

Communications to the Editor

An Improved Catalyst System for Aromatic Carbon–Nitrogen Bond Formation: The Possible Involvement of Bis(Phosphine) Palladium Complexes as Key Intermediates

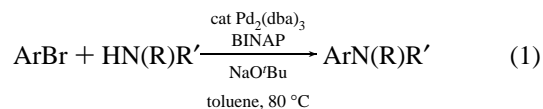
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Reports from several laboratories, including our own, on the palladium-catalyzed cross coupling of aryl bromides with amines have stressed the need to employ $P(o\text{-tolyl})_3$ as a ligand in order to obtain reasonable yields of the desired aniline products.^{1,2} The importance of this ligand was attributed to its steric bulk, which is believed to hinder the formation of bis(phosphine) palladium complexes as intermediates. Hartwig has demonstrated through kinetics studies that oxidative addition, palladium–nitrogen bond formation, and reductive elimination proceed through monophosphine palladium complexes when $P(o\text{-tolyl})_3$ is used as the ligand.³ One drawback of the use of these $P(o\text{-tolyl})_3$ /Pd catalyst systems is that they typically give poor results when applied to the cross coupling of primary amines with aryl bromides. In general, low yields of the desired aniline are realized, and large amounts of arene side products are produced which result from β -hydride elimination from a Pd–amido intermediate. In a number of transition metal complexes, the use of the chelating bis(phosphine) ligand has been found to inhibit β -hydride elimination. Hartwig's results rendered this alternative unattractive since it appeared to us that a chelating ligand would cause difficulty in accessing the requisite three-coordinate monophosphine complexes. Moreover, earlier attempts in our laboratory to utilize chelating bis(phosphines) were unsuccessful. In conjunction with another aspect of our work on palladium-catalyzed carbon–nitrogen bond formation, we had reason to examine the use of BINAP⁴ as the supporting ligand. During this study, we were surprised to find that the combination of $Pd_2(dba)_3$ and BINAP in the presence of NaO^tBu constitutes a superior catalyst system for the cross coupling of amines with aryl bromides. In this communication we report that use of this catalyst system allows for the successful arylation of primary amines and dramatically improves yields with several other types of substrates for which poor results were obtained when $P(o\text{-tolyl})_3$ was employed as the ligand (eq 1). This finding also indicates that bis(phosphine) palladium complexes are not only viable as catalysts (and as intermediates) but in many instances manifest superior efficiency in these aromatic carbon–nitrogen bond-forming procedures.

Previously, we had shown that primary amines could be coupled with a limited class of aryl bromide substrates with good (para electron-withdrawing substituent) to excellent (ortho



substituent) efficiency using a $Pd(0)/P(o\text{-tolyl})_3$ catalyst.^{2a,d} Attempts to generalize the cross coupling of primary amines with aryl bromides by employing $Pd_2(dba)_3/P(o\text{-tolyl})_3$ ⁵ resulted in low conversion of starting materials to products and gave large amounts of arene side products. For example, the coupling of *n*-hexylamine and 5-bromo-*m*-xylene with this catalyst system (2% Pd) resulted in only a partial conversion to products after 22 h at 80 °C and gave 35% (isolated yield) of the desired product. In contrast, an 88% yield was realized when the $Pd_2(dba)_3$ /BINAP (0.5% Pd, 80 °C, 2 h) combination was employed.^{6,7} This catalyst system is significantly more efficient, in general, for the cross coupling of a variety of primary amines with both electron-rich and electron-poor aryl bromides at catalyst loadings as low as 0.05 mol % (~2000 turnovers) as detailed in Table 1. Its high activity also allows for the reactions to be conducted at 80 °C, approximately 20 °C lower than before. The use of BINAP as a ligand for coupling secondary amines with ortho-substituted halides also resulted in much higher yields than were obtained when $P(o\text{-tolyl})_3$ was employed (Table 1). For example, arylation of *N*-methylpiperazine with 2-bromo-*p*-xylene resulted in only 47% yield of the cross-coupled product when the $Pd_2(dba)_3/P(o\text{-tolyl})_3$ catalyst system was used, but when BINAP was substituted for $P(o\text{-tolyl})_3$, the yield improved to 98%.

In analogy to what has previously been reported, we surmise that the catalytic cycle is as shown in Scheme 1. We have isolated two of the presumed intermediates in this sequence. Stirring a purple solution of $Pd_2(DBA)_3$ and BINAP in benzene at room temperature for 2 h gave an orange solution from which (BINAP)Pd(dba) (1) was isolated in 71% yield as an orange powder. The oxidative addition complex (BINAP)Pd(*p*-C₆H₄-CMe₃)(Br) (2) was prepared by the reaction of BINAP with {Pd[P(*o*-tolyl)₃](*p*-C₆H₄CMe₃)(*u*-Br)}₂⁸ in benzene at room temperature and was isolated in 50% yield as a cream-colored solid. No evidence (¹H NMR) for the formation of an amine adduct was detected when a large excess (5 equiv) of benzylamine was added to a C₆D₆ solution of 2. However, addition of sodium *tert*-butoxide to the solution caused the rapid formation of *N*-benzyl-4-*tert*-butylaniline as the only *tert*-butylphenyl-containing product detected (¹H NMR analysis). Both 1 and 2 were shown to catalyze the coupling of amines with aryl bromides with reaction rates and product distributions similar to those observed when mixtures of $Pd_2(dba)_3$ and BINAP were employed.

