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Novel and Selective Palladium-Catalyzed Annulations of 2-Alkynylphenols To Form 2-Substituted 3-Halobenzo[*b*]furans

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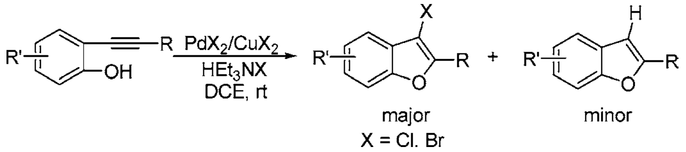
ABSTRACT



A novel and selective palladium-catalyzed annulation of 2-alkynylphenols method for the synthesis of 2-substituted 3-halobenzo[*b*]furans is presented. In the presence of PdX_2, CuX_2, and HEt_3NX, 2-substituted 3-halobenzo[*b*]furans were selectively obtained as the major products. The mechanism of the reaction was also discussed.

Benzo[*b*]furans are a recurring functional group in many natural products and biologically active compounds.[1] For these reasons, a number of efficient and selective methods have been developed for their synthesis.[1e,2−5] Among these transformations, the palladium-catalyzed annulations of *o*-hydroxylarylacetylenes is considered to be one of the most effective strategies.[2−4] Generally, benzo[*b*]furans are prepared by either palladium-catalyzed one-pot annulations of 2-hydroxyaryl iodides with alkynes[3] or palladium-catalyzed annulations of 2-alkynylphenols followed by reaction with electrophilic reagents (unsaturated halides[4a−d] or CO[4e−l] etc.). In the latter transformations, however, the competition between the attack of electrophilic reagents and direct cyclization usually occurs, limiting their applications in organic synthesis. Thus, development of a new route to construct 2,3-disubstituted benzo[*b*]furans efficiently and selectively still remains a challenging area for exploration. To the best of our knowledge, no report on the synthesis of 2-substituted 3-halobenzo[*b*]furans via the Pd-catalyzed

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(1) (a) Donnelly, D. M. X.; Meegan, M. J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 4, pp 657−712. (b) Cagniant, P.; Cagniant, C. *Adv. Heterocycl. Chem.* **1975**, *18*, 343. (c) Ward, R. S. *Nat. Prod. Rep.* **1993**, *10*, 1. (d) Ward, R. S. *Nat. Prod. Rep.* **1995**, *12*, 183. (e) Friedrichsen, W. In *Comprehensive Heterocyclic Chemistry II*; Bird, C. W., Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: London, 1996; Vol. 2, Chapter 2.7, pp 368−378. (f) Ward, R. S. *Nat. Prod. Rep.* **1997**, *14*, 43. (g) Muhammad, I.; Li, X.-C.; Jacob, M. R.; Tekwani, B. L.; Dunbar, D. C.; Ferreira, D. *J. Nat. Prod.* **2003**, *66*, 804.

(2) For recent reviews, see: (a) Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*; Pergamon: Amsterdam, 2000. (b) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002. (c) Liao, Y.; Hu, Y.; Wu, J.; Zhu, Q.; Donovan, M.; Fathi, R.; Yang, Z. *Curr. Med. Chem.* **2003**, *10*, 2285. (d) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285. (e) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079.

(3) For representative papers on the synthesis of benzo[*b*]furans via palladium-catalyzed one-pot annulations of 2-hydroxyaryl iodides with alkynes, see: (a) Arcadi, A.; Marinelli, F.; Cacchi, S. *Synthesis* **1986**, 749. (b) Kundu, N. G.; Pal, M.; Mahanty, J. S.; Dasgupta, S. K. *J. Chem. Soc., Chem. Commun.* **1992**, 41. (c) Torii, S.; Xu, L. H.; Okumoto, H. *Synlett* **1992**, 515. (d) Candiani, I.; Debernardinis, S.; Cabri, W.; Marchi, M.; Bedeschi, A.; Penco, S. *Synlett* **1993**, 269. (e) Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270. (f) Monteiro, N.; Arnold, A.; Balme, G. *Synlett* **1998**, 1111. (g) Bishop, B. C.; Cottrell, I. F.; Hands, D. *Synthesis* **1997**, 1315. (h) Kundu, N. G.; Pal, M.; Mahanty, J. S.; De, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2815. (i) Lutjens, H.; Scammells, P. J. *Synlett* **1999**, 1079. (j) Yue, D.; Larock, R. C. *J. Org. Chem.* **2002**, *667*, 1905.

