Room Temperature Catalytic Amination of Aryl Iodides

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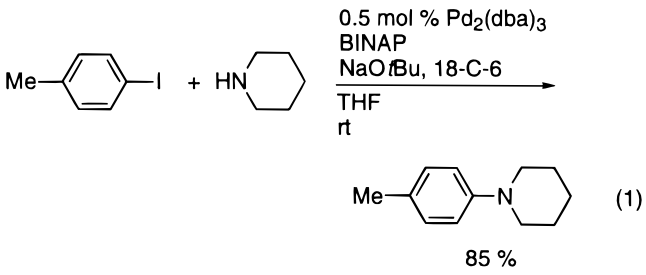
The palladium-catalyzed amination of aryl halides has been shown to be a general method for the formation of aromatic carbon−nitrogen bonds.[1] However, current versions of this method still suffer from the need for relatively high reaction temperatures (65−100 °C) which may pose problems for reactions involving thermally sensitive molecules or in situations where it is inconvenient to heat reactions (e.g., combinatorial chemistry applications).[2] Herein, we report a general procedure for palladium-catalyzed intermolecular carbon−nitrogen bond formation which proceeds at room temperature and affords the desired products in good to excellent yields.

Initial attempts to effect the intermolecular coupling of aryl iodides with amines at room temperature by employing conditions developed for the palladium-catalyzed inter-[1h] or intramolecular[1b,c] amination of aryl iodides were unsuccessful. During the course of kinetics studies on the $Pd_2(dba)_3$/P(*o*-tolyl)$_3$ catalyzed amination of aryl bromides, we observed a rate enhancement when 18-crown-6 was added to the reaction mixture.[3,4] This led us to develop the conditions shown in eq 1, which allows for the successful coupling of aryl iodides with amines at ambient temperature. For example, the reaction of *p*-iodotoluene with piperidine in the presence of stoichiometric quantities of NaO-*t*-Bu and 18-crown-6 and a catalytic amount of $Pd_2(dba)_3$/BINAP proceeds to completion in ∼6 h at room temperature; the product *N*-(4-methylphenyl)piperidine is isolated in 85% yield (eq 1).[5]

Table 1. Solvent/Additive Effects on the Reaction Shown in Eq 1

solvent/additive	% conversion
THF	13
DMF	55[a,b]
THF/18-C-6[d]	100 (85% isolated yield)
THF/TMEDA	13
THF/Bu_4NCl (1.0 eq)	18
THF/poly(ethylene glycol), M_n = 200	0
THF/poly(ethylene glycol), M_n = 3400	46
THF/poly(ethylene oxide), M_n = 200 000	44
THF/tetraglyme	24
tetraglyme[c]	85 (57% isolated yield)
tetraglyme/cat. 18-C-6[c]	96 (77% isolated yield)

[a] This reaction gave a mixture of *N*-(4-methylphenyl)piperidine and *N*,*N*-dimethyl-*p*-toluidine. An amide product resulting from amine exchange with DMF was also observed. [b] A control reaction run in DMF in the presence of 18-C-6 without a palladium catalyst afforded a mixture of the two products mentioned above, as well as their meta regioisomers. [c] Tol-BINAP was used in place of BINAP. Analogous reactions run with BINAP as the supporting ligand resulted in similar conversions. [d] A control reaction run in THF in the presence of 18-C-6 without a palladium catalyst gave no reaction after 24 h at room temperature.



(1)

Studies to optimize this process were undertaken, and the coupling of *p*-iodotoluene and piperidine catalyzed by $Pd_2(dba)_3$/BINAP (1 mol % of Pd) at room temperature was examined using a variety of solvent/additive combinations. As shown in Table 1, the use of THF with added 18-crown-6 was found to be the most effective system. Reactions with THF, triethylamine, toluene, TMEDA, NMP, DMSO, or DME as solvent without additives proceeded to low conversion.[6] Reactions employing 18-crown-6 as an additive in toluene, dioxane, or triethylamine were slower than those conducted in THF with added 18-crown-6. Tetraglyme (tetra(ethylene glycol) dimethyl ether) was the most effective solvent in the absence of 18-crown-6, although these reactions failed to proceed to completion (up to 85% conversion). Addition of catalytic amounts (10 mol %) of 18-crown-6 to reactions run in tetraglyme gave improved results, but these conditions did not prove to be effective with a wide range of substrates.

