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Pd-Catalyzed C−H Activation/C−N Bond Formation: A New Route to 1-Aryl-1*H*-benzotriazoles

Rapolu Kiran Kumar, Md Ashif Ali, and Tharmalingam Punniyamurthy*

Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati-781039, India

tpunni@iitg.ernet.in

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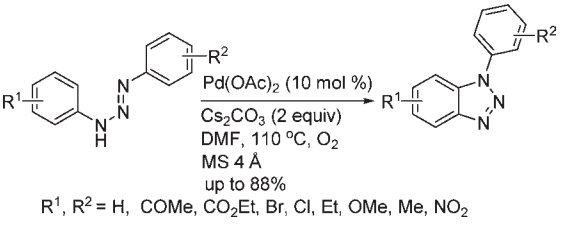
ABSTRACT



A method for the C−H activation of aryl triazene compounds followed by intramolecular amination is described. It involves the use of a catalytic amount of $Pd(OAc)_2$ that efficiently effects the cyclization to provide 1-aryl-1*H*-benzotriazoles at moderate temperature.

Recent advances in cross-coupling reactions using transition metal catalysis provide effective methods for C−N bond formation.[1] Among them, C−H activation and functionalization afford a simple and powerful tool for an atom economical process. Notable progress has been made using predominantly Ru,[2] Rh,[3] Pd,[4] Ag,[5] and Cu[6] based systems. Herein, we report a new approach to the

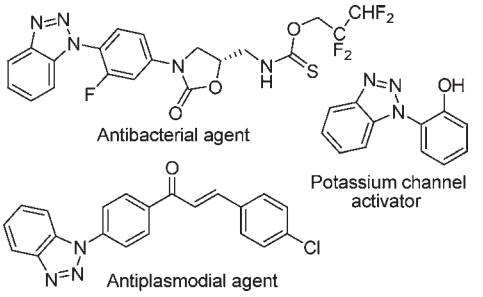


Figure 1. Examples of some biologically active 1-aryl-1*H*-benzotriazoles.

(1) For some recent reviews, see: (a) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954. (b) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651. (c) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (d) Meldal, M.; Tornoe, C. W. *Chem. Rev.* **2008**, *108*, 2952. (e) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395. (f) Wurtz, S.; Glorius, F. *Acc. Chem. Res.* **2008**, *41*, 1523. (g) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400.

(2) For some recent examples, see: (a) Leung, S. K.-Y.; Tsui, W.-M.; Huang, J.-S.; Che, C.-M.; Liang, J.-L.; Zhu, N. *J. Am. Chem. Soc.* **2005**, *127*, 16629. (b) Long, A. K. M.; Yu, R. P.; Timmer, G. H.; Berry, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 12228. (c) Shou, W. G.; Li, J.; Guo, T.; Lin, Z.; Jia, G. *Organometallics* **2009**, *28*, 6847.

(3) For some recent studies, see: (a) Olson, D. E.; Du Bois, J. *J. Am. Chem. Soc.* **2008**, *130*, 11248. (b) Norder, A.; Herrmann, P.; Herdtweck, E.; Bach, T. *Org. Lett.* **2010**, *12*, 3690. (c) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378. (d) Zalatan, D. N.; Du Bois, J. *J. Am. Chem. Soc.* **2008**, *130*, 9220.

(4) For some recent examples, see: (a) Inamoto, K.; Saito, T.; Katsuno, M.; Sakamoto, T.; Hiroya, K. *Org. Lett.* **2007**, *9*, 2931. (b) Xiong, T.; Li, Y.; Lv, Y.; Zhang, Q. *Chem. Commun.* **2010**, 6831. (c) Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676. (d) Jordan-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184. (e) Mei, T.-S.; Wang, X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806. (f) Rice, G. T.; White, M. C. *J. Am. Chem. Soc.* **2009**, *131*, 11707. (g) Wu, L.; Qiu, S.; Liu, G. *Org. Lett.* **2009**, *11*, 2707. (h) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560. (i) Xiao, Q.; Wang, W.-H.; Liu, G.; Meng, F.-K.; Chen, J.-H.; Yang, Z.; Shi, Z.-J. *Chem.—Eur. J.* **2009**, *15*, 7292. (j) Neumann, J. J.; Rakshit, S.; Droge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 6892. (k) Wang, H.; Wang, Y.; Peng, C.; Zhang, J.; Zhu, Q. *J. Am. Chem. Soc.* **2010**, *132*, 13217.

