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Palladium-Catalyzed sp^3 C−H Activation of Simple Alkyl Groups: Direct Preparation of Indoline Derivatives from *N*-Alkyl-2-bromoanilines

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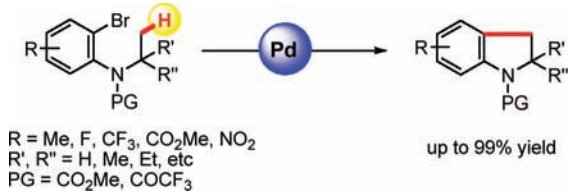
ABSTRACT



The sp^3 C−H activation of a simple alkyl group catalyzed by palladium(0) provides a novel and convenient strategy for the synthesis of various indolines from simple precursors, such as *N*-alkyl-2-bromoanilines. This study demonstrates that assisting moieties in the substrate such as a pyridine or quaternary carbon are not always necessary for sp^3 C−H activation.

Over the past decade, transition-metal-catalyzed C−H bond activation has become an extremely powerful tool for the synthesis of useful compounds including industrial materials, medicines, and natural products.[1] In contrast to the relatively facile sp^2 C−H bond activation due to the existence of π-electrons that interact with metal complexes,[2−4] activation of sp^3 C−H bonds is one of the current challenges in organic chemistry. Except for the activation of sp^3 C−H bonds at the benzylic position[5] or those next to heteroatoms,[6] most of the reported examples of unactivated simple C−H bonds[7] rely upon the assistance of a pyridine[8] or α-quaternary carbon moiety[9] in the substrates. We expect that sp^3 C−H activation

(1) For recent reviews, see: (a) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (b) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698. (c) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633.

(2) For recent reviews, see: (a) Crabtree, R. H. *J. Organomet. Chem.* **2004**, *689*, 4083. (b) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077.

(3) For recent examples of sp^2 C-H activation, see: (a) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581. (b) Garcia-Cuadrado, D.; Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880. (c) Terao, Y.; Wakui, H.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2001**, *123*, 10407. (d) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496.

(4) (a) For our related works, see: Ohno, H.; Miyamura, K.; Takeoka, Y.; Tanaka, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 2647. (b) Ohno, H.; Yamamoto, M.; Iuchi, M.; Tanaka, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 5103. (c) Watanabe, T.; Ueda, S.; Inuki, S.; Oishi, S.; Fujii, N.; Ohno, H. *Chem. Commun.* **2007**, *43*, 4516. (d) Ohno, H.; Iuchi, M.; Fujii, N.; Tanaka, T. *Org. Lett.* **2007**, *9*, 4813.

(5) (a) Dong, C.-G.; Hu, Q.-S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2289. (b) Ren, H.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3462. (c) Ren, H.; Li, Z.; Knochel, P. *Chem. Asian. J.* **2007**, *2*, 416.

(6) (a) Dyker, G. *Angew. Chem., Int. Ed.* **1992**, *31*, 1023. (b) Dyker, G. *J. Org. Chem.* **1993**, *58*, 6426. (c) DeBoef, B.; Pastine, S. J.; Sames, D. *J. Am. Chem. Soc.* **2004**, *126*, 6556. (d) Li, Z.; Bohle, D. S.; Li, C.-J. *Proc. Natl. Acad. Sci. U. S. A.* **2006**, *103*, 8928. (e) Pastine, S. J.; Gribkov, D. V.; Sames, D. *J. Am. Chem. Soc.* **2006**, *128*, 14220.

(7) For rhodium-catalyzed sp^3 C-H activation of simple alkanes without using any assisting groups in the substrate, see: Chen, H.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995.

(8) (a) Jun, C.-H.; Hwang, D.-C.; Na, S.-J. *Chem. Commun.* **1998**, 1405. (b) Chatani, N.; Asaumi, T.; Yorimitsu, S.; Ikeda, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2001**, *123*, 10935. (c) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330. (d) Shabashov, D.; Daugulis, O. *Org. Lett.* **2005**, *7*, 3657. (e) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (f) Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, *8*, 3391. (g) Chen, X.; Goodhue, C. E.; Yu, J.-Q *J. Am. Chem. Soc.* **2006**, *128*, 12634. (h) For pyridine- or oxime-assisted reactions, see: Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542.