(4) BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl.

(5) P/Pd ratio = 2/1.

(6) Both racemic and nonracemic BINAP as expected give similar results in the amination reaction. The related *tol*-BINAP also gave satisfactory results in some systems.

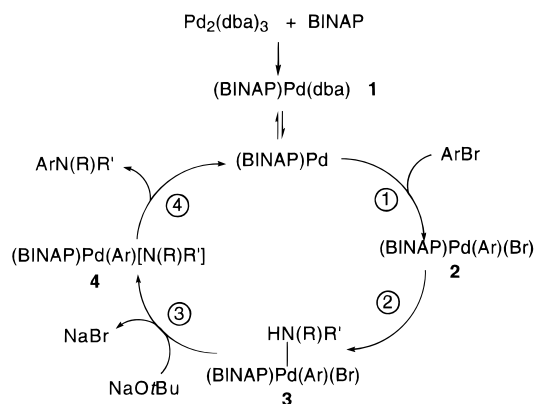
(7) *Representative procedure*: A Schlenk tube was charged with aryl halide (1.0 mmol), amine (1.1–1.2 mmol), sodium *tert*-butoxide (1.4 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.0025 mmol, 0.5 mol % Pd), BINAP (0.0075 mmol), and toluene (2–9 mL) under argon. The tube was heated to 80 °C with stirring until the starting material had been completely consumed as judged by GC analysis. The solution was then allowed to cool to room temperature, taken up in ether (15 mL), filtered, and concentrated. The crude product was then purified further by flash chromatography on silica gel. Alternatively, the reaction could be performed without solvent. The procedure employed was similar to that described above; see supporting information for details.

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Scheme 1. Proposed Catalytic Cycle**Table 1.** Pd-Catalyzed Arylation

Halide	Amine	Product	Catalyst Loading (mol % Pd)	Rxn Time (h)	Isolated Yield (%)	
	RNH ₂		R = <i>n</i> -Hexyl	0.5	2	88 (35) ^a
			R = Bn	0.5	4	79
				0.05	7	79
			R = Cyclohexyl	0.5	18	83
			0.5	20	84	
	<i>n</i> HexNH ₂		0.5	<1	98 ^b	
			0.05	1.5	97	
	H ₂ NBn		0.5	2	81	
			0.5	3.5	71	
	<i>n</i> HexNH ₂		0.5	6	95	
			0.5 ^c	29	75	
			2.0	14	61 (0)	
			1.0 ^c	39	66	
			2.0	36	65 (0)	
			0.5 ^c	36	94	
			2.0	4	79 (5)	
			0.5 ^c	4	98	
			2.0	15	98 (47)	
			0.05 ^c	6	94	

^a Yields in parentheses refer to yields obtained when P(*o*-tolyl)₃ was used as the phosphine ligand. ^b Control experiments showed no formation of the desired product after 17 h at 100 °C in the absence of palladium. ^c Reaction run neat.

The effectiveness of Pd₂(dba)₃/BINAP suggests that any or all of steps 1–4 (Scheme 1) may occur from intermediates without prior phosphine dissociation. In particular, coordination of the amine to **2** would form pentacoordinate **3**.⁹ Deprotonation of the coordinated amine by NaOtBu would give **4** which

Table 2. Ligand Effects on Arylation of *n*-Hexylamine

Ligand	% Conversion (Time)	Ratio of Product/Reduced S.M.	Ratio of Product/Doubly Arylated Amine	Isolated Yield 5
BINAP	100% (2 h)	40/1	39/1	88%
P(<i>o</i> -tolyl) ₃	88% (22 h)	1.5/1	7.6/1	35%
DPPE	7% (6 h)	1/5.4	—	—
DPPP	<2% (6 h)	—	—	—
DPPB	18% (3 h)	1/1.6	—	—
DPPF	100% (3 h)	13.2/1	2.2/1	—
	22% (12 h)	2.5/1	10/1	—

reductively eliminates to give (BINAP)Pd and the aniline product. Structural features specific to BINAP may be key to the success of this catalyst system. This supposition is consistent with the observation that a variety of other chelating bis(phosphines) are significantly less effective in these amination reactions (Table 2). β -Hydride elimination of **4** is presumably inhibited due to the inaccessibility of a three-coordinate monophosphine intermediate.¹⁰ The efficiency of BINAP as a ligand in the Pd-catalyzed cross coupling of primary amines may result from its ability to inhibit the formation of both catalytically inactive palladium bis(amine) aryl halide complexes and bridging amido complexes which resist reductive elimination.⁸

In conclusion, we have demonstrated that the combination of Pd₂(dba)₃ and BINAP serves as an efficient catalyst for the amination of aryl bromides, even at catalyst loadings as low as 0.05% Pd. This new protocol greatly expands the scope of Pd catalyzed C–N bond formation. Additionally, in contrast to prior reports,³ the results presented here indicate that bis(phosphine) palladium complexes are viable as catalysts and intermediates in the amination of aryl bromides.

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Supporting Information Available: Detailed experimental procedures, as well as spectroscopic and analytical characterization of all products (6 pages). See any current masthead page for ordering and Internet access instructions.

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