(5) Cho, S. H.; Kim, J. Y.; Lee, S. Y.; Chang, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 9127.

(6) For some recent examples, see: (a) Zhang, L.; Ang, G. Y.; Chiba, S. *Org. Lett.* **2010**, *12*, 3682. (b) Allen, C. P.; Benkovics, T.; Turek, A. K.; Yoon, T. P. *J. Am. Chem. Soc.* **2009**, *131*, 12560. (c) Monguchi, D.; Fujiwara, T.; Furukawa, H.; Mori, A. *Org. Lett.* **2009**, *11*, 1607. (d) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932. (e) Guo, S.; Qian, B.; Xie, Y.; Xia, C.; Huang, H. *Org. Lett.* **2010**, *13*, 522.

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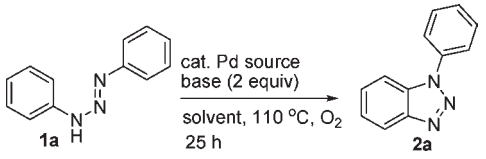
Table 1. Optimization of Reaction Conditions



entry	Pd source	base	solvent	yield (%)[a,b]
1	$Pd(OAc)_2$	Cs_2CO_3	DMSO	36
2	$PdCl_2$	Cs_2CO_3	DMSO	30
3	$PdCl_2(PPh_3)_2$	Cs_2CO_3	DMSO	15
4	**$Pd(OAc)_2$**	**Cs_2CO_3**	**DMF**	65(**80**[c])
5	$Pd(OAc)_2$	Cs_2CO_3	DMF	23[d]
6	$Pd(OAc)_2$	Cs_2CO_3	xylene	n.d.
7	$Pd(OAc)_2$	Cs_2CO_3	chlorobenzene	n.d.
8	$Pd(OAc)_2$	Cs_2CO_3	1,4-dioxane	3
9	$Pd(OAc)_2$	Na_2CO_3	DMF	12
10	$Pd(OAc)_2$	K_2CO_3	DMF	72
11	$Pd(OAc)_2$	KOH	DMF	5
12	$Pd(OAc)_2$	K_3PO_4	DMF	25
13	$Pd(OAc)_2$	KO^tBu	DMF	n.d.
14	$Pd(OAc)_2$	Cs_2CO_3	DMF	55[e]
15	$Pd(OAc)_2$	Cs_2CO_3	DMF	32[f]
16	-	Cs_2CO_3	DMF	n.d.

[a] (Phenylimino)-2-phenylhydrazine **1a** (1 mmol), Pd source (10 mol %), and base (2 mmol) were stirred at 110 °C in solvent (1 mL) under an oxygen balloon. [b] Isolated yield. [c] With MS 4 Å (100 mg). [d] $Pd(OAc)_2$ (5 mol %) used. [e] 1.5 equiv of Cs_2CO_3 was used [f] Reaction temperature = 100 °C. n.d. = not detected.

synthesis of substituted 1-aryl-1*H*-benzotriazoles[7] *via* Pd-catalyzed intramolecular C−H amination of triazene moieties. This method features the use of $Pd(OAc)_2$ that successfully effects C−H activation followed by C−N cross-coupling to afford the cyclized products at moderate temperatures.

