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Synthesis of *N*-Heteroaryl-7-azabicyclo[2.2.1]heptane Derivatives via Palladium–Bisimidazol-2-ylidene Complex Catalyzed Amination Reactions

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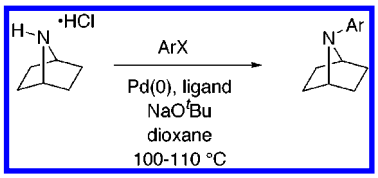
ABSTRACT



A one-step approach to novel *N*-heteroaryl-substituted-7-azabicyclo[2.2.1]heptanes from readily available heteroaryl halides and 7-azabicyclo-[2.2.1]heptane has been achieved. The cross-coupling amination reaction employs palladium–bisimidazol-2-ylidene complexes as catalysts to give good to moderate yields over a wide variety of substrates.

Recently developed palladium- or nickel-catalyzed amination of aryl halides and triflates has opened great opportunities in many areas of organic synthesis.[1] General, reliable, and practical *N*-arylations of a wide variety of amines and anilines with both electron-rich and electron-deficient aryl halides have been achieved.[2−6] These pioneering studies have shown that a well-tailored metal−ligand catalyst system is crucial for successful aryl C−N bond formation.[7]

The nucleophilic *N*-heterocyclic carbenes have attracted considerable attention as ligands for a variety of palladium-catalyzed coupling reactions.[4,8] We recently reported on the utility of the $Pd_2(dba)_3$−Imes·HCl and $Pd(OAc)_2$−DiImes·HCl catalyst systems for Suzuki-type C−C bond formation reactions of aryl chlorides and arylboronic acids.[9,10] As part of a drug discovery program aimed at the synthesis of *N*-heteroaryl-substituted 7-azabicyclo[2.2.1]heptanes, we sought to investigate the Pd−DiImes·HCl catalyst system in cross-coupling amination reactions of heteroaryl halides with 7-azabicyclo[2.2.1]heptane.

Prior to development of the amination methodology, it was necessary to develop an efficient and practical route for the preparation of 7-azabicyclo[2.2.1]heptane hydrochloride (**1**).[11] To date, the most practical synthesis of **1** was reported by

(1) For a recent review of metal-catalyzed amination reactions, see: (a) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125−146. (b) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046−2067.

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(6) Desmarets, C.; Schneider, R.; Fort, Y. *Tetrahedron Lett.* **2000**, *41*, 2875−2879.

(7) For recent examples of catalytic aryl amination, see: (a) Old, D. W.; Harris, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1403−1406. (b) Harris, M. C.; Buchwald, S. L. *J.Org. Chem.* **2000**, *65*, 5327−5333. (c) Bei, X.; Uno, T.; Norris, J.; Turner, H. W.; Weinberg, W. H.; Guram, A. S.; Petersen, J. L. *Organometallics* **1999**, *18*, 1840−1853. (d) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369−7370.

(8) (a) Regitz, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 725−728. (b) Hermann, W. A.; Kocher, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2163-2187.

(9) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804−3805.

(10) Zhang, C.; Trudell, M. L. *Tetrahedron Lett.* **2000**, *41*, 595−598.

(11) For a recent review on 7-azabicyclo[2.2.1]heptanes, see: Chen. Z.; Trudell, M. L. *Chem. Rev.* **1996**, *96*, 1179−1193.

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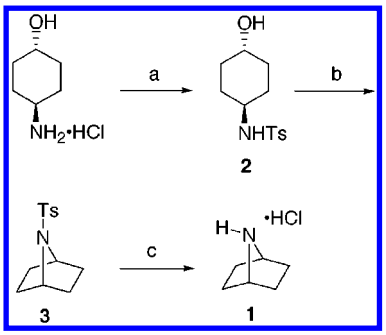
Fraser and Swingle.[12] Their five-step sequence furnished **1** with an overall yield of 18−36%. Alternatively, Nelsen et al. demonstrated that *trans*-4-aminocyclohexanol could be directly converted into **1** (26%) when diethoxytriphenylphosphorane was employed as a cyclodehydrating reagent.[13] However, the utility of this approach was limited due to the formation of 7-ethyl-7-azabicyclo[2.2.1]heptane (18% yield) as a side product which required additional steps to separate it from **1**.

As illustrated in Scheme 1, a three-step synthesis of **1** from commercially available *trans*-4-aminocyclohexanol hydrochloride was achieved by treatment of *trans*-4-aminocyclohexanol hydrochloride with tosyl chloride in the presence of potassium hydroxide with a catalytic amount of triethylamine in acetonitrile. This afforded the desired tosylamide **2** in nearly quantiative yield.[14] The tosylamide **2** was then subjected to Mitsunobu reaction conditions employing PPh_3 (2.5 equiv) and DEAD (2.5 equiv) in THF at room temperature.[15] This effected the ring closure and generated the 7-azabicyclo[2.2.1]heptane **3** in 80% yield. It was determined that excess PPh_3 and DEAD were necessary to achieve high yields of **3**. For example, 1.2 equiv of PPh_3 and DEAD gave only a 66% yield of **3**. In addition, other *N*-acyl groups (e.g., BOC, CBZ) proved to be less effective for ring closure under these reaction conditions. This direct cyclization was a significant improvement over existing methods which required additional protection and deprotection steps prior to ring closure.[12] In addition, the intramolecular cyclization reaction does not appear to be limited by the reaction scale. High yields have been obtained on either a milligram or multigram scale.

