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# Regioselective Synthesis of Aryl Hydrazides by Palladium-Catalyzed Coupling of *t*-Butylcarbazate with Substituted Aryl Bromides

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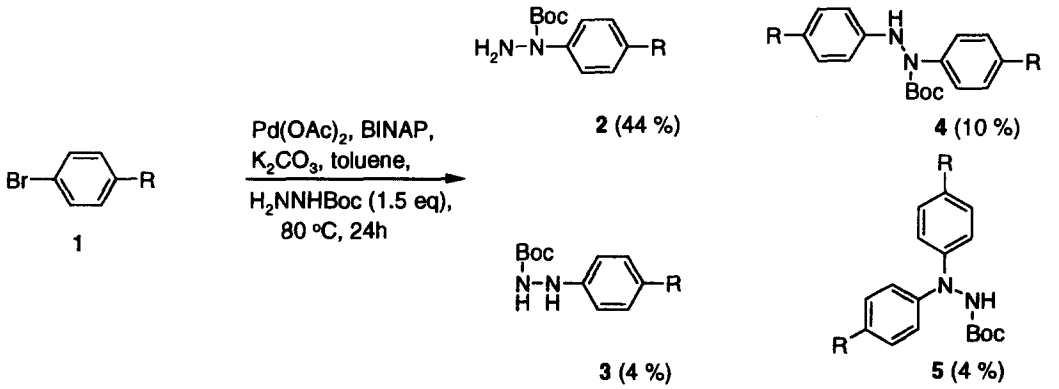
**Abstract:** Substituted aryl bromides are coupled with *t*-butylcarbazate in the presence of a palladium catalyst and base to afford regioselectively, the corresponding amidation product or amination product depending upon the position of the substituents on the aryl bromide. 

As part of our program to develop $^{99m}$Tc labeled linkers for radiodiagnostic imaging,[1] we required a regioselective synthesis of substituted aryl hydrazides. Since both Buchwald[2] and Hartwig[3] have demonstrated that the palladium-catalyzed amination of aryl halides is a powerful tool for the facile construction of carbon-nitrogen bonds, we were interested in extending the utility of this reaction to the construction of aryl hydrazides by investigating the coupling of aryl bromides with *t*-butylcarbazate. Herein, we report the first example of an intermolecular palladium-catalyzed amidation[4] reaction for the efficient synthesis of aryl hydrazides. Moreover, we wish to report that when *o*-substituted aryl bromides are used, a reversal in regioselectivity is observed affording the corresponding amination products.

Our initial attempts to couple methyl 4-bromobenzoate **1** (R=$CO_2Me$) with *t*-butylcarbazate (Scheme 1) gave a mixture of four compounds: the regioisomers **2** (amidation product) and **3** (amination product), and the dimeric compounds **4** and **5**.[5]




**Scheme 1**

To our surprise, the regioisomer **2** arising from amidation of the aryl bromide was the predominant product isolated, in a **2**:**3** ratio of 11:1. Further experimentation[6] to improve the yield of **2** provided the optimum reaction conditions: *t*-butylcarbazate (2.0 equivalents), $Pd_2(dba)_3$ (1 mol %)/DPPF (3 mol %), $Cs_2CO_3$ (1.0 equivalent) in toluene at 100 °C. Under these conditions, compound **2** was obtained in an isolated yield of 84 % and the ratio of **2**:**3** was 23:1 with complete suppression of the dimeric products **4** and **5**.

