

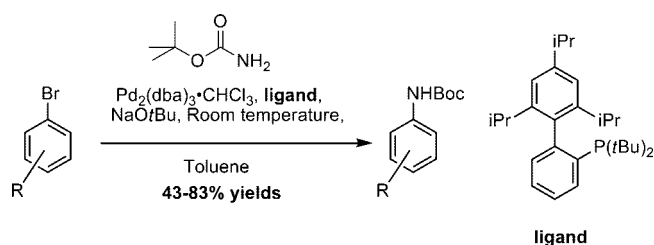
Room-Temperature Pd-Catalyzed Amidation of Aryl Bromides Using *tert*-Butyl Carbamate

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Received February 27, 2009



The scope of Pd-catalyzed synthesis of *N*-Boc-protected anilines from aryl bromides and commercially available *tert*-butyl carbamate is described. For the first time, this process can be conducted at room temperature (17–22 °C) using a combination of $\text{Pd}_2\text{dba}_3 \cdot \text{CHCl}_3$ and a monodentate ligand, *tert*-butyl X-Phos. Use of sodium *tert*-butoxide is crucial to the success of the reaction, which proceeds in 43–83% yield.

Pd-catalyzed conversion of aryl halides and their equivalents to primary anilines traditionally incorporates an ammonia equivalent.¹ Benzophenone imine,^{1,2} (di)allyl amine,³ lithium bis(trimethylsilyl)amide,⁴ and lithium amide⁵ have all been successfully exploited to affect this conversion. Although general scope has been established with these ammonia equivalents, the reaction conditions remain relatively harsh because of high temperatures and/or the use of strong bases. An exception is the use of zinc bis(hexamethyldisilazide),⁶ which can be used to convert *activated* aryl bromides to anilines at room temperature. In this case, however, an air-sensitive ligand, tri-*tert*-butyl phosphine, is required for the transformation. Recently, both

Hartwig⁵ and Buchwald⁷ have reported catalyst systems that support use of ammonia in the Pd-catalyzed conversion of aryl halides to anilines. We also recently reported mild conditions for the Pd-catalyzed conversion of aryl bromides to anilines using benzophenone imine as the ammonia equivalent.² The use of benzophenone imine, however, generates an intermediate ketimine that does not provide a convenient protecting group for the aniline.

During the course of our medicinal chemistry efforts around an oncology target, it became desirable to perform a Pd-catalyzed amination or amidation of an aryl bromide that directly delivered an ammonia equivalent in a conveniently protected form. Nearly all of the published ammonia equivalents cannot fulfill this criterion, with one notable exception. The *tert*-butyloxycarbonyl (Boc) group is a convenient and robust amine protecting group, and there are a few examples of *tert*-butyl carbamate being used as the ammonia equivalent in Cu-⁸ and Pd-catalyzed^{9–13} amidations. In 1999, while reporting room-temperature amination of aryl bromides using tri-*tert*-butylphosphine as ligand, Hartwig also first reported a few examples of Pd-catalyzed amidation of aryl bromides using *tert*-butyl carbamate.⁹ These reactions were conducted at 100 °C and employed sodium phenoxide as the base. Xantphos^{10,12,13} or tri-*tert*-butylphosphine^{9,11} are frequently encountered as ligands to effect this conversion, generally at elevated temperatures. Two exceptions are a single conversion of an activated aryl bromide at 45 °C¹² and a few examples using a different carbamate (Cbz-NH₂) at 45 °C.¹⁰ As we were concomitantly pursuing milder conditions for Pd-catalyzed aminations with benzophenone imine, we wondered if similar conditions might be employed to deliver a milder Pd-catalyzed amidation of aryl bromides using *tert*-butyl carbamate. We now report the first reaction conditions for amidations of aryl bromides with *tert*-butyl carbamate at room temperature.

