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Improved Functional Group Compatibility in the Palladium-Catalyzed Amination of Aryl Bromides

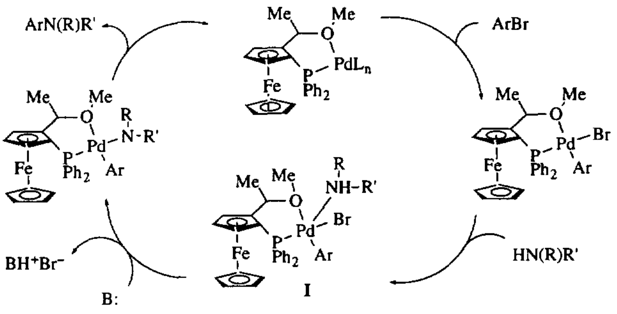
John P. Wolfe and Stephen L. Buchwald*

Department of Chemistry
Massachusetts Institute of Technology
Cambridge, MA, 02139

Abstract: Aryl bromides are coupled with amines in the presence of a palladium catalyst and a stoichiometric amount of cesium carbonate. Using these conditions base-sensitive functional groups, which were incompatible with our previously reported catalytic-amination reaction conditions, are well tolerated. © 1997 Elsevier Science Ltd.

Work from our laboratory and that of Hartwig has documented that the palladium-[1] and nickel-catalyzed[1c] formation of anilines from aryl halides and triflates is a process with wide scope. We were frustrated, however, by the lack of tolerance of the reaction protocols for a number of common functional groups. Our work indicated that sodium *t*-butoxide, the most effective base for most procedures, was the source of much of the problem. We recently reported that (*rac*)-PPF-OMe[2] was a superior ligand for aminations with acyclic secondary amines.[1d] Our working hypothesis suggested that the intermediate palladium complex was less electron-rich than analogous complexes formed when chelating bis-phosphines were employed. We felt that the amine adduct **I**, a presumed intermediate, might be relatively acidic and, hence, the reaction might proceed with weaker bases.

Scheme 1: Catalytic Cycle



After some experimentation, we found that reactions of electronically-neutral aryl bromides went to completion using 1.5 mol% $Pd_2(dba)_3$/4.5 mol% (*rac*)-PPF-OMe in the presence of cesium carbonate in dioxane at 100 °C .[3] For electron-deficient aryl bromides, 0.5-1.5 mol% $Pd_2(dba)_3$/BINAP (L/Pd=1.5) in toluene at 100 °C was an effective catalyst system, although attempts to use this system to couple electronically-neutral aryl bromides with amines resulted in the formation of large amounts of arene side products.

Table 1: Catalytic Amination of Aryl Bromides[a]

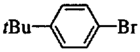
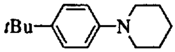
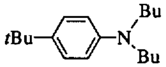
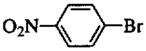
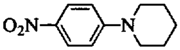
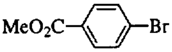
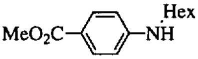
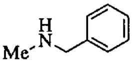
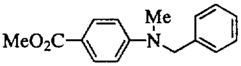
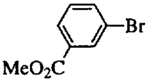
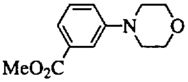
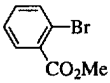
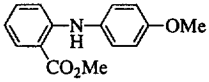
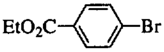
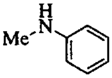
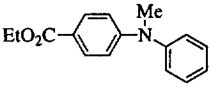
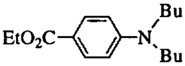
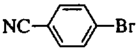
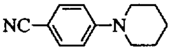
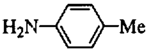
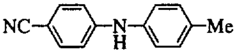
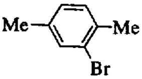
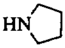
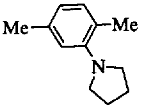
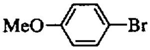
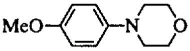
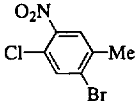
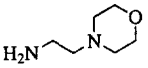
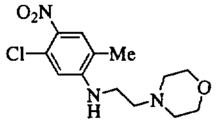
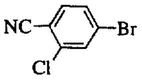
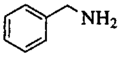
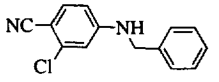
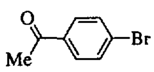
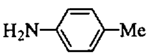
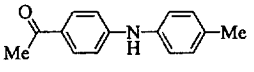
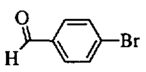
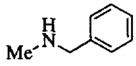
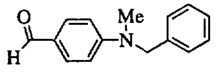
Entry	Halide	Amine	Product	Precatalyst[b]	mol% Pd	Rxn Time (h)	Yield(%)[d]
1				C[c]	3	15.5	92
2		Bu_2NH		C[c]	3	27	73
3				A	1	18	83
4		H_2NHex		A	2	21	72
5				B	3	16	75
6				B	1	20	86
7				B	3	20	92
8				C	3	26	80
9				A	1	24	87
10		Bu_2NH		D	4	24	73
11				A	1	26	87
12				A	1	26	80
13				B[c]	4	17	93
14				D[c]	4	7	73