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**Table 1. Catalytic Hydrazination of Aryl Bromides**

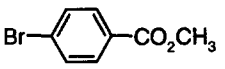
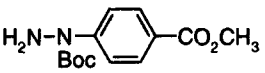
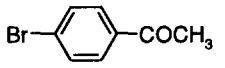
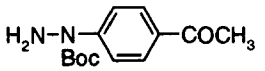
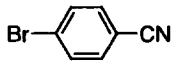
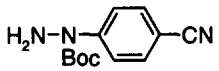
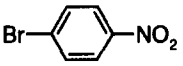
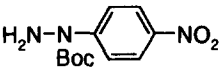
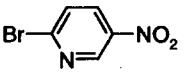
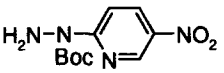
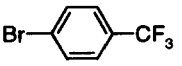
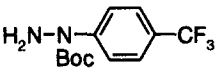
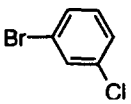
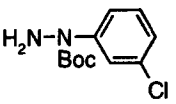
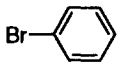
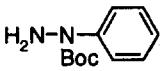
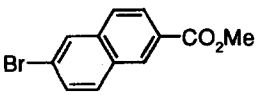
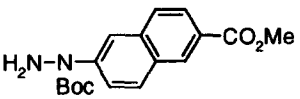
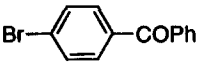
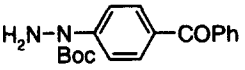
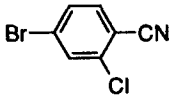
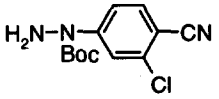
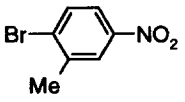
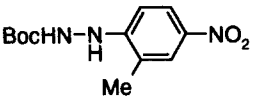
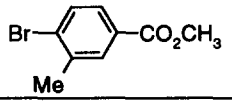
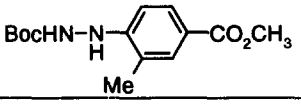
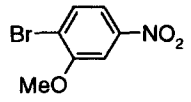
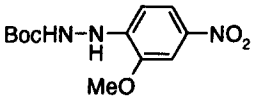
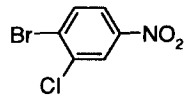
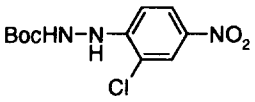
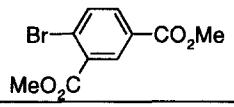
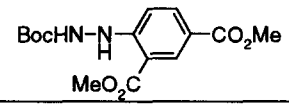
| Entry | Bromide | Product | Condition[a] | Mol % Pd | Yield % |
|---|---|---|---|---|---|
| 1 |  |  | A | 1 | 83 |
| 2 |  |  | A | 1 | 65 |
| 3 |  |  | A | 1 | 81 |
| 4 |  |  | A | 1 | 81 |
| 5 |  |  | A | 1 | 56 |
| 6 |  |  | B | 4 | 76 |
| 7 |  |  | C | 1 | 26 |
| 8 |  |  | C | 1 | 18 |
| 9 |  |  | D | 4 | 65 |
| 10 |  |  | A | 1 | 84 |
| 11 |  |  | E | 1 | 74 |
| 12 |  |  | D | 4 | 73 |
| 13 |  |  | A | 1 | 69 |

**Table 1. Catalytic Hydrazination of Aryl Bromides contd.**

| Entry | Bromide | Product | Condition[a] | Mol % Pd | Yield % |
|---|---|---|---|---|---|
| 14 |  |  | D | 4 | 71 |
| 15 |  |  | D | 4 | 74 |
| 16 |  |  | D | 4 | 73 |

