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Synthesis of 2-Arylpiperidines by Palladium Couplings of Aryl Bromides with Organozinc Species Derived from Deprotonation of *N*-Boc-Piperidine

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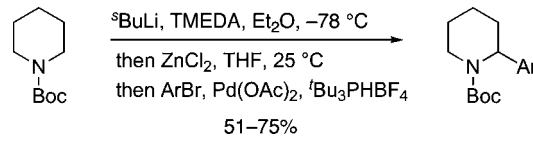
ABSTRACT



The organolithium species derived from proton abstraction of *N*-Boc-piperidine with *s*-BuLi and TMEDA can be transmetalated to the organozinc reagent, and this organometallic species can be coupled directly with aryl bromides in a Negishi-type reaction using palladium catalysis with the ligand tri-*tert*-butylphosphine (*t*-Bu_3P-HBF_4). The chemistry was applied to a very short synthesis of the alkaloid anabasine.

Aryl-substituted saturated heterocyclic compounds are a very important class of compounds, present in many natural products and biologically active molecules (for example, NK_1 antagonists).[1] Various methods have been developed for their synthesis, although the most obvious is by coupling the aryl unit with the intact heterocycle. Despite this, the direct arylation by metalation and then coupling of saturated heterocycles is rare.[2] Dieter and co-workers reported the lithiation of *N*-*tert*-butoxycarbonyl-pyrrolidine (*N*-Boc-pyrrolidine) followed by transmetalation with CuCN and palladium coupling.[3] Other substrates were less successful under these conditions, although a few examples using *N*-Boc-piperidine were described.[3] Recently, Campos and co-workers at Merck found that 2-aryl-pyrrolidines could be prepared by transmetalation of enantioenriched *N*-Boc-2-lithiopyrrolidine to the organozinc species and coupling with aryl bromides.[4] This organozinc method using $Pd(OAc)_2$ and tri-*tert*-butylphosphine (as its HBF_4 salt[5]) was superior to the use of CuCN. We therefore investigated this Negishi-type coupling[6] methodology for the preparation of 2-aryl-piperidines[7] and report herein the results of this study.

Following the procedure reported by Beak and Lee,[8] *N*-Boc-piperidine **1** was treated with *s*-BuLi and TMEDA (1.05 equiv of each) in Et_2O at −78 °C to effect lithiation at the 2-position. Transmetalation with zinc chloride (1.3 equiv) and warming to room temperature gave the required organozinc species, to which was added a solution containing the palladium salt (4 mol %), the phosphine ligand (8 mol

(1) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893.

(2) O'Brien, P.; Bilke, J. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 2734.

(3) (a) Dieter, R. K.; Li, S. *J. Org. Chem.* **1997**, *62*, 7726. (b) Dieter, R. K. *Tetrahedron Lett.* **1995**, 3613. (c) Dieter, R. K.; Oba, G.; Chandupatla, K. R.; Topping, C. M.; Lu, K.; Watson, R. T. *J. Org. Chem.* **2004**, *69*, 3076.

(4) (a) Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C. *J. Am. Chem. Soc.* **2006**, *128*, 3538. (b) Klapars, A.; Campos, K. R.; Waldman, J. H.; Zewge, D.; Dormer, P. G.; Chen, C. *J. Org. Chem.* **2008**, *73*, 4986.

(5) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295.

(6) Negishi, E.; Hu, Q.; Huang, Z.; Wang, G.; Yin, N. In *The Chemistry of Organozinc Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley: Chichester, 2006; Chapter 11.

(7) For alternative methods to prepare 2-arylpiperidines, see for example: (a) Beak, P.; Wu, S.; Yum, E. K.; Jun, Y. M. *J. Org. Chem.* **1994**, *59*, 276. (b) Madan, S.; Milano, P.; Eddings, D. B.; Gawley, R. E. *J. Org. Chem.* **2005**, *70*, 3066. (c) Xiao, D.; Lavey, B. J.; Palani, A.; Wang, C.; Aslanian, R. G.; Kozlowski, J. A.; Shih, N.-Y.; McPhail, A. T.; Randolph, G. P.; Lachowicz, J. E.; Duffy, R. A. *Tetrahedron Lett.* **2005**, *46*, 7653. (d) Hunt, J. C. A.; Laurent, P.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2378. (e) Abrunhosa-Thomas, I.; Roy, O.; Barra, M.; Besset, T.; Chalard, P.; Troin, Y. *Synlett* **2007**, 1613.