Table 1: Catalytic Amination of Aryl Bromides[a] (cont.)

Entry	Halide	Amine	Product	Precatalyst[b]	mol% Pd	Rxn Time (h)	Yield(%)[d]
15				A	2	16.5	75
16				A	1	20	84
17				A	1	15	73
18				A	1	22	54

(a) Reaction Conditions: 1.0 eq halide, 1.2 eq amine, 1.4 eq Cs_2CO_3, cat. $Pd_2(dba)_3$ or $Pd(OAc)_2$, cat BINAP or (*rac*)-PPF-OMe (L/Pd=1.5), toluene (0.5 M), 100 °C. (b) A= $Pd_2(dba)_3$/BINAP; B=$Pd(OAc)_2$/BINAP; C= $Pd_2(dba)_3$/(*rac*)-PPF-OMe; D= $Pd(OAc)_2$/(*rac*)-PPF-OMe. (c) Reaction run in 1,4-dioxane. (d) All yields reported are isolated yields (average of two runs) of compounds estimated to be 95% pure as judged by ^1H NMR and either GC analysis or combustion analysis. All compounds were characterized by NMR (^1H, ^{13}C), and IR. Halogen-containing products were also characterized by GC/MS. Combustion analyses were obtained for new compounds, and for compounds which had been previouly reported[7] with limited spectroscopic data.

As shown in Table 1, these new reaction conditions are sufficiently mild to tolerate the presence of methyl[4] and ethyl esters, aldehydes, enolizable ketones,[5] and nitro groups, which are incompatible with reaction conditions which employ sodium *t*-butoxide as the stoichiometric base. The reaction may be carried out using both electron-poor and electron-rich aryl bromides, and provides a wide variety of anilines. While aryl bromides containing nitro groups are sufficiently activated to react slowly in toluene and fairly rapidly in DMF with amines in the absence of a palladium catalyst,[6] useful selectivity can be obtained using the catalytic protocol. For example, the palladium-catalyzed reaction of 2-bromo-4-chloro-5-nitrotoluene with 4-(2-aminoethyl)morpholine afforded exclusive substitution of the bromide (Table 1, entry 15). In the absence of a palladium catalyst, this substrate reacted slowly in toluene (~10% conversion/day) to form exclusively the product resulting from chloride substitution; no products resulting from bromide substitution were observed in DMF in the absence of a palladium catalyst. Similarly, selective substitution of Br over Cl can be achieved in the reaction of 4-bromo-2-chlorobenzonitrile with benzylamine (entry 16).

In conclusion, we have developed conditions for the palladium-catalyzed amination of aryl bromides which do not require the use of sodium *t*-butoxide. These conditions greatly improve the functional group tolerance of the catalytic-amination reactions, further expanding the utility of this process.

Acknowledgments. We thank the National Science Foundation, Pfizer, and Eastman Kodak for their support of this work.