a. All reactions were performed in toluene (0.5 M solutions of aryl bromide). Conditions: **A**=Aryl bromide (1 eq), *t*-butylcarbazate (2.0 eq), $Cs_2CO_3$ (1.0 eq), $Pd_2(dba)_3$ (1 mol %), DPPF (3 mol %), 100 °C for 16 h; **B**=Aryl bromide (1 eq), *t*-butylcarbazate (4.0 eq), $Cs_2CO_3$ (1.0 eq), $Pd_2(dba)_3$ (4 mol %), DPPF (12 mol %), 110 °C for 26 h; **C**=Aryl bromide (1 eq), *t*-butylcarbazate (2.0 eq), $Cs_2CO_3$ (1.0 eq), $Pd_2(dba)_3$ (1 mol %), (R)-(-)-1-[(S)-2-(diphenylphosphino)ferrocenyl]ethyldi-*t*-butylphosphine[3a] (3 mol %), 100 °C for 16 h; **D**=Aryl bromide (1 eq), *t*-butylcarbazate (4.0 eq), $Cs_2CO_3$ (1.0 eq), $Pd_2(dba)_3$ (4 mol %), DPPF (12 mol %), 100 °C for 16 h; **E**=Aryl bromide (1 eq), *t*-butylcarbazate (4.0 eq), $Cs_2CO_3$ (1.0 eq), $Pd_2(dba)_3$ (1 mol %), DPPF (3 mol %), 100 °C for 16 h; All compounds were fully characterized by NMR ($^1H$, $^{13}C$), MS, and combustion analysis.

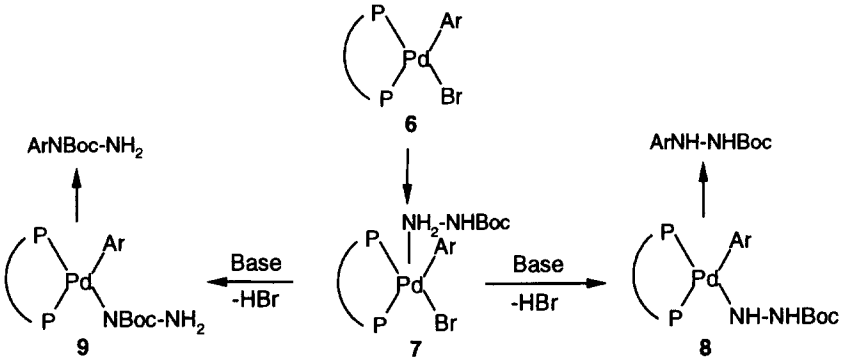
The scope of this reaction was explored by looking at a variety of aryl bromides and the results are summarized in Table 1.[7] Aryl bromides bearing electron-withdrawing *p*-substituents undergo the amidation reaction most efficiently while the corresponding *m*-analogs react in low yield (16-26%; data not shown in Table 1). For example, *para*- nitro, cyano, keto, trifluoromethyl or methyl ester functional groups afforded the amidation product in 65-83 % yield (entries 1-4, 6, 9-11). Interestingly, and in support of a Pd-mediated coupling mechanism, 2-bromo-5-nitropyridine (entry 5) afforded the expected amidation product in 56 % yield but when the reaction was repeated in the absence of catalyst, the corresponding amination product was obtained (16% yield; data not shown in Table 1) resulting from nucleophilic aromatic subsitution.

Unactivated aryl bromides such as bromobenzene, however, failed to react under the standard coupling conditions. The major product isolated in this case was the homo-coupled product.[8] A recent report by Hartwig et al.[3b] which described rate accelerations in the palladium-catalyzed amination of aryl halides with (R)-(-)-1-[(S)-2-(diphenylphosphino)ferrocenyl]ethyldi-*t*-butylphosphine, prompted us to examine this ligand for the Pd-catalyzed coupling of *t*-butylcarbazate with bromobenzene. In combination with $Pd_2(dba)_3$ (entry 8), this catalyst provided the desired amidation product, albeit in a low yield of 18 %.

For aryl bromides with an additional substituent in the *o*-position, a reversal in the regioselectivity of coupling was observed. For example, when the *o*-substituent is methyl, methoxy, chloro or carbomethoxy the corresponding amination products (entries 12-16) were isolated. $^1H$ NMR clearly distinguished between the two regioisomers since the amination products contained two distinct exchangeable NH signals.