The *N*-tosyl group of **3** was removed with freshly prepared sodium naphthalide in THF to furnish the desired 7-azabicyclo-[2.2.1]heptane (**1**).[16] Removal of the tosyl group was also attempted with HBr/HOAc. However, this method was less effective. As previously reported, due to the volatile nature of **1**, the 7-azabicyclo[2.2.1]heptane was routinely isolated as the hydrochloride salt.[12] This short and practical synthetic sequence afforded 7-azabicyclo[2.2.1]heptane (**1**) in 53% overall yield.

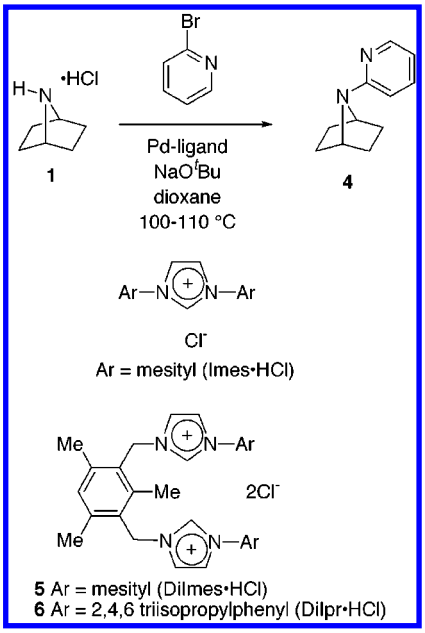
The catalytic cross-coupling reaction of 7-azabicyclo-[2.2.1]heptane (**1**) and 2-bromopyridine in dioxane at 100−110 °C which furnished 7-(2-pyridinyl)-7-azabiyclo[2.2.1]-heptane (**4**) was selected as a model reaction for investigation of the efficiencies of different Pd−ligand catalyst systems (Table 1). As summarized in Table 1, the PPh_3, DPPB, DPPP, and P(*o*-tol)$_3$ ligands exhibited low conversion and were found to be less efficient than the two bisimidazolium salt catalyst precursors, mesityl bisimidazolium salt **5** (DiImes·HCl, entry 6) and the 2,4,6-triisopropylphenyl bisimidazolium salt **6** (DiIpr·HCl, entry 7).[17,18] Comparing the two

Scheme 1[a]



[a] Reagents and conditions: (a) TsCl, KOH, Et_3N (catalytic), CH_3CN; (b) PPh_3, DEAD, THF, 25 °C; (c) NaNp, DME, −35 to 25 °C.

Table 1. Influence of the Pd/Ligand Catalyst System on the Cross-Coupling Amination of **1** with 2-Bromopyridine



entry[a]	Pd−ligand	time (h)	yield (%)[b]
1	$Pd(OAc)_2$−PPh_3	42	37[c]
2	$Pd(OAc)_2$−DPPP	40	25[c]
3	$Pd(OAc)_2$−DPPB	40	11[c]
4	$Pd_2(dba)_3$−P(o−Tol)$_3$	36	51
5	$Pd_2(dba)_3$−DPPF[d]	36	66
6	$Pd_2(dba)_3$−DiImes•HCl (5)	36[e]	61
7	$Pd_2(dba)_3$−DiIpr•HCl (6)	36[e]	67

[a] Typical reaction conditions: 4 mol % of Pd, 4 mol % of ligand, 2.8 mmol of NaOtBu, 1 mmol of 2-bromopyridine, 1.2 mmol of **1**, 5 mL of dioxane, 100−110 °C. [b] Isolated yields. [c] 2-Bromopyridine was not completely consumed and Pd black was observed. [d] Pd/ligand ratio was 1:1.5. [e] Reaction time after a 30 min catalyst activation period.

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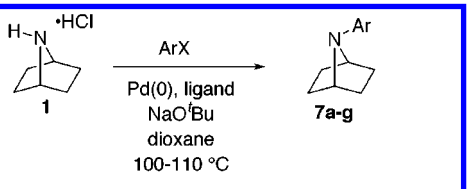
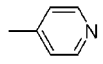
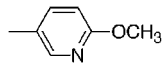
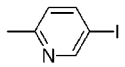
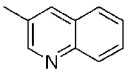
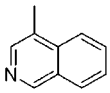
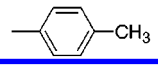
(16) (a) Palmgren, A.; Larsson, A. L. E.; Bäckvall, J. E.; Helquist, P. *J. Org. Chem.* **1999**, *64*, 836−847. (b) Heathcock, C. H.; Blumenkopf, T. A.; Smith, K. M. *J. Org. Chem.* **1989**, *54*, 1548−1562.

bisimidazolium salts, the catalyst precursor **6** gave a slightly higher yield (entry 7) than **5** (entry 6). The higher performance of the bisimidazolium salt **6** is thought to be due to its better electron-donating ability and more steric hindrance. Only the DPPF ligand gave a yield similar (entry 5) to that of the bisimidazolium salt **6**. However, this required a higher Pd−ligand ratio (1:1.5) to furnish the optimized yield (66%). In addition, when the amination reactions were attempted with the Pd−bisimidazolium salt system, only *tert*-butyl aryl ethers were isolated and no amination products were observed.