(8) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109.

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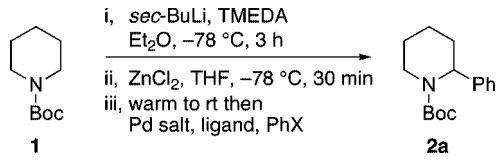
Table 1. Optimization of the Coupling Reaction To Give **2a**

Pd salt	phosphine	aryl halide	yield (%)
$Pd(OAc)_2$	PPh_3	PhBr	0
$Pd(OAc)_2$	Cy_3P-HBF_4	PhBr	52
$Pd(OAc)_2$	t-Bu_3P-HBF_4	PhBr	75
$Pd(OAc)_2$	t-Bu_3P-HBF_4	PhBr	56[a]
$PdCl_2(PhCN)_2$	t-Bu_3P-HBF_4	PhBr	trace
$Pd(OAc)_2$	t-Bu_3P-HBF_4	PhCl	trace
$Pd(OAc)_2$	t-Bu_3P-HBF_4	PhI	61

[a] Inverse addition.

%), and the aryl halide (1.3 equiv). A selection of reagents was screened as shown in Table 1 and Scheme 1. The best

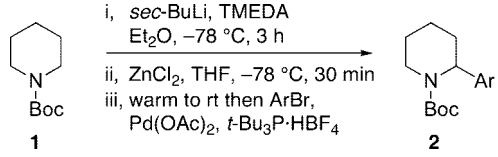
Scheme 1. Negishi Coupling To Give **2a**



conditions were the use of palladium acetate and tri-*tert*-butylphosphine·HBF_4. Both bromobenzene and iodobenzene were successful, although the bromide gave slightly superior results. It is feasible that substoichiometric amounts of zinc chloride could be used, depending on the active zinc species in solution,[4] although reaction with 0.3 equiv of $ZnCl_2$ gave only recovered starting material **1**.

Using the optimized conditions for the coupling reaction, a range of aryl bromides were tested (Scheme 2, Figure 1).

Scheme 2. Optimized Conditions for the Coupling To Give **2**



The reaction was found to be general for a variety of substituted aromatic bromides, and successful couplings were achieved with both electron-donating and electron-withdrawing aryl substituents. Thus, methyl- and alkoxy-substituted aryl bromides gave the products **2b**−**f**. The coupling tolerated unprotected 4-bromoaniline to give the product **2g**. In addition, 1-bromo-4-chlorobenzene, 3-bromoacetophenone, and 1-bromonaphthalene were successful (to give **2h**−**j**).

The chemistry was amenable to the use of heteroaromatic bromides, as illustrated in Scheme 3. Coupling with 3-bromopyridine gave the 2-arylpiperidine **2k**. In this case the yield was slightly improved (from 47% to 51%) by warming

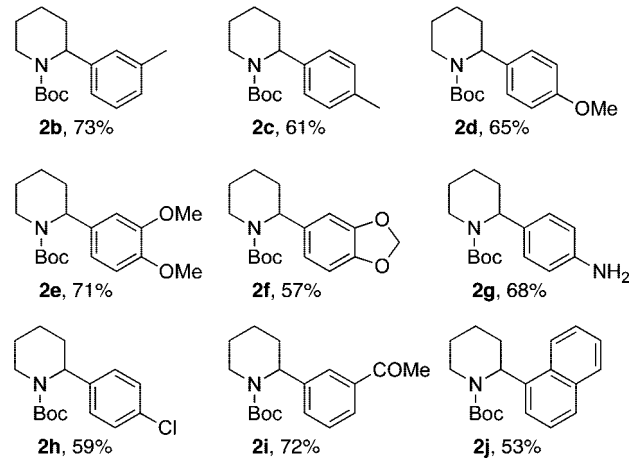


Figure 1. Structures and yields of the products **2b**−**j**.