1*H*-Benzotriazoles are among the most important classes of heterocycles in biological and medicinal sciences. For example, 1*H*-benzotriazoles are structural motifs of many compounds that possess antibacterial, anticancer, antidepressant, antifungal, and antimalarial activities (Figure 1).[8] They are also useful synthons in some versions of the Graebe−Ullmann reaction,[9] especially in the synthesis of pyridoacridine,[10] carboline,[11] and tetraazapentalenes.[12] 1*H*-Benzotriazoles also serve as synthetic auxiliaries in amidoalkylation, insertion, and imidoylation that have been used for the synthesis of heterocyclic compounds.[10,11a,13] Development of newer methods for the construction of the functionalized 1*H*-benzotriazoles is thus important in synthetic organic chemistry.

First, the reaction conditions were optimized using (phenylimino)-2-phenylhydrazine **1a** as a model substrate with different Pd sources, solvents, and bases at varied temperature (Table 1). The reaction occurred to afford the desired 1-aryl-1*H*-benzotrizole **2a** in 36% yield when the substrate was stirred with 10 mol % $Pd(OAc)_2$ in DMSO at

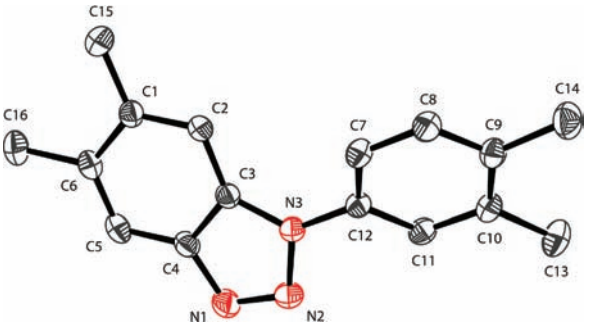
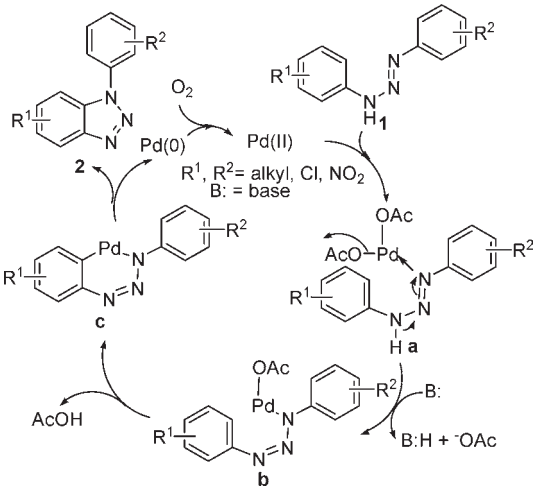


Figure 2. ORTEP diagram of 5,6-dimethyl-1-(3,4-dimethylphenyl)-1*H*-benzo[*d*][1,2,3]triazole **2m**. H-Atoms are omitted for clarity.[14]

Scheme 1. Proposed Catalytic Cycle



(7) For some recent studies for 1-aryl-1*H*-benzotriazole synthesis, see: (a) Shi, F.; Waldo, J. P.; Chen, Y.; Larock, R. C. *Org. Lett.* **2008**, *10*, 2409. (b) Zhang, F.; Moses, J. E. *Org. Lett.* **2009**, *11*, 1587. (c) Chen, Z.-Y.; Wu, M.-J. *Org. Lett.* **2005**, *7*, 475.

(8) For some recent studies, see: (a) Dixit, P. P.; Nair, P. S.; Patil, V. J.; Jain, S.; Arora, S. K.; Sinha, N. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3002. (b) Mishra, N.; Arora, P.; Kumar, B.; Mishra, L. C.; Bhattacharya, A.; Awasthi, S. K.; Bhasin, V. K. *Eur. J. Med. Chem.* **2008**, *43*, 1530. (c) Rezaei, Z.; Khabnadideh, S.; Pakshir, K.; Hossaini, Z.; Amiri, F.; Assadpour, E. *Eur. J. Med. Chem.* **2009**, *44*, 3064.

(9) (a) Graebe, C.; Ullmann, F. *Justus Liebigs Ann. Chem.* **1896**, *291*, 16. (b) Burgess, E. M.; Carithers, R.; McCullagh, L. *J. Am. Chem. Soc.* **1968**, *90*, 1923. (c) Mehta, L. K.; Parrick, J.; Payne, F. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1261. (d) Mitchell, G.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **1987**, 403. (e) Borsche, W.; Feise, M. *Chem. Ber.* **1907**, *40*, 378.

