β-Hydrogen-Containing Sodium Alkoxides as Suitable Bases in Palladium-Catalyzed Aminations of Aryl Halides

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The synthesis of N-unsubstituted anilines generally requires nitration of an aromatic compound followed by reduction of the nitro group. This route is not desirable on a large scale because of the unsafe nature of the nitration reaction. Palladium- and nickel-catalyzed aminations of aromatic halides and triflates, pioneered by Buchwald[2,3] and Hartwig,[4,5] provide not only an efficient route to substituted anilines but also a safer route to N-unsubstituted anilines when using benzophenone imine as an ammonia equivalent.[6] Commonly used bases in palladium-catalyzed aminations are sodium *tert*-butoxide, cesium carbonate, and tripotassium phosphate. The use of *β*-hydrogen-containing sodium alkoxide bases, e.g., sodium methoxide or sodium isopropoxide, has not been reported in these amination reactions because of their known ability[6] to reduce palladium−aryl−alkoxide complexes to palladium−aryl−hydride complexes, which results in the reduction of aryl halide to arene, as was observed during palladium-catalyzed etherification of aromatic halides with sodium methoxide.[7,8] A method for the palladium-catalyzed reduction of aromatic halides by sodium methoxide has also been reported.[9] In this paper, we report that sodium methoxide and sodium isopropoxide, both of which contain a *β*-hydrogen, are suitable bases for palladium-catalyzed aminations of aromatic halides.

Nitrations have been successfully eliminated in a number of projects in our laboratories using palladium-catalyzed aminations of aryl halides with benzophenone imine as an ammonia equivalent. In one of our projects, amination of a highly substituted aromatic halide (**I**, Scheme 1), which also contained a methylcarbamate moiety, with benzophenone imine (1.2 equiv) using sodium *tert*-butoxide (1.4 equiv) as a base in the presence of $Pd_2(dba)_3$ (0.5 mol %) and (±)-BINAP (1.5 mol %) at 105 or 80 °C yielded a complicated mixture. In addition to the desired product (**II**, 55%), substantial amounts of the corresponding *tert*-butylcarbamate (**III**, 9%) and dimeric urea (**IV**, 11%) byproducts were also isolated. Thus, sodium *tert*-butoxide was not compatible with the methylcarbamate functionality. Reactions were also not clean or were incomplete with other bases, e.g., cesium carbonate and tripotassium phosphate. This prompted us to investigate this reaction with sodium methoxide, even though palladium-catalyzed reduction of aromatic halides with sodium methoxide had been identified.[7−9] Sodium methoxide not only would eliminate the *tert*-butylcarbamate byproduct (**III**) but also would minimize the urea dimer (**IV**), as it is less basic than sodium *tert*-butoxide. We rationalized that sodium methoxide could be a suitable base, because these amination reactions do not necessarily require a palladium−aryl−alkoxide complex as an intermediate, which might undergo reduction in the case of sodium methoxide. This supposition was based on the fact that cesium carbonate and tripotassium phosphate are also suitable bases, and amination reaction using these bases may involve a pentacoordinated intermediate, as proposed by Buchwald, which simply requires a deprotonation of the coordinated amine with the base to generate a palladium−amido−aryl complex.[10] Even if the reaction involved a palladium−aryl−alkoxide complex, as proposed by Hartwig,[8] the differences in the reaction rates of the displacement of the *β*-hydrogen-containing alkoxide in this complex with an amine to generate a palladium−amido−aryl complex and of the reduction to a palladium−aryl−hydride complex would determine the outcome. Such a study with *β*-hydrogen-containing sodium alkoxides, e.g., sodium methoxide, was not reported. Treatment of our substrate (**I**) with benzophenone imine in the presence of sodium methoxide using $Pd_2(dba)_3$ and (±)-BINAP at 80 °C yielded the desired product (**II**) in 80% yield with <3% of the dimeric urea (**IV**, Scheme 1). No reduction product could be detected, even at 105 °C.

To test the general synthetic utility of sodium methoxide as a base in palladium-catalyzed aminations, several aryl halides were reacted with benzophenone imine. Hydrolysis of the resulting imine adduct with HCl in THF under known conditions[6] yielded anilines in excellent yields (Table 1). Similar results were also obtained using sodium isopropoxide as the base. The yields were comparable to those reported with sodium *tert*-butoxide.[6] The synthetic utility of sodium methoxide and sodium isopropoxide was further demonstrated during amination of several aromatic halides (electronically neutral, with an electron-withdrawing or electron-donating group) with primary amines, secondary amines, and anilines. The results are listed in Table 2. In all cases, yields were good to excellent and were comparable to those reported with sodium *tert*-butoxide.[10,11]

In summary, the *β*-hydrogen-containing alkoxides sodium methoxide and sodium isopropoxide are suitable bases in palladium-catalyzed amination reactions of aromatic halides. These results suggest that either the reaction mechanism with *β*-hydrogen-containing alkoxide bases does not involve a palladium−aryl−alkoxide complex as an intermediate or that the displacement of the

(1) Undergraduate summer intern (1999) from Princeton University.