BINAP and Tol-BINAP[7] were the only phosphine ligands tested which were found to be generally effective in these reactions. In one case the use of DPPF[8] gave similar results (Table 2, entry 2), but for other substrates examined its use as the supporting ligand led to slower reactions and incomplete consumption of the starting aryl halide.

(1) (a) Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett.* **1983**, 927−928. (b) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348−1350. (c) An example of an intramolecular carbon−nitrogen bond forming process which proceeds at room temperature has been reported: Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *52*, 7525−7546. (d) Wolfe, J. P.; Wagaw. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215−7216. (e) Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240−7241. (f) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609−3612. (g) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217−7218. (h) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133−1135. (i) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1264−1267. (j) Louie, J.; Driver, M. S.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 1268−1273. (k) Marcoux, J.-F.; Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1568−1569.

(2) Jeffery has reported that Heck arylations may be run at lower temperatures in the presence of stoichiometric amounts of tetraalkylammonium salts. We found that these reagents were not effective promoters of the aryl amination process at room temperature. (a) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113−10130. Suzuki reactions which proceed at room temperature in the presence of TlOH have also been reported. (b) Uenishi, J.-I.; Beau, J.-M.; Armstrong, R. W.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4756−4758. (c) Anderson, J. C.; Namli, H. *Synlett* **1995**, 765−766.

(3) Widenhoefer, R. A.; Buchwald, S. L. Unpublished results.

(4) Use of 18-crown-6 to promote one example of the Ullmann aryl ether synthesis (at 150 °C) has been reported. Jung, M. E.; Jachiet, D.; Rohloff, J. C. *Tetrahedron Lett.* **1989**, *30*, 4211−4214.

(5) Our original amination protocol for iodides[1h] afforded this product in only 59% isolated yield (Table 2, entry 9). The reaction of *N*,*N*-diethyl-4-iodobenzamide with *n*-hexylamine also gave a higher yield when the room temperature conditions were employed (Table 2, entry 1).

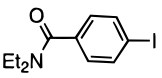
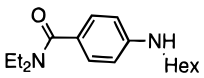
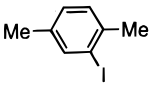
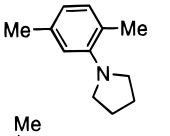
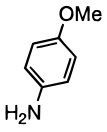
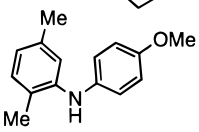
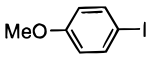
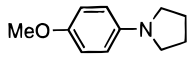
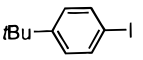
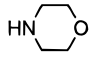
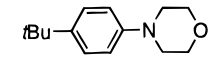
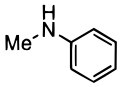
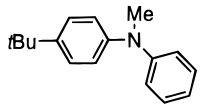
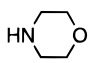
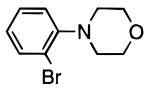
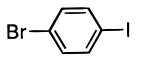
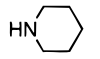
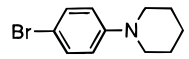
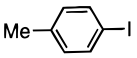
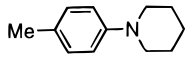
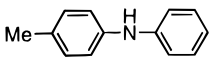
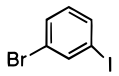
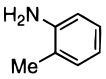
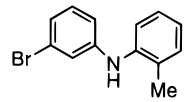
(6) It is interesting to note that the reaction of 4-bromoiodobenzene with piperidine only proceeded to 79% conversion in THF at 65 °C in the absence of 18-C-6 (1 mol % Pd catalyst). This coupling went to completion and afforded the product in high yield (Table 2, entry 8) when the room temperature/18-C-6 conditions were employed.

(7) (*S*)-BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; (*R*)-Tol-BINAP = 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl. Racemic BINAP is now commercially available from Strem Chemical Company.

(8) DPPF = 1,1′-bis(diphenylphosphino)ferrocene.