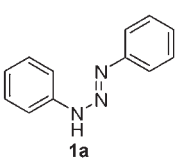
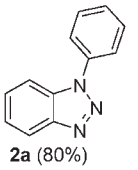
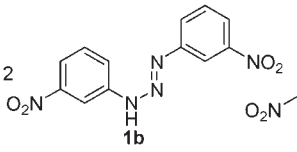
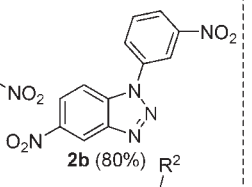
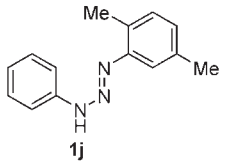
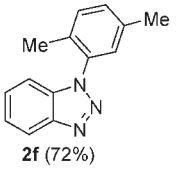
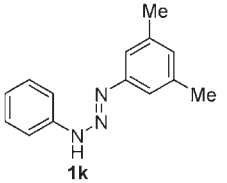
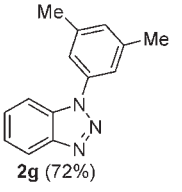
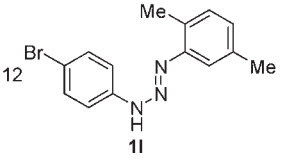
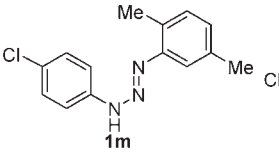
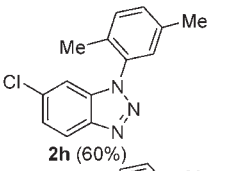
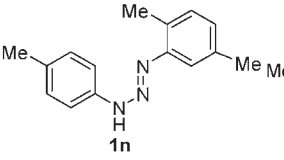
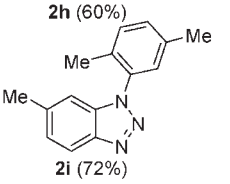
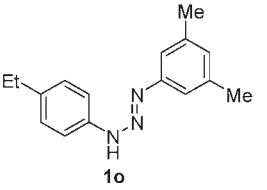
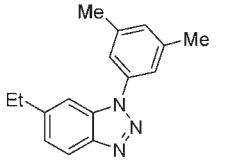
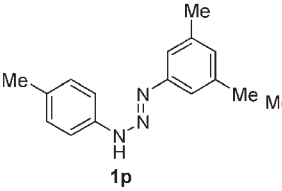
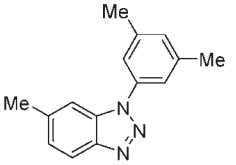
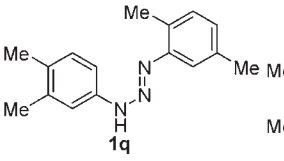
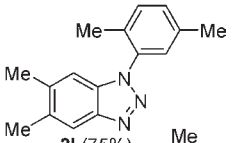
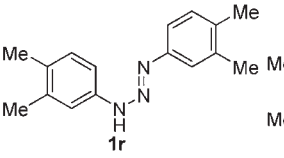
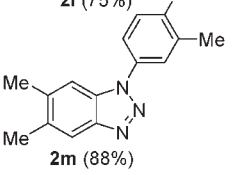
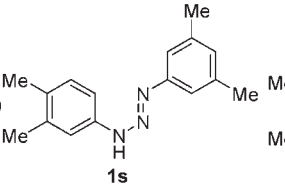
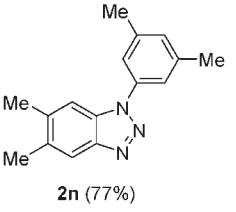
(10) Hagan, D. J.; Gimenez-Arnau, E.; Schwalbe, C. H.; Stevens, M. F. G. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2739.