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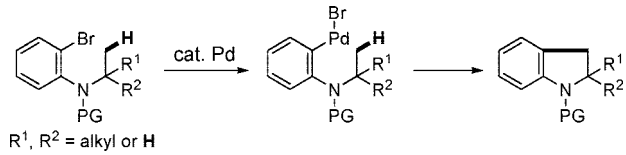
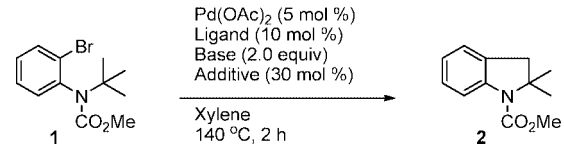
Scheme 1. sp^3 C−H Activation of *N*-Alkyl-2-bromoaniline Derivatives



of *N*-alkyl-2-bromoaniline derivatives (Scheme 1) would provide a straightforward access to the construction of the indoline framework that is a common structural motif found in many biologically active compounds including indoline alkaloids.[10,11] Herein, we report the palladium-catalyzed cyclization of functionalized *N*-alkyl-2-bromoanilines via sp^3 C−H activation, leading to various indolines, as well as the 2,3-dihydropyrrolo[3,2-*b*]pyridine derivative.[12] This study includes the first palladium-catalyzed sp^3 C−H activation of a simple alkyl group without the assistance of a pyridine or quaternary carbon (R^1 and/or R^2 = H, Scheme 1).

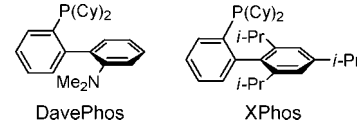
We first investigated the palladium-catalyzed cyclization of *N*-protected 2-bromo-*N*-*tert*-butylaniline **1**, since this would have the benefit of a quaternary carbon as well as nine reactive C−H bonds in the vicinity of the palladium atom when forming the arylpalladium(II) intermediate. Among various ligands examined (Table 1, entries 1−5), PCy_3·HBF_4[13] was found to be the most effective for this cyclization: treatment of aniline **1** with $Pd(OAc)_2$ (5 mol %) in the presence of PCy_3·HBF_4 (10 mol %) and K_2CO_3 at 140 °C gave the desired indoline **2** in 66% yield with 33% recovery of the starting material (entry 5). When Cs_2CO_3 was used instead of K_2CO_3, the yield was improved to 96% (entry 6). A more promising result was obtained by the addition of pivalic acid (30 mol %) to the reaction mixture, as reported by Fagnou and co-workers quite recently (entry 7).[3d,9f,12] Polar solvents such as DMA were not suitable for this cyclization (entry 8). Lowering the catalyst loading to 2 mol % slightly decreased the yield of **2** (97%, entry 9), while a comparable result to entry 7 was obtained when using 3 mol % of $Pd(OAc)_2$ and 1.4 equiv of Cs_2CO_3 (quant., entry 10).

Table 1. Optimization of Reaction Conditions



				yield (%)[a]	
entry	ligand[b]	base	additive	**2**	**1**
1	Davephos	K_2CO_3		56	20
2	PPh_3	K_2CO_3		51	46
3	XPhos	K_2CO_3		6	94
4	P(*t*-Bu)$_3$·HBF_4	K_2CO_3		2	93
5	PCy_3·HBF_4	K_2CO_3		66	33
6	PCy_3·HBF_4	Cs_2CO_3		96	4
7	PCy_3·HBF_4	Cs_2CO_3	*t*-$BuCO_2H$	>99 (98)	
8[c]	PCy_3·HBF_4	Cs_2CO_3	*t*-$BuCO_2H$	52	5
9[d]	PCy_3·HBF_4[e]	Cs_2CO_3	*t*-$BuCO_2H$	97	2
10	PCy_3·HBF_4[f]	Cs_2CO_3[g]	*t*-$BuCO_2H$	>99 (98)	

[a] Yields based on ^1H NMR (isolated yields in parentheses). [b] Structures of DavePhos and XPhos are shown below. [c] DMA was used in place of xylene. [d] Reaction time was 5 h. [e] Pd/ligand = 2/4 mol %. [f] Pd/ligand = 3/6 mol %. [g] With 1.4 equiv of Cs_2CO_3.