The reaction optimization using *tert*-butyl carbamate was conducted concurrent to our benzophenone imine work. The ligands surveyed (1–5) are shown in Figure 1, and Table 1 summarizes this study using conditions similar to our benzophenone imine ligand screen. 4-*tert*-Butylbromobenzene (6) with *tert*-butyl carbamate (7) was used as the model substrate and $\text{Pd}_2\text{dba}_3 \cdot \text{CHCl}_3$ as the source of Pd(0). Conversion to the Boc-

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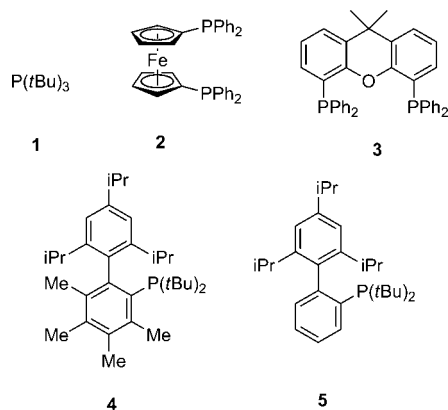


FIGURE 1. Ligands surveyed in optimization.

TABLE 1. Optimization of *tert*-Butyl Carbamate as Ammonia Equivalent^a

entry	ligand	base	solvent	time (h)	conversion by LC/MS ^b (%)
1 ^c	1	NaO- <i>t</i> -Bu	PhMe	24	0
2 ^d	2	NaO- <i>t</i> -Bu	PhMe	22	0
3	3	NaO- <i>t</i> -Bu	PhMe	22	0
4	4	NaO- <i>t</i> -Bu	PhMe	48	0
5 ^e	4	NaO- <i>t</i> -Bu	PhMe	48	(0)
6 ^{f,g}	5	K ₃ PO ₄	DME	24	0
7 ^f	5	K ₃ PO ₄	PhMe	24	0
8	5	NaO- <i>t</i> -Bu	PhMe	24	100 (76)
9	5	NaO- <i>t</i> -Bu	DME	41	(48)
10	5	NaO- <i>t</i> -Bu	DMF	28	100 (33)
11	5	NaO- <i>t</i> -Bu	THF	28	100 (65)
12	5	NaO- <i>t</i> -Bu	1,4-dioxane	28	100 (63)

^a Reaction conditions: 1.3 mmol of substrate, 1.2 equiv of **7**, 1.4 equiv of NaO*t*-Bu or 2.5 equiv of K₃PO₄, 3 mol % of Pd₂(dba)₃·CHCl₃, 9 mol % of ligand, 0.25 M in solvent, room temperature (17–22 °C). ^b Values in parentheses indicate yield. ^c 1:1 Pd/ligand; 3 mol % of Pd₂(dba)₃·CHCl₃, 6 mol % of ligand **1**. ^d 2 mol % of Pd₂(dba)₃·CHCl₃, 6 mol % of ligand **5**. ^e Substrate: 4-bromobenzonitrile. ^f Inorganic bases were ground to a fine powder using a mortar and pestle. ^g Room temperature to 30 °C.

protected aniline (**8**) was monitored by LC/MS. Keeping with our goal, all reactions were conducted at room temperature.

No product was detected in the presence of tri-*tert*-butylphosphine (**1**), dppe (**2**), or Xantphos (**3**) as ligand after 22–24 h at room temperature (entries 1–3). Ligand **4**, which has recently been shown to form one of the most active Pd complexes for aminations,¹⁴ was also unable to effect the conversion despite increased reaction times (entry 4), even when employing a more activated aryl bromide substrate (entry 5). The combination of ligand **5**, potassium phosphate (K₃PO₄) as base, and 1,2-dimethoxyethane (DME) or toluene as solvent, which was successful for amination using benzophenone imine at 30 °C,² also failed to form the desired product (entries 6 and 7). The combination of ligand **5** with sodium *tert*-butoxide as base and toluene as solvent, however,

afforded 100% conversion (76% yield) in 24 h (entry 8). DME was unsuitable as solvent as its use led to incomplete conversion and a lower (48%) yield (entry 9). Although complete conversion was observed when polar solvents were used (entries 10–12), the yields were found to be lower than the average yields obtained with toluene (entry 8). Conversions were also monitored in three control experiments: in the absence of Pd₂(dba)₃·CHCl₃, ligand **5**, and NaO-*t*-Bu, respectively. No product was detected in any of the three experiments.