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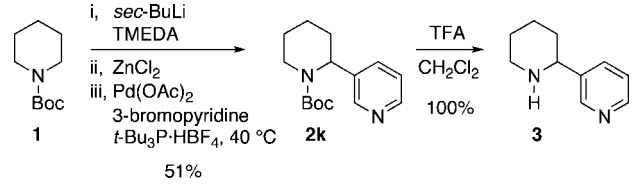
the reaction to 40 °C. Quantitative removal of the *N*-Boc group (using trifluoroacetic acid, TFA) gave the alkaloid

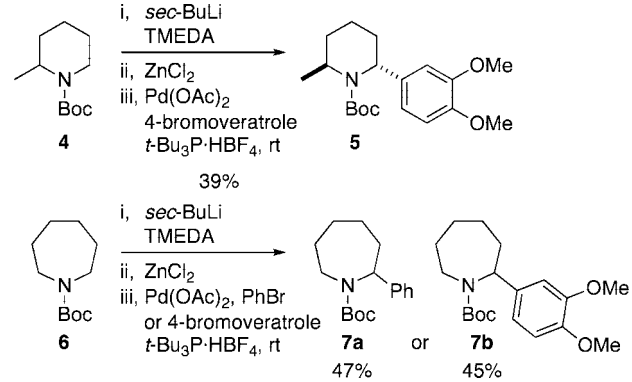
Scheme 3. Synthesis of (±)-Anabasine **3**



(±)-anabasine **3**.[9] This represents an extremely short (two steps) synthesis of this alkaloid.

We have explored two other substrates for this chemistry (Scheme 4). Deprotonation of *N*-Boc-2-methylpiperidine **4**

Scheme 4. Application to Other Substrates



is known to occur at the 6-position to give, after electrophilic quench, *trans*-2,6-disubstituted piperidines.[8] Deprotonation

of **4** and transmetalation to the organozinc compound followed by cross-coupling with 4-bromoveratrole (using 8 mol % $Pd(OAc)_2$ and 12 mol % *t*-Bu_3P-HBF_4) gave the desired *trans* product **5**. The lithiation of the seven-membered ring compound **6** and electrophilic quench is known[8] but is less efficient than that of smaller ring analogs or of more rigid carbamates.[10] However, the Negishi-type coupling was successful with this substrate to give the products **7a** and **7b**.

In summary, we have extended the range of substitution products that can be accessed from, in particular, *N*-Boc-2-lithiopiperidine. A variety of 2-aryl-piperidines can be prepared in good yield using transmetalation to the organozinc species and palladium-catalyzed cross-coupling. This chemistry provides a direct access to aryl-substituted piperidines and was applied to the shortest known synthesis of (±)-anabasine. Current work is investigating the asymmetric synthesis of these products, which could derive from asymmetric deprotonation of *N*-Boc-piperidine,[11] or dynamic resolution of the intermediate organolithium species.[12]

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Supporting Information Available: Experimental procedures and spectroscopic data for the products **2a**−**k**, **3**, **5**, and **7a,b**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL801579R

(9) (a) Larivee, A.; Mousseau, J. J.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 52. (b) Castro, A.; Ramirez, J.; Juarez, J.; Teran, J. L.; Orea, L.; Galindo, A.; Gnecco, D. *Heterocycles* **2007**, *71*, 2699. (c) Amat, M.; Canto, M.; Lior, M.; Bosch, J. *Chem. Commun.* **2002**, 526. (d) Felpin, F.-X.; Girard, S.; Vo-Thanh, G.; Robins, R. J.; Villiéras, J.; Lebreton, J. *J. Org. Chem.* **2001**, *66*, 6305. (e) Wanner, M. J.; Koomen, G.-J. *J. Org. Chem.* **1996**, *61*, 5581.

(10) Gross, K. M. B.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 315.

(11) (a) Bailey, W. F.; Beak, P.; Kerrick, S. T.; Ma, S.; Wiberg, K. B. *J. Am. Chem. Soc.* **2002**, *124*, 1889. (b) McGrath, M. J.; Bilke, J. L.; O'Brien, P. *Chem. Commun.* **2006**, 2607. (c) Coldham, I.; O'Brien, P.; Patel, J. J.; Raimbault, S.; Sanderson, A. J.; Stead, D.; Whittaker, D. T. E. *Tetrahedron: Asymmetry* **2007**, *18*, 2113.

(12) (a) Coldham, I.; Patel, J. J.; Raimbault, S.; Whittaker, D. T. E. *Chem. Commun.* **2007**, 4534. (b) Coldham, I.;Raimbault, S.;Chovatia, P. T.;Patel, J. J.;Leonori, D.;Sheikh, N. S.;Whittaker, D. T. E. *Chem. Commun.* **2008**, DOI: 10.1039/B810988E.