

General and Efficient Palladium-Catalyzed Aminations of Aryl Chlorides

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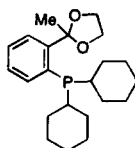
Abstract: Pd(dba)₂/Ligand A catalyst efficiently catalyzes the aminations of a variety of aryl chlorides with a variety of amines in high rates, selectivities, and isolated yields. © 1999 Elsevier Science Ltd. All rights reserved.

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The palladium-catalyzed cross-coupling reactions of aryl- bromides, iodides, and triflates with primary and secondary amines provide a general and efficient route to a wide variety of substituted aryl amines, and have now been extensively developed.¹ However, the related palladium-catalyzed reactions of the comparatively inexpensive and readily available *aryl chlorides*, which represent the most attractive candidates for industrial applications of these reactions, have been underdeveloped.^{2,3} In particular, the efficient aminations of aryl chlorides with secondary acyclic alkyl amines have not been generally achieved. Herein, we describe a new, general, and efficient catalyst for the aminations of aryl chlorides with primary, and secondary cyclic and acyclic amines.

As part of our ongoing efforts to identify, develop, and utilize high throughput methods for rapid discovery of useful materials,⁴ we recently reported the discovery of novel homogeneous palladium catalysts, based on rigid hemi-labile PCCCX (X = N, O) backbone containing ligands, for the aminations of aryl bromides and iodides.⁵ We envisioned that replacement of the diphenylphosphino group with the more basic dicyclohexylphosphino group in the ligand framework would result in increased electron

density at the palladium center thereby facilitating the oxidative addition of the usually unreactive aryl chlorides.^{2,3} Thus, we synthesized 2-(2'-dicyclohexylphosphinophenyl)-2-methyl-1,3-dioxolane (ligand A) and investigated its scope in assisting palladium-catalyzed aminations of aryl chlorides.⁶

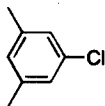
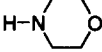
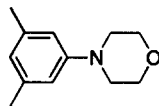
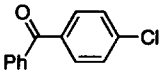
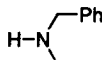
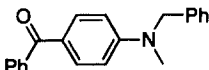
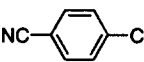
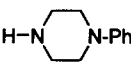
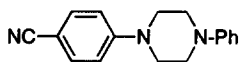
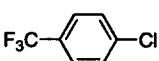
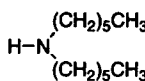
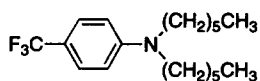
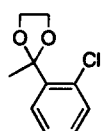
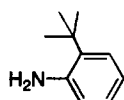
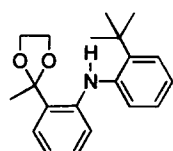
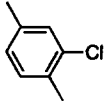
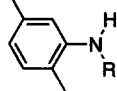
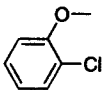
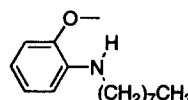
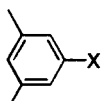
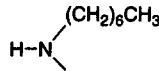
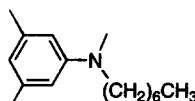


Ligand A

The Pd(dba)₂/Ligand A catalyst was found to be generally efficient in catalyzing the aminations of a wide variety of aryl chlorides (Table 1).⁶ Aryl chlorides containing both electron-deficient and electron-rich substituents reacted efficiently with a wide variety of secondary cyclic and acyclic alkyl amines to afford the desired aryl amines in very high selectivity and isolated yields (entries 1-4, and 9, Table 1). These reactions were essentially complete in 1 hour and formed undetectable to only trace (less than 1%) amounts of the undesired hydrodehalogenated product. Such high rates and selectivities for the aminations of aryl chlorides with secondary acyclic alkyl amines are unprecedented and particularly notable. Aryl chlorides containing *ortho* substituents also reacted efficiently with primary aromatic and aliphatic amines to afford the desired aryl amines in high selectivity and isolated yields (entries 5-8, Table 1). These reactions also proceeded rapidly and were complete in 3 hours. Products resulting from diarylation were not detected in these reactions. The Pd(dba)₂/Ligand A catalyst system was also found to be equally efficient in catalyzing the aminations of aryl bromides and iodides with secondary amines in high selectivities and isolated yields (entries 10-11, Table 1), although our studies were limited to the illustrated substrates.

In summary, we have shown that Pd(dba)₂/Ligand A catalyst efficiently catalyzes the aminations of a variety of aryl chlorides with a variety of amines in high rates, selectivities and isolated yields, and thus greatly expands the scope of palladium-catalyzed aminations of the industrially significant aryl chlorides.

Table 1. Pd(dba)₂/Ligand A - Catalyzed Aminations of Aryl Chlorides.^a

entry	starting materials	product	yield ^b
1	 		92
2	 		96
3	 		90
4	 		97
5 ^c	 		89
6	 		
7 ^d		R = 2,4,6-trimethylphenyl R = octyl	96 92
8 ^d	 		83
9	 		95
10	X = Cl		93
11 ^e	X = Br X = I		91

^a Unless otherwise noted, all reactions were performed at 105 °C for 1 hour using 1.0 equiv of aryl halide, 1.1 - 1.2 equiv of amine, 1.2 - 1.3 equiv of NaO^tBu, 2 mol% Pd(dba)₂/ 6 mol% Ligand as catalyst, and toluene as the reaction solvent. ^b Yields reported correspond to isolated material of > 95 % purity. ^c 2 hour reaction time. ^d 3 hour reaction time. ^e 15 min reaction time.

References and Notes

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- ⁵ Parallel Thin Layer Chromatography (TLC) employing 48 analysis per plate was used as an assay method for screening of catalyst libraries. Guram, A. S.; Bei, X.; Uno, T.; Turner, H. W.; Weinberg, W. H., submitted.
- ⁶ All aryl amine products were characterized by ¹H and ¹³C NMR, GCMS and elemental analysis. *Representative Experimental Procedure:* A mixture of aryl halide (1.0 equiv.), amine (1.1 – 1.2 equiv.), NaO^tBu (1.2 equiv.), Pd(dba)₂ (2 mol%), ligand A (4 – 6 mol%) in toluene (4 mL) was heated at 105 °C with stirring until the starting material was completely consumed as judged by GCMS analysis. The reaction was cooled to room temperature, taken up in diethyl ether (125 mL), washed with water (2 X 30 mL) and brine (30 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel to afford desired aryl amine product, after drying under vacuum.