The scope of this reaction is shown in Table 2. The reactions were monitored by LC/MS until starting aryl bromides were completely consumed. The *N*-Boc-protected anilines were isolated in >95% purity by flash chromatography. Electron-neutral (Table 2, entries 1, 13), electron-withdrawing (entries 3–4, 12), and electron-donating (entries 7–10) bromobenzenes all gave moderate to good yields of the corresponding *N*-Boc-anilines. Additionally, a protected aldehyde (entry 2) was a competent substrate. Aryl bromides containing a heterocycle (entry 11) or an enolizable ketone (entry 12) afforded the desired products, albeit in more modest yield. Although aryl bromides containing enolizable hydrogens can undergo α-arylation under Pd-catalyzed cross-coupling reaction conditions in the presence of sodium *tert*-butoxide,¹⁵ no significant side product arising from α-arylation was isolated for entry 12. Although not directly observed, it can be reasonably hypothesized that polymerization¹⁶ and/or aldol product formation were significant side reactions reducing the effective yield of the amidation product. In a substrate containing both chloro and bromo substituents (entry 3), reaction occurred selectively at the bromo substitution. Also notable was the conversion of an *ortho*-substituted substrate, 2-bromo-*p*-xylene, to the Boc-protected *p*-xylidine in 67% yield (entry 13).

Methyl 4-bromobenzoate (entry 5) and 4-nitrobromobenzene (entry 6) decomposed under the reaction conditions. Ester hydrolysis in the presence of the *tert*-butoxide anion¹⁷ is a possible decomposition pathway for methyl 4-bromobenzoate under the reaction conditions. It has been previously hypothesized that direct reaction between a strong base and substrates containing a nitro substituent can have a deleterious effect on the desired Pd-catalyzed reaction.¹⁶ As noted above, while electron-rich aryl bromides were amenable to this transformation, increased Pd and ligand loads (5 and 15 mol %, respectively) were required for the 4-*N,N*-dimethylamino substrate (entry 10). Noteworthy, however, is that this particular reaction with *tert*-butyl carbamate proceeds faster than when conducted under the benzophenone imine protocol² (33 h vs 7 d). The 3-methoxy (entry 8) and 3-*N,N*-dimethylamino (entry 9) substrates also gave higher yields with *tert*-butyl carbamate than with benzophenone imine.

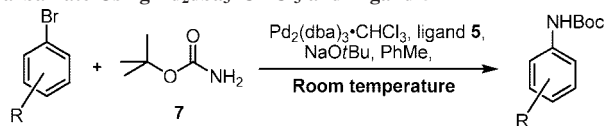
There are some similarities of Pd-catalyzed amidations using *tert*-butyl carbamate and our previously reported reactions using benzophenone imine.² The choice of ligand (**5**) for a successful reaction at low temperature with both ammonia equivalents is the same. Ligand **5**, the *tert*-butyl analogue of X-Phos, appears to provide the precise steric

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TABLE 2. General Scope of Amidations with *tert*-Butyl Carbamate Using Pd₂(dba)₃·CHCl₃ and Ligand **5**^a

Entry	Substrate	Time (h) ^b	Yield (%) ^c
1		24	76
2		24	73
3		45	83
4		27	70
5 ^d		28-48	decomp.
6		24	decomp.
7		30	74
8		22	73
9		24	70
10 ^e		33	81
11		24	47
12		48	43
13		24	67

^a Reaction conditions: 1.3 mmol of substrate, 1.2 equiv of **7**, 1.4 equiv of NaOtBu, 3 mol % of Pd₂(dba)₃·CHCl₃, 9 mol % of ligand **5**, 0.25 M in PhMe, room temperature. ^b Times are reported for complete conversion of aryl bromide. ^c Reported yields are average of two runs. ^d 2 mol % of Pd₂(dba)₃·CHCl₃, 6 mol % of ligand **5**. ^e 5 mol % of Pd₂(dba)₃·CHCl₃, 15 mol % of ligand **5**.

environment required for efficient amidation. Increasing ligand bulk further (e.g., **4**) or switching to bidentate ligands (e.g., **2**, **3**) completely abolishes amidation activity at room temperature. These observations suggest that fine stereoelectronic tuning is particularly important in the case of weakly nucleophilic, sterically bulky nitrogen nucleophiles. This reactivity contrasts with observations by Buchwald et al.¹⁴

in the Pd-catalyzed amidations of aryl chlorides using various amides/lactams, where it was hypothesized that the additional *o*-methyl substituent next to the phosphino group in **4** would function to inhibit formation of the κ^2 -amidate complexes.^{14b} Such complexes have a negative impact on catalytic turnover since they prevent or reduce the rate of reductive elimination.¹⁸