Under the optimized conditions (Table 1, entry 10), we examined the reaction of a variety of 2-halo-*N*-*tert*-butylaniline derivatives (Table 2). First, we investigated the influence of the halogen atom on the cyclization and found the chloride **3** and iodide **4** showed lower reactivity than the bromide **1** to afford the indoline **2** in 47% and 84% respective yields (entries 1 and 2).[14] The reaction of the *N*-unprotected substrate **5a** led to the recovery of the starting material (93%) without producing any detectable amounts of the desired indoline **5b** (entry 3).[15] In contrast, *N*-trifluoroacetamide **6a** gave 87% yield of the corresponding indoline **6b**. Next, the reaction of bromoanilines **7a**−**13a** bearing various substituent(s) on the arene was investigated (entries 5−10). The monomethyl and dimethyl-substituted anilines **7a** and **8a** underwent smooth ring closure providing the indolines **7b**

(9) (a) Dyder, G. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 103. (b) Baudoin, O.; Herrbach, A.; Guéritte, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 5736. (c) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685. (d) Hitce, J.; Retailleau, P.; Baudoin, O. *Chem. Eur. J.* **2007**, *13*, 792. (e) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510. (f) Lafrance, M.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 14570.

(10) (a) Llabres, J. M.; Viladomat, F.; Bastida, J.; Codina, C.; Rubiralta, M. *Phytochemistry* **1986**, *25*, 2637. (b) Ghosal, S.; Rao, P. H.; Jaiswal, D. K.; Kumar, Y.; Frahm, A. W. *Phytochemistry* **1981**, *20*, 2003. (c) Kam, T.-S.; Subramaniam, G.; Lim, K.-H.; Choo, Y.-M. *Tetrahedron Lett.* **2004**, *45*, 5995.

(11) For synthesis of indolines, see: (a) Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 2426. (b) Thansandote, P.; Raemy, M.; Rudolph, A.; Lautens, M *Org. Lett.* **2007**, *9*, 5255, and references therein.

(12) During the course of our investigation and preparation of this manuscript, a related Pd(0)-catalyzed sp^3 C-H activation of 2-*tert*-butoxy-bromobenzene in the presence of pivalic acid and its related substrates to form 2,2-dialkyldihydrobenzofurans has appeared in the literature: see ref 9f. Mechanistic consideration as well as the effect of pivalic acid based on DFT calculations was also reported.

(13) This phosphonium salt was used because it is more stable than the corresponding free phosphine.

(14) Decreased yield in entry 2 can be attributed to catalyst poisoning by the iodide anion, see for example: Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581.

(15) (a) The unsuccessful result with the N-unprotected substrate **5a** might be due to the formation of the four-membered azapalladacycle **18**. For related azapalladacycles, see: Solé, D.; Serrano, O. *Angew. Chem., Int. Ed.* **2007**, *46*, 7270. (b) Solé, D.; Vallverdú, L.; Solans, X.; Font-Bardia, M.; Bonjoch, J. *J. Am. Chem. Soc.* **2003**, *125*, 1587. (c) See also: Gies, A.-E.; Pfeffer, M.; Sirlin, C.; Spencer, J. *Eur. J. Org. Chem*, **1999**, *8*, 1957. (d) Vicente, J.; Abad, J.-A.; Frankland, A. D.; Ramírez de Arellano, M. C. *Chem. Eur. J.* **1999**, *5*, 3066.