(2) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125−146.
(3) Wolfe, J. P.; Wagaw, S.; Marcoux, J. F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805−818.
(4) Hartwig, J. F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2046−2067.
(5) Hartwig, J. F. *Synlett* **1997**, 327−340.
(6) Wolfe, J. P.; Ahman, J.; Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6367−6370.
(7) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 3395−3396.
(8) Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 13109−13110.
(9) Zask, A.; Helquist, P. *J. Org. Chem.* **1978**, *43*, 1619−1620.
(10) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215−7216.

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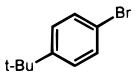
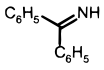
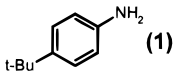
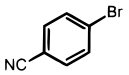
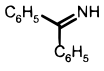
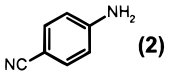
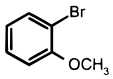
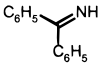
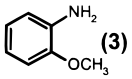
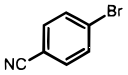
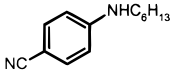
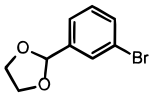
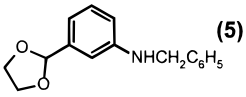
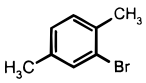
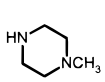
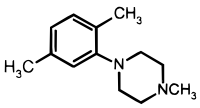
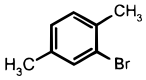
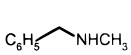
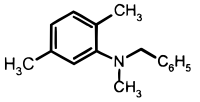
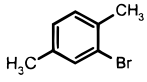
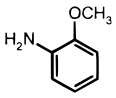
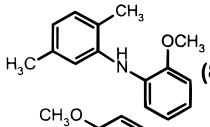
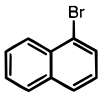
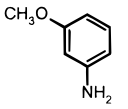
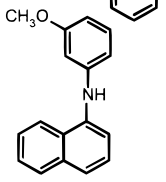
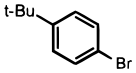
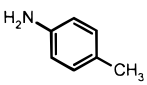
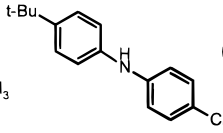
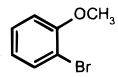
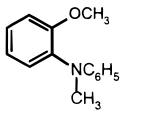
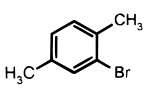
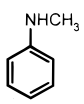
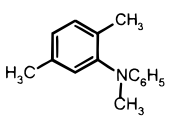
Table 1. Palladium-Catalyzed Amination of Aryl Bromides[a]

Halide	Imine (1.2 eq.)	Product	Base (1.4 eq.)	Temp. (°C)	Time (h)	Yield[b] (%)
		 (1)	CH_3ONa	80	14	82
			$(CH_3)_2CHONa$	80	14	96
		 (2)	CH_3ONa	80	16	81
			$(CH_3)_2CHONa$	80	18	90
		 (3)	CH_3ONa	80	16	92
			$(CH_3)_2CHONa$	80	17	88

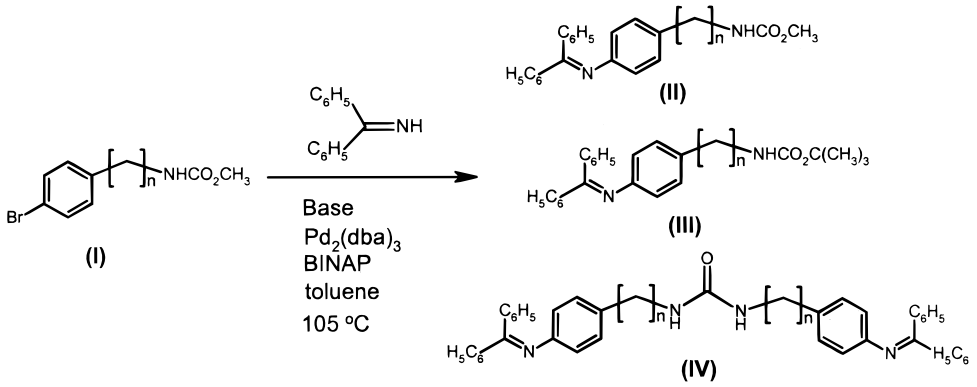
[a] In all cases, 0.25 mol % of $Pd_2(dba)_3$ and 0.75 mol % of BINAP were used. The imine adduct was hydrolyzed with 2.0 M HCl in THF in each case (see ref 6). [b] For reported yields with sodium *tert*-butoxide, see ref 6.