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annulation reactions of 2-alkynylphenols has been described. Here, we report a novel and selective palladium-catalyzed annulation of 2-alkynylphenols method for the synthesis of 2-substituted 3-halobenzo[*b*]furans.[5a,h,i] Furthermore, the method affords products with a halide (Cl or Br) at the 3 position, which provides an attractive and useful route to introduce new groups for the synthesis of natural products (Scheme 1).

Scheme 1

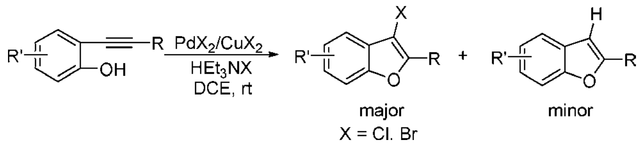
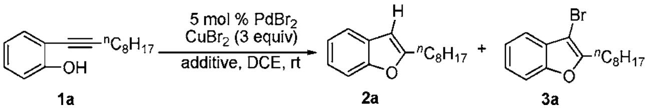


Table 1. Screening the Effect of Additives on the Palladium Bromide-Catalyzed Annulation of 2-(2-*n*-Octylethynyl)phenol (**1a**)[a]



entry	additive (equiv)	yield (%)[b] 2a	yield (%)[b] 3a
1[c]		97 (91)	0
2[d]		50	4
3		84 (81)	10
4[e]		85	8
5[f]		0	0
6[g]		95 (90)	5 (**4a**)
7	HEt_3NI (0.1)	40	43
8	HEt_3NI (0.2)	10	77 (75)
9	HEt_3NI (0.5)	0	0
10	HEt_3NCl (0.2)	75	14
11	HEt_3NBr (0.2)	69	17
12	TBAB (0.2)	83 (80)	8
13	KI (0.2)	81	10
14	PPh_3 (0.2)	81	9
15	Et_3N (1.0)	78	12

[a] Reaction conditions: **1** (0.3 mmol), $PdBr_2$ (5 mol %), and $CuBr_2$ (3 equiv) in DCE (5 mL) at room temperature for 5 h. [b] GC yield. Isolated yield is given in parentheses. [c] Without $CuBr_2$. [d] $CuBr_2$ (1 equiv). Conversion of **1a** was 60% as determined by GC analysis. [e] $CuBr_2$ (5 equiv). [f] Without $PdBr_2$. 2-(1,2-Dibromo-2-phenylvinyl)phenol was isolated in 10% yield. [g] $PdCl_2$ (5 mol %) and $CuCl_2$ (3 equiv) instead of both $PdBr_2$ and $CuBr_2$.

As shown in Table 1, 2-(2-*n*-octylethynyl)phenol (**1a**) was annulated smoothly to afford a 95% isolated yield of the desired 2-octyl benzo[*b*]furan (**2a**) in the presence of 5 mol % of $PdBr_2$ (entry 1). It is noteworthy that the presence of $CuBr_2$ affected the reaction, and 2-octyl bromobenzo[*b*]furan (**3a**), a byproduct, was observed (entries 1−4). In the presence of 1 equiv of $CuBr_2$, the reaction was slow, resulting in the formation of **2a** and **3a** in 50% and 4% GC yields, respectively (entry 2). When 3 equiv of $CuBr_2$ was added, substrate **1a** was converted completely to **2a** and **3a** in 84 and 10% GC yields, respectively, for 5 h (entry 3). Identical results were observed when the amount of $CuBr_2$ was further increased to 5 equiv (entry 4). The results also demonstrated that $PdBr_2$ played a crucial role in the reaction (entry 5). Without $PdBr_2$, no benzo[*b*]furans were observed. Another catalytic system ($PdCl_2$/$CuCl_2$) was also tested (entry 6). It was found that $PdCl_2$ was also effective for the annulation reaction of **1a**. The addition of $PdCl_2$ and $CuCl_2$ gave a 90% isolated yield of **2a** together with a 5% GC yield of 2-octyl 3-chlorobenzo[*b*]furan (**4a**).