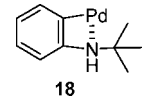


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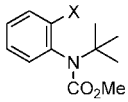
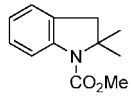
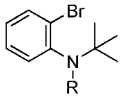
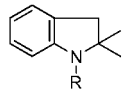
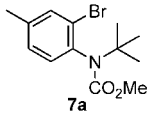
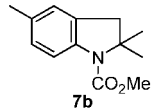
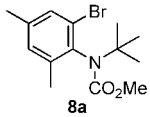
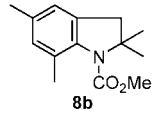
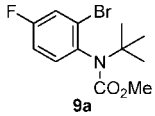
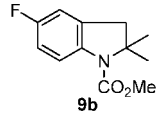
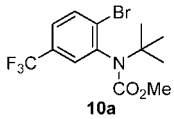
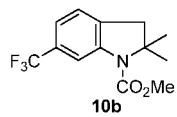
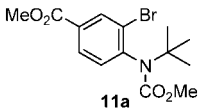
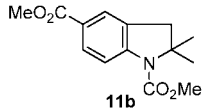
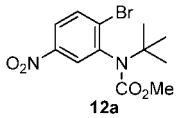
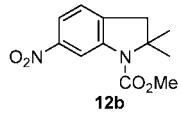
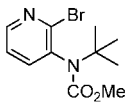
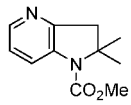
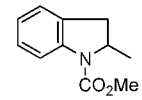
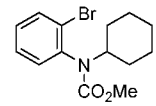
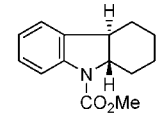
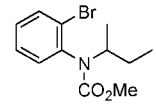
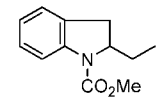
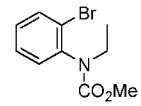
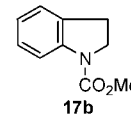
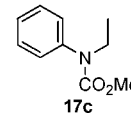
Table 2. Pd-Catalyzed Cyclization of *N*-*tert*-Butylaniline Derivatives[a]

entry	substrate	time (h)	product	yield (%)[b]
1	 **3**: X = Cl	4	 **2**	47%[c]
2	**4**: X = I	2		84%
3	 **5a**: R = H	12	 **5b**: R = H	0%[d]
4	**6a**: R = $COCF_3$	3	**6b**: R = $COCF_3$	87%
5	 **7a**	2	 **7b**	99%
6	 **8a**	2	 **8b**	100%
7	 **9a**	2	 **9b**	94%
8	 **10a**	2	 **10b**	99%
9	 **11a**	2	 **11b**	91%
10	 **12a**	1	 **12b**	98%
11	 **13a**	2[e]	 **13b**	98%

[a] Reaction conditions: substrates (0.2 mmol), $Pd(OAc)_2$ (3 mol %), PCy_3·HBF_4 (6 mol %), Cs_2CO_3 (0.28 mmol) and *t*-$BuCO_2H$ (0.06 mmol), xylene (2.0 mL), 140 °C. [b] Yields of isolated products. [c] The starting material was recovered at 49%. [d] The starting material was recovered at 93%. [e] With 5 mol % of $Pd(OAc)_2$.

and **8b** in essentially quantitative yields (entries 5 and 6). Cyclization of the fluoroaniline derivative **9a** under identical conditions led to the formation of the fluoroindoline **9b** in 94% yield (entry 7). Similarly, the reaction of the aniline derivatives **10a**−**12a** having an electron-withdrawing group such as trifluoromethyl, methoxycarbonyl, or nitro group, afforded the corresponding indolines **10b**−**12b** in high yields (entries 8−10). The wide applicability of this C−H activation

Table 3. Pd-Catalyzed Cyclization of *N*-Alkylaniline Derivatives[a]

entry	substrate	time (h)	product	yield (%)[b]
1	 **14a**	6	 **14b**	80%
2	 **15a**	16[c]	 **(±)-15b**	76%
3	 **16a**	6	 **16b**	89%
4	 **17a**	24[c]	 **17b**	38%
			 **17c**	22%

[a] Reaction conditions: substrates (0.2 mmol), $Pd(OAc)_2$ (3 mol %), PCy_3·HBF_4 (6 mol %), Cs_2CO_3 (0.28 mmol), and *t*-$BuCO_2H$ (0.06 mmol), xylene (2.0 mL), 140 °C. [b] Yields of isolated products. [c] With 5 mol % of $Pd(OAc)_2$.

assisted by a quaternary carbon can be readily understood by the formation of the azaindoline derivative **13b** in 98% yield (entry 11).[16]