Table 2. Palladium-Catalyzed Amination of Aryl Bromides[a]

Halide	Amine (1.2 eq.)	Product	Base (1.4 eq.)	Temp. (°C)	Time (h)	Yield[b] (%)
	$n\text{-}C_6H_{13}NH_2$	 (4)	CH_3ONa	80	20	85
			$(CH_3)_2CHONa$	80	20	90
	Benzylamine	 (5)	CH_3ONa	80	15	88
			$(CH_3)_2CHONa$	80	15	80
		 (6)	CH_3ONa	110	7	66
			$(CH_3)_2CHONa$	110	7	68
		 (7)	CH_3ONa	110	14	68
			$(CH_3)_2CHONa$	110	14	63
			$(CH_3)_3CONa$	110	14	70
		 (8)	CH_3ONa	110	16	86
			$(CH_3)_2CHONa$	110	19	97
		 (9)	CH_3ONa	110	18	83
			$(CH_3)_2CHONa$	110	14	96
			$(CH_3)_3CONa$	110	14	90
		 (10)	CH_3ONa	110	14	84
			$(CH_3)_2CHONa$	110	14	77
			$(CH_3)_3CONa$	110	14	80
		 (11)	CH_3ONa	110	14	68
			$(CH_3)_2CHONa$	110	18	60
		 (12)	CH_3ONa	110	23	82
			$(CH_3)_2CHONa$	110	22	85

[a] In all cases, 0.25 mol % $Pd_2(dba)_3$ and 0.75 mol % BINAP were used, except for **7** and **10**, for which 0.5 mol % $Pd_2(dba)_3$ and 1.5 mol % BINAP were used, and **11**, for which 1.0 mol % $Pd_2(dba)_3$ and 3.0 mol % BINAP were used. [b] For reported yields with sodium *tert*-butoxide, see ref 10 for examples **4**−**6**, **11**, and **12** and ref 11 for example **8**.

Scheme 1



	Isolated yield (%)		
Base	II	III	IV
CH_3ONa	80	0	<3
$(CH_3)_3CONa$	55	9	11
Cs_2CO_3	40	0	7
K_3PO_4	<5	0	0

alkoxide in this complex with an amine to form a palladium−amido−aryl complex is much faster than its reduction to the palladium−aryl−hydride complex.

Experimental Section

General Procedure. A dry three-neck flask, equipped with a magnetic stirrer bar, septum, and a condenser with a nitrogen inlet−outlet, was charged with the aromatic halide (5.0 mmol), the imine or amine (6.0 mmol), $Pd_2(dba)_3$ (0.0125 mmol), (±)-BINAP (0.0375 mmol), and the base (7.0 mmol). The flask was evacuated and flushed with nitrogen. Dry and de-aerated toluene (10 mL) was added. The mixture was heated to 80−110 °C, and the reaction was allowed to continue for the specified time (Tables 1 and 2). The reaction mixture was cooled to room temperature. Water (10 mL) and ethyl acetate (20 mL) were added sequentially. The organic layer was separated, washed with water (10 mL), dried over anhydrous sodium sulfate, and concentrated. The crude material was purified by silica gel chromatography in cases **4**−**12** or hydrolyzed with HCl in cases **1**−**3**.[6] All of the compounds gave satisfactory spectroscopic data (**1**−**3**;[6] **4**−**6**, **11**, and **12**;[10] **8**;[11] and **10**[12]).

Spectral Data of Selected Compounds. 7: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.17 (s, 3H), 2.23 (s, 3H), 2.43 (s, 3H), 3.88 (s, 2H), 6.67 (d, 1H, J = 7.5 Hz), 6.77 (s, 1H), 6.95 (d, 1H, J = 7.5 Hz), 7.13−7.28 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 17.96, 21.18, 40.75, 60.82, 120.7, 123.63, 126.9, 128.24, 129.52, 130.92, 135.93, 139.22, 152.3.

9: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 (s, 3H), 5.96 (bs, 1H), 6.56−6.61 (m, 3H), 7.9 (dd, 1H, J = 8.07 and 8.06 Hz), 7.43 (m, 2H), 7.51 (m, 2H), 7.61 (m, 1H), 7.88 (m, 1H), 8.06 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 55.11, 102.87, 105.52, 109.73, 116.74, 121.87, 123.25, 125.67, 125.96, 126.08, 127.97, 128.45, 130.05, 134.63, 138.37, 146.29, 160.67.

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Supporting Information Available: Spectra of compounds **7** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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