References and Notes

1. (a) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1264-1267 and references cited therein. (b) Louie, J.; Driver, M. S.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 1268-1273 and references cited therein. (c) Wolfe, J. P.; Buchwald, S. L. Manuscript submitted. (d) Marcoux, J-F.; Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1568-1569.

2. (*rac*)-PPF-OMe = 1-[2-(Diphenylphosphino)ferrocenyl]ethyl methyl ether. (a) Hayashi, T.; Mise, T.; Fukushima, M.; Kagotani, M.; Nagashima, N.; Hamada, Y.; Matsumoto, A.; Kawakami, S.; Konishi, M.; Yamamoto, K.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1138-1151. (b) Togni, A.; Häusel, R. *Synlett* **1990**, 633-635.

3. Representative Procedure: An oven-dried Schlenk tube was charged with cesium carbonate which had been finely ground with a mortar and pestle (1.4 eq) in a nitrogen-filled glovebox. The tube was capped with a rubber septum and removed from the glovebox. The tube was then charged with $Pd_2(dba)_3$ or $Pd(OAc)_2$ and BINAP or PPF-OMe (see Table 1), and purged with argon. The aryl bromide (1.0 eq), the amine (1.2 eq), and toluene (2 mL/mmol halide) were added, and the mixture was heated to 100 °C with stirring until the starting material had been consumed as judged by GC analysis. The mixture was cooled to room temperature, diluted with ether (20 mL), filtered, and concentrated. The crude product was then purified by flash chromatography on silica gel. A reaction which employed cesium carbonate that had been finely ground in the air and stored in a dessicator outside of the glovebox gave comparable results to the analogous reaction which employed cesium carbonate from the glovebox.

4. Differences in the reactivity of methyl-4-bromobenzoate purchased from different commercial sources were observed. Material purchased from Aldrich (99% pure) gave satisfactory results, however use of material purchased from Lancaster (98%) resulted in reactions which failed to go to completion and gave significantly different product distributions. The ^1H NMR spectra of the material from these sources were identical.

5. Reactions of the enolizable ketone, 4'-bromoacetophenone, were only successful with 4-methylaniline. Attempts to couple this substrate with morpholine or piperidine afforded only low yields (~15 % by GC) of the desired product.

6. The reaction of 4-bromonitrobenzene with piperidine in DMF in the absence of a palladium catalyst proceeded to completion in 28 h and afforded a 78% isolated yield of N-(4-nitrophenyl)piperidine.

7. Previously reported compounds: (a) N-(4-*t*-butylphenyl) piperidine (entry 1)[1a]. (b) N,N-dibutyl-*p*-*t*-butylaniline (entry 2)[1d]. (c) N-(4-nitrophenyl) piperidine (entry 3) and N-(4-cyanophenyl) piperidine (entry 11): Verardo, G.; Giumanini, A. G.; Favret, G.; Strazzolini, P. *Synthesis* **1991**, 447-450. (d) N-(2-carbomethoxyphenyl)-*p*-anisidine (entry 7): Legrand, L.; Lozac'h, N. *Bull. Chem. Soc. Fr.* **1969**, 1173-1182. (e) N-(4-carboethoxyphenyl) piperidine (entry 8): Khuthier, A-H., Al-Mallah, K. Y.; Hanna, S. Y.; Abdulla, N-A. I. *J. Org. Chem.* **1987**, *52*, 1710-1713. (f) N-methyl-N-(4-carboethoxyphenyl) aniline (entry 9): Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901-7902. (g) N-(2,5-xylyl) pyrrolidine (entry 13): Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* In Press. (h) N-(4-methoxyphenyl) morpholine (entry 14): Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* In Press. (i) N-(4-acetylphenyl)-*p*-toluidine (entry 17): Itier, J.; Casadevall, A. *Bull. Chem. Soc. Fr.* **1969**, 2342-2355. (j) 4-(N-methyl-N-benzyl) aminobenzaldeyde (entry 18): Hora, I. M.; Gupta, V.; Ittyerah, P. I. *J. Ind. Chem. Soc.* **1972**, *49*, 901-905.

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