S0022-3263(97)00876-1 CCC: $14.00

Table 2. Room Temperature Catalytic Amination of Aryl Iodides

Entry	Aryl Iodide	Amine	Product	Time	Temp.	Ligand[a]	Mol% Pd	Yield(%)[b]
1		$HexNH_2$		20 h	rt	BINAP	1	88 (19)
				17 h	rt	Tol-BINAP	1	78
2				9 h	rt	BINAP	1	82
				22 h	rt	Tol-BINAP	1	73
				20 h	rt	DPPF	1	78[c]
3				22 h	40 °C	BINAP	4	85
4				3 h	rt	BINAP	1	83
				12 h	rt	Tol-BINAP	1	91
5				17 h	rt	BINAP	1	90
				18 h	rt	Tol-BINAP	1	91
6				25 h	40 °C	BINAP	5	71[d]
7				25 h	rt	BINAP	1	78
				19 h	rt	Tol-BINAP	1	77
8				14 h	rt	BINAP	1	84
				13 h	rt	Tol-BINAP	1	90
9				6 h	rt	BINAP	1	85 (59)
				9 h	rt	Tol-BINAP	1	84
10		$PhNH_2$		20 h	40 °C	BINAP	4	78
11				29 h	40 °C	BINAP	5	72

(a) Reaction Conditions: 1.0 equiv. halide, 1.2 equiv. amine, 1.4 equiv. NaO*t*Bu, 1.4 equiv. 18-C-6, 0.5–2.5 mol% $Pd_2(dba)_3$ (1–5 mol% Pd), 1.5–7.5 mol% ligand (1.5 L/Pd), THF (0.5M), rt–40 °C. (b) Yields represent isolated yields (average of two experiments) unless otherwise noted. Yields in parentheses were obtained using the original iodide amination protocol.[1h] (c) Isolated yield from a single experiment. (d) Product isolated as an 6.6/1 mixture (as determined by ^1H NMR) of N-methyl-N(4-*t*-butylphenyl)aniline/N-methyl-diphenylamine.

As shown in Table 2, the THF/18-crown-6 conditions are effective for the reactions of both electron-rich and electron-deficient aryl iodides with primary and secondary aliphatic amines at room temperature using relatively low catalyst loadings (1 mol % of Pd). This procedure is most effective for cyclic secondary amines, while attempted arylation of acyclic secondary amines often resulted in low conversion to and/or poor ratios of the desired products:reduced arene side products.[9] Reactions which used anilines as substrates required slightly higher temperatures (40 °C) and catalyst levels (4−5 mol % of Pd) to proceed to completion. The reaction of 4-*tert*-butyliodobenzene with *N*-methylaniline afforded a 6.6:1 mixture of the desired product and a side product resulting from the unexpected cleavage of the *tert*-butyl group (Table 2, entry 6), although no products resulting from a similar process were detected in the reaction of 4-*tert*-butyliodobenzene with morpholine (Table 2, entry 5). An additional benefit of this new procedure is that the selective substitution of the iodide in *o*-, *m*-, or *p*-bromo(iodo)benzene (Table 2, entries 7, 8, and 11) can be achieved. Attempts to carry out this selective substitution using our original conditions resulted in the formation of a mixture of products.

While we have not conducted a detailed study, we believe that the mechanism of this process likely is analogous to that of the catalytic amination of aryl bromides using BINAP as the supporting ligand.[1d] Our current view is that the 18-crown-6 activates the NaO-*t*-Bu by increasing solvation of the Na^+.

(9) In general, secondary acyclic amines are not good substrates in reactions catalyzed by mixtures of $Pd_2(dba)_3$/BINAP. Wolfe, J. P.; Marcoux, J. F.; Buchwald, S. L. Unpublished results. For a successful method for the coupling of these amines, see ref 1k.

In conclusion, we have developed a general procedure for the palladium-catalyzed intermolecular amination of aryl iodides which proceeds at ambient temperatures. Further studies are underway to devise mild, general reaction conditions which allow for enhanced functional group tolerance in palladium-catalyzed amination reactions.

Experimental Section

General. All reactions were carried out under an argon atmosphere in oven-dried glassware. Elemental analyses were performed by E & R Microanalytical Laboratory Inc., Corona, NY. THF was continuously refluxed and distilled from sodium benzophenone ketyl under argon. Aryl iodides were purchased from commercial sources and were used without further purification except for 3-bromoiodobenzene which was passed through alumina before use. Amines were purchased from commercial sources and were purified by being passed through alumina or distilled from calcium hydride under argon or vacuum. Sodium *tert*-butoxide was purchased from Aldrich Chemical Co. and stored in a Vacuum Atmospheres glovebox under nitrogen or argon. Small amounts of sodium *tert*-butoxide were removed from the glovebox, stored in a desiccator for up to 1 week, and weighed in the air. 18-Crown-6 was purchased from Lancaster Synthesis and was stored under nitrogen in a Vacuum Atmospheres glovebox. For reasons of convenience, the reaction vessels were charged with 18-crown-6 in the glovebox. All other reagents were weighed and loaded into the reaction vessels in the air. A reaction employing 18-crown-6 which had been stored and weighed in the air gave comparable results to the analogous reaction run with 18-crown-6 from the glovebox. BINAP, Tol-BINAP, DPPF, and $Pd_2(dba)_3$ were purchased from Strem Chemical Co. and used without further purification. Preparative flash chromatography was performed on ICN Biomedicals Silitech 32-63d silica gel. Yields in Table 1 refer to isolated yields (average of two runs) of compounds estimated to be ≥95% pure as determined by ^{1}H NMR and either capillary GC (known compounds) or combustion analysis (new compounds). The procedures described below are representative; thus the yields may differ from those given in Table 1.