We have demonstrated the reaction scope of room temperature Pd-catalyzed amidations of aryl bromides using *tert*-butyl carbamate. The Boc group in the reaction products can be conveniently hydrolyzed under acidic conditions to reveal the free primary aniline. A number of practical advantages are inherent in this method, namely: (1) the reaction is conducted at room temperature, an important advantage to the industrial chemist; (2) a conveniently protected aniline is delivered; (3) no glovebox or Schlenk techniques are necessary; (4) the precatalyst and ligand are air stable and commercially available; and (5) the ammonia equivalent, *tert*-butyl carbamate, is a commercially available crystalline solid. A remaining limitation of the method, even with deployment of state-of-the-art catalyst/ligand combinations, is the continued need for a strong base. In an industrial chemistry setting, however, the use of a strong base coupled with a reduction in temperature may often be preferred over a weaker base at elevated temperature. Regardless, it is hoped that the present exploration of the capabilities and limitations of current catalyst systems will help to inspire the design of new catalysts with expanded reactivity.

Experimental Section

Representative Procedure: *tert*-Butyl *N*-(4-Methoxyphenyl)-carbamate (Table 2, Entry 7). An air-dried glass reaction vessel equipped with a magnetic stir bar was charged with, in order: Pd₂(dba)₃·CHCl₃ (40 mg, 0.039 mmol), ligand **5** (51 mg, 0.117 mmol), NaO-*t*-Bu (175 mg, 1.82 mmol), *tert*-butyl carbamate (183 mg, 1.56 mmol), and 4-bromoanisole (1.3 mmol). Anhydrous toluene (5.2 mL) was added, and the resultant solution was degassed using one cycle of vacuum and nitrogen purge. The reaction mixture was stirred at room temperature under nitrogen. Once the reaction was judged complete by LC/MS and TLC (30 h), it was diluted with 20 volumes of diethyl ether and filtered through a pad of Celite. The filtrate was concentrated in vacuo. The residue was purified by flash chromatography (2–45% ethyl acetate/hexanes) to afford 220 mg (76%) of *N*-(4-methoxyphenyl)carbamate as a crystalline solid: LC/MS purity >95%; ¹H NMR (400 MHz, CDCl₃) δ 7.28–7.26 (m, 2H), 6.85–6.83 (m, 2H), 6.38 (br s, 1H), 3.78 (s, 3H), 1.52 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 155.67, 153.14, 131.40, 120.54, 114.16, 80.20, 55.49, 28.35. The spectroscopic data (¹H and ¹³C NMR) are in good agreement with reported values.¹⁹

The procedure followed for the reaction and reaction workup were the same for all aryl bromides reported in Table 2 except for Pd and ligand loading. All products in Table 2 except entry 9 (*vide infra*) are known compounds and were trivially identified by comparison to literature spectroscopic data. The purity of all compounds was determined by ¹³C NMR and LC/MS.

***tert*-Butyl [3-(dimethylamino)phenyl]carbamate (Table 2, entry 9):** ¹H NMR (400 MHz, CDCl₃) δ 7.14 (t, 1H, *J* = 8.1 Hz), 6.89 (br s, 1H), 6.63 (d, 1H, *J* = 7.9 Hz), 6.43 (dd, 2H, *J* = 8.1, 2.2 Hz), 2.95 (s, 6H), 1.53 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 152.7, 151.3, 139.2, 129.4, 107.6, 106.9, 102.7, 80.1,

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40.6, 28.4; HRMS (ESI) m/z calcd for $C_{13}H_{21}N_2O_2$ $[M + H]^+$ 237.1603, found 237.1598.

Acknowledgment. This work was carried out as the summer internship project of S.B. (University of Minnesota) as part of the GlaxoSmithKline Summer Talent Identification Program. S.B. thanks Prof. R. L. Johnson (Department of Medicinal Chemistry, University of Minnesota) for the opportunity to pursue this internship. We also thank Matthew

Lochansky and Zachary Giles for assistance with the LC/MS instrumentation.

Supporting Information Available: Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO9004537