We next investigated the C−H activation without using the assistance of an α-quaternary carbon (Table 3). Upon treatment of *N*-isopropylaniline **14a** under optimal reaction conditions, the expected cyclization via C−H activation proceeded smoothly thus providing the indoline **14b** in 80% yield (entry 1). Although the reaction of *N*-cyclohexylaniline **15a** required a longer reaction time (16 h) presumably due to the decreased number of reactive C−H bonds and steric factors, the trans-fused tricyclic product **15b** was obtained in 76% yield (entry 2). The C−H activation of the *N*-*sec*-butylaniline derivative **16a** regioselectively proceeded at the methyl group on the carbon bearing the nitrogen atom to afford 2-ethylindoline **16b** as the sole product (entry 3). It should be clearly noted that C−H activation of an ethyl group is also possible: by use of *N*-ethylaniline **17a**, the desired indoline **17b** was obtained in 38% yield along with 22% of

(16) (a) Related aza-oxindole derivatives are known as potent kinase inhibitors, see : Adams, C.; Aldous, D. J.; Amendola, S.; Bamborough, P.; Bright, C.; Crowe, S.; Eastwood, P.; Fenton, G.; Foster, M.; Harrison, T. K. P.; King, S.; Lai, J.; Lawrence, C.; Letallec, J.-P.; McCarthy, C.; Moorcroft, N.; Page, K.; Rao, S.; Redford, J.; Sadiq, S.; Smith, K.; Souness, J. E.; Thurairatnam, S.; Vine, M.; Wyman, B. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3105. (b) Wood, E. R.; Kuyper, L.; Petrov, K. G.; Hunter, R. N.; Harris, P. A.; Lackey, K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 953.

the debrominated product **17c** (entry 4). These are the first examples of palladium(0)-catalyzed sp^3 C−H activation of a simple alkyl group without the need for an assisting group in the substrate.[17]

A possible mechanism for this reaction is shown in Scheme 2. The oxidative addition of arylbromide **1** to palladium(0) followed by ligand exchange would give the arylpalladium pivalate complex **B**. The intramolecular activation of the sp^3 C−H bond of a methyl group with a high energy barrier could be efficiently promoted by the basicity of the pivalate in the proximity of the C−H bond,[9f,12] as well as by the formation of energetically favorable palladacycles **C**.[8] Finally, reductive elimination would produce the indoline derivative **2**, and the regeneration of the reactive palladium(0) species.

In conclusion, we have developed an efficient method for the construction of an indoline skeleton through sp^3 C−H activation. This study has demonstrated for the first time that palladium(0)-catalyzed sp^3 C−H activation of a simple alkyl group can be performed without the need for beneficial substrates having a pyridine or quaternary carbon moiety.

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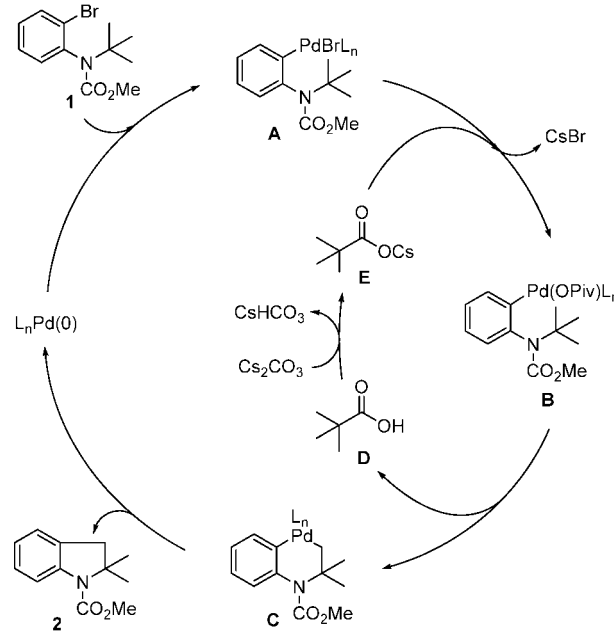
(17) For a related C–H activation of an isopropyl group assisted by a quaternary carbon, see ref 9d.

Scheme 2. Proposed Mechanism for the Cyclization of **1**



Supporting Information Available: Representative experimental procedure, as well as ^1H and ^{13}C NMR spectra for the novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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