General Procedure. In a nitrogen-filled glovebox, an oven-dried Schlenk tube was charged with 18-crown-6 (185 mg, 0.7 mmol), which was capped with a rubber septum and removed from the glovebox. The Schlenk tube was then charged with the aryl iodide (0.5 mmol), the amine (0.6 mmol), NaO-*t*-Bu (67 mg, 0.7 mmol), $Pd_2(dba)_3$ (2.3 mg, 0.0025 mmol, 1 mol % of Pd), and BINAP (4.7 mg, 0.0075 mmol) and purged with argon. THF (1 mL) was added, and the reaction mixture was stirred at room temperature under argon until the reaction had proceeded to completion as judged by GC or TLC analysis. The reaction mixture was taken up in ether (20 mL), filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.

***N*-(3-Bromophenyl)-*o*-toluidine.** The general procedure using 2.5 mol % of $Pd_2(dba)_3$, 7.5 mol % of BINAP, and a reaction temperature of 40 °C gave 88 mg (67%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.24 (s, 3H), 5.39 (s, br, 1H), 6.80 (dd, 1H, J = 3.2 Hz, 8.9 Hz), 6.92−7.25 (m, 7H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 17.9, 114.9, 118.9, 120.9, 122.7, 126.9, 128.0, 130.0, 130.5, 131.1, 139.9, 146.0; IR (neat, cm^{-1}) 3397, 3058, 1587, 1478, 1310, 1068; GC/MS m/z 261, 263. Anal. Calcd for $C_{13}H_{12}BrN$: C, 59.56; H, 4.61. Found: C, 59.74; H, 4.75.

***N*-(4-Bromophenyl)piperidine.**[10] The general procedure gave 110 mg (92%) of a white solid, mp 69−70 °C (lit.[10] mp 77 °C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.53−1.60 (m, 2H), 1.65−1.72 (m, 4H), 3.12 (t, 4H, J = 5.2 Hz), 6.79 (d, 2H, J = 8.6 Hz), 7.31 (d, 2H, J = 8.6 Hz); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 24.1, 25.6, 50.4, 111.0, 113.5, 118.0, 131.7; IR (KBr, cm^{-1}) 2939, 1494, 1244, 807; GC/MS (m/z) 238, 239, 240, 241. Anal. Calcd for $C_{11}H_{14}BrN$: C, 55.02; H, 5.88. Found: C, 55.23; H, 6.01.

***N*-Phenyl-*p*-toluidine.**[1g,11] The general procedure using 2 mol % of $Pd_2(dba)_3$, 6 mol % of BINAP, and a reaction temperature of 40 °C gave 74 mg (80%) of a white solid, mp 87−88 °C (lit.[11] mp 89 °C): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.30 (s, 3H), 5.60 (s, br, 1H), 6.88 (t, 1H, J = 7.3 Hz), 6.90−7.10 (m, 6H), 7.21−7.26 (m, 2H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 20.6, 116.8, 118.9, 120.2, 129.3, 129.8, 130.9, 140.2, 143.9; IR (KBr, cm^{-1}) 3394, 1596, 1513, 1308, 746.

***N*-(2,5-Xylyl)pyrrolidine.**[12] The general procedure gave 74 mg (84%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.84−1.94 (m, 4H), 2.28 (s, 3H), 2,29 (s, 3H), 3.16−3.22 (m, 2H), 6.65 (d, 1H, J = 7.8 Hz), 6.70 (s, 1H), 7.00 (d, 1H, J = 7.5 Hz).