(11) (a) Miller, R. B.; Stowell, J. G. *J. Org. Chem.* **1983**, *48*, 886. (b) Peczynska-Czoch, W.; Pognan, F.; Kaczmarek, L.; Boratynski, J. *J. Med. Chem.* **1994**, *37*, 3503. (c) Molina, A.; Vaquero, J. J.; Garcia-Navio, J. L.; Alvarez-Builla, J. *Tetrahedron Lett.* **1993**, *34*, 2673.

(12) (a) Kauer, J. C.; Carboni, R. A. *J. Am. Chem. Soc.* **1967**, *89*, 2633. (b) Biagi, G.; Giorgi, I.; Livi, O.; Scartoni, V.; Barili, P. L. *J. Heterocycl. Chem.* **1995**, *32*, 1709.

(13) For examples, see: Katritzky, A. R.; Rachwal, S. *Chem. Rev.* **2010**, *110*, 1564.

Table 2. Cyclization of (Phenylimino)-2-phenylhydrazines with Various Substituents on the Aryl Rings[a]

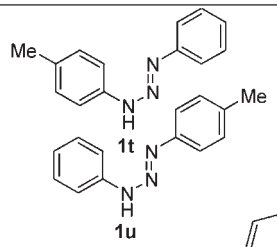
entry	substrate	product (yield)[a,b,c]
1	 **1a**	 **2a** (80%)
2	 **1b**	 **2b** (80%)
3	R^1, R^2 = $COCH_3$ **1c**	n.d.
4	R^1, R^2 = CO_2Et **1d**	n.d.
5	R^1, R^2 = Br **1e**	R^1, R^2 = H **2a** (55%)
6	R^1, R^2 = Cl **1f**	R^1, R^2 = Cl **2c** (85%)
7	R^1, R^2 = Et **1g**	R^1, R^2 = Et **2d** (70%)
8	R^1, R^2 = OMe **1h**	n.d.
9	R^1, R^2 = Me **1i**	R^1, R^2 = Me **2e** (84%)
10	 **1j**	 **2f** (72%)
11	 **1k**	 **2g** (72%)
12	 **1l**	**2f** (57%)
13	 **1m**	 **2h** (60%)
14	 **1n**	 **2i** (72%)
15	 **1o**	 **2j** (75%)
16	 **1p**	 **2k**(72%)
17	 **1q**	 **2l** (75%)
18	 **1r**	 **2m** (88%)
19	 **1s**	 **2n** (77%)

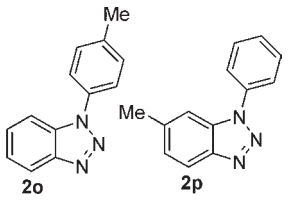
[a] Reaction conditions: substrate **1a**−**s** (1 mmol), $Pd(OAc)_2$ (10 mol %), Cs_2CO_3 (2 mmol), and MS 4 Å (100 mg) were stirred in DMF (1 mL) at 110 °C under an O_2 balloon. [b] Isolated yield. [c] Single isomer. n.d. = not detected.

110 °C under an oxygen balloon. The catalytic activity of the Pd sources were compared, and $Pd(OAc)_2$ was found to be superior to $PdCl_2$ and $PdCl_2(PPh_3)_2$. Replacing the solvent from DMSO to DMF gave **2a** in 65% yield. The yield of **2a** was further increased to 80% when a 4 Å molecular sieve was added as an additive. In contrast, solvents such as xylene, chlorobenzene, and 1,4-dioxane gave inferior results. The reaction was effective with Cs_2CO_3, K_2CO_3, K_3PO_4, KOH, and Na_2CO_3, and Cs_2CO_3 yielded the best results. No product was obtained using KO^tBu as the base. Lowering of the reaction temperature

(14) Recrystallization of **2m** in CH_2Cl_2 gave single crystals whose X-ray data were collected on a Bruker SMART APEX equipped with a CCD area detector using Mo Kα radiation in the scan range 1.47°−28.02°: $C_{16}H_{17}N_3$, M_w = 251.3304, orthorhombic; *Pbca*; a = 13.2943(7) Å, b = 7.4099(4) Å, c = 27.6216(14) Å; α = 90°, β = 90°, γ = 90°; V = 2721.0(2) Å^3; Z = 8; D_{calcd} = 1.227 mg m^{-3}; T = 296(2) K; Scan range 1.47° < θ < 28.02°; crystal dimension 0.44 × 0.36 × 0.26 mm^3; 3161 reflns, 1810 unique reflections ($I > 2\sigma(I)$); R_1 = 0.0497; wR_2 = 0.1191; GOF (on F^2) = 0.995.