To explain the regiochemical outcome of the coupling reaction we propose the following mechanism (Scheme 2). The first step most likely involves the more nucleophilic amino portion of *t*-butylcarbazate adding to the electrophilic Pd (II) complex **6** (which itself arises from oxidative addition of Pd (0) to the aryl bromide), to form the five-coordinate complex **7**. In the presence of base, and subsequent loss of HBr (either concomitant or stepwise), one could envisage an intramolecular rearrangement to afford complex **9**, which upon reductive elimination would afford the Pd (0) complex and the corresponding amidation product. However, if the

intramolecular rearrangement is sterically hindered as in the case of *o*-substituted aryl bromides, loss of HBr would give complex **8**, and subsequent reductive elimination affords the Pd (0) complex and the corresponding amination product.




**Scheme 2**

In conclusion, we have developed a method for the regioselective synthesis of aryl hydrazides by the palladium-catalyzed coupling of aryl bromides with *t*-butylcarbazate. Efforts are currently underway to expand the utility of this reaction to aryl bromides substituted with electron donating groups.

***Acknowledgement:*** We thank Andrea Kranack for analytical support.

### *References and Notes*

1. a) Ultee, M. E.; Bridger, G. J.; Abrams, M. J.; Longley, C. B.; Burton, C. A.; Larson, S.; Henson, G.; Padmanabhan, S.; Gaul, F.; Schwartz, D. *J. Nucl. Med.* **1997**, 38, 133. b) Bridger, G. J.; Abrams, M. J.; Padmanabhan, S.; Gaul, F.; Larson, S.; Henson, G.; Schwartz, D. A.; Longley, C. B.; Burton, C. A.; Ultee, M. E. *Bioconjugate Chem.* **1996**, 7, 255.
2. a) Old, D.W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, 120, 9722. b) Sadighi, J. P.; Harris, M. C. Buchwald, S. L. *Tetrahedron Lett.* **1998**, 39, 5327. c) Wolfe, J. P.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, 38, 6359. d) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, 118, 7215. e) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, 61, 1133.
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4. For an example of an intramolecular amidation, see: Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, 52, 7525.
5. For examples of selective aminations see: a) Hong, Y.; Senanayake, C. H.; Xiang, T.; Vandenbossche, C. P.; Tanoury, G. J.; Bakale, R. P.; Wald, S. A. *Tetrahedron Lett.* **1998**, 39, 3121. b) Beletskaya, I. P.; Bessmertnykh, A. G.; Guilard, R. *Tetrahedron Lett.* **1997**, 38, 2287.
6. Other palladium catalyst/ligand combinations such as $Pd(OAc)_2$/DPPF and $Pd_2(dba)_3$/BINAP gave lower yields and the coupling reaction failed when $Pd_2(dba)_3$/(2-furyl)$_3$P, $Pd_2(dba)_3$/(o-tolyl)$_3$P or $Pd(PPh_3)_4$ were employed. Alternative alkali metal bases such as $KHCO_3$, KOAc and $K_2CO_3$ also gave lower yields; the reaction failed with bases such as $Et_3N$, $Li_2CO_3$ or $KH_2PO_4$. It should be noted that aryl chlorides failed to couple under the reaction conditions.
7. Representative procedure: An oven dried reagent vial was charged with aryl bromide (1.0 eq), *t*-butylcarbazate (2.0 eq), $Pd_2(dba)_3$/DPPF (see Table 1) and $Cs_2CO_3$ (1.0 eq), then evacuated and purged with nitrogen (repeated three times). Degassed toluene was added (to give a 0.5 M solution of aryl bromide), the vial was sealed and heated to 100 $^0$C with stirring for 16 h. The reaction mixture was allowed to cool to room temperature, diluted with dichloromethane, filtered and concentrated. The crude product was then purified by flash column chromatography on silica gel or basic alumina.
8. Penalva, V.; Hassan, J.; Lavenot, L.; Gozzi, C.; Lemaire, M. *Tetrahedron Lett.* **1998**, 39, 2559.