***N*,*N*-Diethyl-*p*-(hexylamino)benzamide.**[1h] The general procedure gave 119 mg (86%) of a purple solid, mp 37−38 °C (lit.[1h] oil):[2] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.9 (m, 3H), 1.18 (t, 6H, J = 6.9 Hz), 1.29−1.42 (m, 6H), 1.61 (p, 2H, J = 6.9 Hz), 3.11 (t, 2H, J = 7.2 Hz), 3.43 (q, 4H, J = 6.9 Hz), 3.80 (s, br, 1H), 6.53−6.56 (m, 2H), 7.23−7.27 (m, 2H).

***N*-(4-Methoxyphenyl)pyrrolidine.**[12,13] The general procedure gave 76 mg (85%) of a white solid, mp 41−42 °C (lit.[12] 41 °C): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.96−2.01 (m, 4H), 3.23−3.26 (m, 2H), 3.76 (s, 3H), 6.53 (d, 2H, J = 8.8 Hz), 6.84 (d, 2H, J = 9.1 Hz).

***N*-(2,5-Xylyl)-*p*-anisidine.**[12,14] The general procedure using 2 mol % of $Pd_2(dba)_3$, 6 mol % of BINAP, and a reaction temperature of 40 °C gave 95 mg (83%) of a white solid, mp 37 °C (lit.[14] mp 34−35 °C): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.20 (s, 3H), 2.23 (s, 3H), 3.80 (s, 3H), 5.17 (s, br, 1H), 6.63 (d, 1H, J = 7.0 Hz), 6.82−6.89 (m, 3H), 7.02 (m, 3H).

***N*-(4-Methylphenyl)piperidine.**[14] The general procedure gave 74 mg (84%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.50−1.73 (m, 6H), 2.26 (s, 3H), 3.09 (t, 4H, J = 5.4 Hz), 6.85 (d, 2H, J = 8.4 Hz), 7.05 (d, 2H, J = 8.4 Hz).

4-(2-Bromophenyl)morpholine.[15] The general procedure gave 100 mg (83%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.05 (t, 4H, J = 4.6 Hz), 3.88 (t, 4H, J = 4.6 Hz), 6.93 (dt, 1H, J = 1.6 Hz, 7.3 Hz), 7.05 (dd, 1H, J = 1.6 Hz, 7.9 Hz), 7.29 (dt, 1H, J = 1.1 Hz, 7.3 Hz), 7.57 (dd, 1H, J = 1.6 Hz, 8.0 Hz); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 52.1, 67.1, 119.8, 120.8, 124.6, 128.3, 133.9, 150.3; IR (neat, cm^{-1}) 2853, 1475, 1115; GC/MS (m/z) 241, 243. Anal. Calcd for $C_{10}H_{12}BrON$: C, 49.61; H, 5.00. Found: C, 50.51; H, 5.20. The material was homogeneous by GC, ^{1}H NMR, and ^{13}C NMR. A small amount of material was Kugelrohr distilled and resubmitted for analysis. Found: C, 49.64; H, 5.00.

4-(4-*tert*-Butylphenyl)morpholine.[16] The general procedure gave 104 mg (95%) of a white solid, mp 59 °C (lit.[16] mp 50−52 °C): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.30 (s, 9H), 3.14 (t, 4H, J = 4.9 Hz), 3.86 (t, 4H, J = 4.7 Hz), 6.87 (d, 2H, J = 8.9 Hz), 7.30 (d, 2H, J = 8.9 Hz); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 31.4, 33.9, 49.5, 66.7, 115.3, 125.9, 142.7, 148.9; IR (KBr, cm^{-1}) 2961, 1521, 1238, 927, 820. Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65. Found: C, 76.86; H, 9.87.

***N*-Methyl-*N*-(4-*tert*-butylphenyl)aniline.** The general procedure using 2.5 mol % of $Pd_2(dba)_3$, 7.5 mol % of BINAP, and a reaction temperature of 40 °C gave a 6.6/1 mixture (^{1}H NMR) of the title compound and *N*-methyldiphenylamine (84 mg, 68%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.32 (s, 9H), 3.30 (s, 3H), 3.32 (s, 0.45H), 6.86 (m, 5H), 7.20−7.31 (m, 4H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 19.5, 31.4, 34.2, 40.2, 119.0, 120.2, 120.4, 121.2, 126.1, 129.0, 129.2, 144.8; IR (neat, cm^{-1}) 2960, 1498, 1133; HRMS calcd for $C_{17}H_{21}N$ 239.167400, found 239.16762.

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