The successful amination of **1** then prompted a further investigation of the scope and limitations of the $Pd_2(dba)_3$−bisimidazolium salt **6** catalyst system for general cross-coupling amination reactions. As summarized in Table 2, a

Table 2. Pd−Bisimidazol-2-ylidene (**6**) Complex Catalyzed Cross-Coupling Reactions of Aryl Halides and **1**

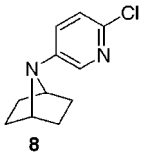


cmpd [a]	X	Ar	time (h) [b]	yield (%) [c]
4	Br		36	67
7a	Br		24	71 [d]
7b	Br[e]		25	58
7c	Br		41	36 [f]
7d	Cl		30	56 [g]
7e	Br		36	67
7f	Br		36	71
7g	Cl		30	66

[a] All products were characterized by NMR, IR, MS, and C, H, N analysis. [b] Reaction time after a 30 min catalyst activation period. [c] Isolated yields. [d] $Pd(OAc)_2$ was used as the Pd source. [e] 4-Bromopyridine•HCl was employed with 4.2 equiv of NaO^{t}Bu. [f] Yield based on recovered starting material. [g] 7-(2-Chloro-5-pyridinyl)-7-azabicyclo[2.2.1]heptane (**8**) was also isolated in 5% yield.

number of structurally and electronically diverse aryl halides were employed. Under the reaction conditions, 2- and 3-bromopyridines gave the corresponding *N*-pyridinyl-7-azabicyclo[2.2.1]heptane derivatives (**4** and **7a**) in 67% and 71% yields, respectively. 4-Bromopyridine hydrochloride also underwent the amination reaction and furnished **7b** in 58% yield (4.2 equiv of NaO^{t}Bu employed). Conversely, introduction of a methoxy group as electron donor on the pyridine ring resulted in an incomplete reaction even after long reaction times (41 h), and the yield of **7c** was low (36%). The quinoline and isoquinoline heterocyclic systems gave results similar to those of the pyridine analogues and afforded **7e** and **7f** in good yields. However, longer reaction times were needed to complete the cross-coupling reaction of quinoline and isoquinoline heterocyclics relative to the formation of **4**. As a comparison, the tolyl bromide provided **7h** in 66% yield.

As expected, the 2-chloro-5-iodopyridine gave a predominant coupling product at the 2-position (**7d**). However, a small amount of 7-(2-chloro-5-pyridinyl)-7-azabicyclo-[2.2.1]heptane (**8**) was isolated (5% yield) that resulted from amination at the 5-iodo substituent. The regioselectivity of this reaction is noteworthy since it has been shown that the reaction of the polyfunctionalized heteroaromatic core in the cross-coupling reaction gave a regioisomeric mixture.[19]



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In summary, application of the Pd−bisimidazolium salt catalyzed cross-coupling amination methodology provides a general and convenient route for the construction a wide range of *N*-aryl-substituted-7-azabicyclo[2.2.1]heptane derivatives. The synthetic utility of this catalyst system appears to be broad and useful for the construction of *N*-arylamine systems. The biological results and structure−activity relationships of the *N*-aryl-substituted-7-azabicyclo[2.2.1]heptane

(17) For recent examples of catalytic amination with modified phosphine ligands, see: (a) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144−1157. (b) Yang, B. H.; Buchwald, S. L. *Org. Lett.* **1999**, *1*, 35−37. (c) Singer, R. A.; Buchwald, S. L.; *Tetrahedron Lett.* **1999**, *40*, 1095−1098. (d) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413−2416. (e) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369−7370. (f) Singer, R. A.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 213-214. (g) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722−9723. (h) Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 8451−8458. (i) Louie, J.; Hartwig, J. F.; Fry, A. J *J. Am. Chem. Soc.* **1997**, *119*, 11695−11696. (j) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 6066−6068. (k) Wolfe, J. P.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *36*, 6359−6362. (l) Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054−6058. (m) Marcoux, J.; Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1568−1569.

(18) The bisimidazolium salt **6** was made in a fashion similar to that of the bisimidzolium salt **5** (ref 9). A mixture of 1,3-di(α-chloromethyl)-2,4,6-trimethylbenzene (1.0 mmol) and *N*-(2,4,6-triisopropylphenyl)imidazole (2.0 mmol) was heated in xylene at 120 °C for 48 h and furnished **6** in 76% yield.

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derivatives are under further investigation and will be reported in due course.

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Supporting Information Available: Experimental procedures and spectroscopic data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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