Table 3. Cyclization of Unsymmetrical (Phenylimino)-2-phenylhydrazines[a]

entry	substrate	products[b] 2o:2p	yield[c]
1	 **1t**	2:1	75%
2	**1u**	2:1	75%


2o **2p**

[a] Reaction conditions: substrate **1t**−**u** (1 mmol), $Pd(OAc)_2$ (10 mol %), Cs_2CO_3 (2 mmol), and MS 4 Å (100 mg) were stirred in DMF (1 mL) at 110 °C under an O_2 balloon. [b] Regioisomeric ratio was determined by 400 MHz ^1H NMR of the crude reaction mixture. [c] Isolated yield.

(100 °C) or the amount of the catalyst (5 mol %) or the base (1.5 equiv) gave **2a** in < 55% yield. Control experiments confirmed that no product was obtained in the absence of the palladium source. In summary, the optimal conditions in DMF include $Pd(OAc)_2$ (10 mol %) and Cs_2CO_3 (2 equiv) at 110 °C for 25 h under an oxygen balloon.

Next, the scope of the protocol was studied for the substrates having substituents on the aryl rings (Table 2). (Phenylimino)-2-phenylhydrazines **1b**, **1e**−**g**, and **1i** having two 3-NO_2, 4-Cl, 4-Et, and 4-Me substituents proceeded in the C−H amination to afford the benzotriazoles **2b** and **2c**−**e** in 70−85% yield. In contrast, the substrates **1c**−**d** and **1h** with two 4-COMe, 4-CO_2Et, and 4-OMe groups showed no cyclization and the starting materials were recovered, whereas (phenylimino)-2-phenylhydrazines **1j**−**s** having Cl, Me, and Et substituents readily underwent cyclization to give the corresponding benzotriazoles **2f**−**n** in 55−88% yield. Recrystallization of **2m** in CH_2Cl_2 gave single crystals whose structure was confirmed by X-ray analysis (Figure 2). The substrates **1e** and **1l** with a Br group provided the debrominated products **2a** and **2f** exclusively.[4a] These results suggest that the cyclization is controlled by both steric and electronic factors on the aryl rings.

Finally, to reveal the regioselectivity, the reactions of the unsymmetrical substrates **1t**−**u** were studied (Table 3). Both of the substrates underwent cyclization to provide a 2:1 mixture of the regioisomers **2o** and **2p** in 75% yield. In both of the substrates, the cyclization occurred preferentially on the nonsubstituted aryl ring. These results suggest that the isomerization of triazenes can occur easily under the conditions used in this system.

The proposed catalytic cycle is shown in Scheme 1.[4a] The substrates **1a**−**l** may undergo coordination with Pd(II) to give intermediate ***a*** that could lead to the formation of ***b*** in the presence of base. The latter may undergo C−H activation to give the six-membered palladacycle ***c*** that could afford the target 1-aryl-1*H*-benzotriazole and Pd(0). The reduced Pd could be oxidized in the presence of oxygen to complete the catalytic cycle.

In summary, a novel protocol for the synthesis of 1-aryl-1*H*-benzotriazole is developed via C−H activation followed by intramolecular amination employing a Pd(II) catalyst under relatively milder conditions. Further study to understand the precise mechanism as well as to expand the range of substrates is currently underway in our laboratory.

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Supporting Information Available. Experimental procedure, characterization data, and NMR spectra (^1H and ^{13}C) of the products. This material is available free of charge via the Internet at http://pubs.acs.org.