, and elemental analysis. [ii] Three equiv of *n*-hexylamine was used. Reaction conditions A employ 2 mol % $Pd_2(DBA)_3$ and 4 mol % dppp. Reaction conditions B employ 2 mol % $Pd_2(DBA)_3$ and 4 mol % (±) BINAP. Reaction conditions C employ 4 mol % $Pd(OAc)_2$ and 4 mol % dppp. Reaction conditions D employ 4 mol % $Pd(OAc)_2$ and 4 mol % (±)-BINAP.



Attempts to couple 4-bromopyridine hydrochloride or 2-chloropyridine with amines employing mixtures of $Pd_2(DBA)_3$ and either dppp or (±)-BINAP were unsuccessful. However, these substrates were efficiently transformed when $Pd(OAc)_2$ was employed as the palladium source. For example, mixtures of $Pd(OAc)_2$ and dppp catalyzed the cross-coupling of 4-bromopyridine hydrochloride and morpholine (Table 1, entry 11), while mixtures of $Pd(OAc)_2$ and (±)-BINAP effectively cross-coupled 2-chloropyridine and cyclohexylamine (Table 1, entry 4) and also 4-bromopyridine hydrochloride and hexylamine (Table 1, entry 12). $Pd(OAc)_2$ also served as a suitable palladium source for coupling reactions involving 2- and 3-bromopyridines.

The major limitation of the Pd/(±)-BINAP or dppp-catalyzed amination protocol is the inability of this system to cross-couple halopyridines with acyclic dialkylamines. For example, attempts to couple di-*n*-butylamine with 2-, 3-, or 4-bromopyridine or 2-chloropyridine using various chelating bis(phosphine) ligands provided only low yields of the (di-*n*-butylamino)pyridine.

Table 2. Multiple Palladium-Catalyzed Coupling Reactions

entry	halopyridine	amine	product	reaction condns	reaction time (h)	yield(%)
1[ii]		H_2N-(*n*-hexyl)		B	4	74
2[iii]		H_2N-(*n*-hexyl)		B	1	71
3[iv]				B	20	77
4[v]				B	3	70
5[vi]				A	18	86

[i] Yields refer to the average of two isolated yields of >95% purity as determined by GC, ^{1}H NMR, and elemental analyses. [ii] Entry 3 was run with 3 equiv of *n*-hexylamine. [iii–v] Entries 2–4 were run with 2, 3, and 4 equiv of 2-bromopyridine. [vi] Two equiv of aniline was used. Reaction conditions A employ 2 mol % $Pd_2(dba)_3$ and 4 mol % dppp. Reaction conditions B employ 2 mol % $Pd_2(dba)_3$ and 4 mol % (±)-BINAP.

In summary, palladium(0) complexes with chelating bis(phosphines) effectively catalyze the amination of halopyridines to form aminopyridines. This procedure[24] represents a significant improvement relative to existing procedures for the synthesis of aminopyridines. Activated substrates are not required, and relatively non-nucleophilic amines such as primary amines and anilines are efficiently arylated. This work also demonstrates a second, distinct, scenario in which the use of catalysts containing chelating bisphosphines in aromatic aminations procedures is superior to employing those containing (*o*-tolyl)$_3$P. In this instance, the chelating ligands prevent formation of bis-pyridyl complexes that terminate the catalytic cycle.

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Supporting Information Available: Experimental procedures and characterization data for all compounds (9 pages).

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(24) A general procedure is as follows: Bromopyridine (1 mmol), amine (1.2 mmol), $Pd_2(DBA)_3$ (0.02 mmol, 4 mol % Pd, 18 mg), 1,3-bis(diphenylphosphino)propane (dppp, 0.04 mmol, 16 mg), NaO-*t*-Bu (1.4 mmol, 134 mg), and toluene (0.11 M with 2-bromopyridine, 9 mL) were added to an oven-dried Schlenk flask that was purged with argon for approximately 5 min. The reaction mixture was then heated to 70 °C under argon until the bromopyridine was consumed as determined by GC analysis. The reaction mixture was then allowed to cool to room temperature, taken up in diethyl ether (10 mL), washed three times with saturated brine (10 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give the crude product. Purification by flash column chromatography afforded the analytically pure product.