Although 2-octyl benzo[*b*]furan (**2a**) was obtained in good yields, our interest is focused on the synthesis of 2-substituted 3-halobenzo[*b*]furans, the side products **3a** and **4a** in the above transformations. Accidentally, we found that HEt_3NI could shift the selectivity of the reaction from 2-substituted benzo[*b*]furan toward 2-substituted 3-halobenzo[*b*]furan (entries 3 and 7−9). In the presence of 5 mol % of $PdBr_2$, 3 equiv of $CuBr_2$, and 0.1 equiv of HEt_3NI, the ratio of **2a** to **3a** was 1:1 (40 and 43% GC yields, respectively; entry 7), whereas in the presence of 0.2 equiv of HEt_3NI, a 77% GC yield of **3a** was obtained as the major product together with a 10% GC yield of **2a** (entry 8). Surprisingly, further increasing the loading of HEt_3NI to 0.5 equiv led to no reaction (entry 9). Other reagents, including HEt_3NCl, HEt_3NBr, TBAB, KI, Et_3N, and PPh_3, were also evaluated, and the results demonstrated that they affected the selectivity slightly (entries 10−15).

Under the optimized reaction conditions, palladium-catalyzed annulations of 2-alkynylphenols **1a**−**g**[6] provided good yields of the corresponding 2-substituted 3-halobenzo[*b*]furans **3** and **4** selectively, and the results are summarized in Table 2. For example, treatment of 2-alkynylphenol (**1b**) with 5 mol % of $PdBr_2$, 3 equiv of $CuBr_2$, and 0.2 equiv of HEt_3NI afforded a 92% isolated yield of 2-phenyl 3-bro-

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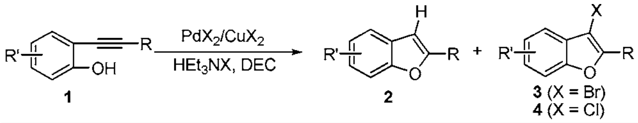
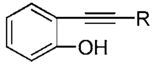
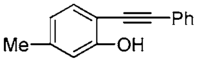
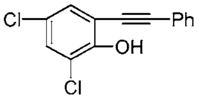
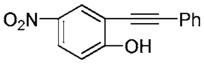
(4) For representative papers on the synthesis of benzo[*b*]furans via palladium-catalyzed annulations of 2-alkynylphenols, see: (a) Arcadi, A.; Cacchi, S.; Rosario, M. D.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280. (b) Chaplin, J. H.; Flynn, B. L. *Chem. Commun.* **2001**, 1594. (c) Flynn, B. L.; Hamel, E.; Jung, M. K. *J. Med. Chem.* **2002**, *45*, 2670. (d) Hu, Y.; Nawoschik, K. J.; Liao, Y.; Ma, J.; Fathi, R.; Yang, Z. *J. Org. Chem.* **2004**, *69*, 2235 and references therein. (e) Kondo, Y.; Shiga, F.; Murata, N.; Sakamoto, T.; Yamanaka, *Tetrahedron* **1994**, *50*, 11803. (f) Nan, Y.; Miao, H.; Yang, Z. *Org. Lett.* **2000**, *2*, 297. (g) Hu, Y.; Yang, Z. *Org. Lett.* **2001**, *3*, 1387. (h) Liao, Y.; Reitman, M.; Zhang, Y.; Fathi, R.; Yang, Z. *Org. Lett.* **2002**, *4*, 2067. (i) Hu, Y.; Zhang, Y.; Yang, Z.; Fathi, R. *J. Org. Chem.* **2002**, *67*, 2365. (j) Liao, Y.; Fathi, R.; Yang, Z. *Org. Lett.* **2003**, *5*, 909. (k) Liao, Y.; Fathi, R.; Yang, Z. *J. Comb. Chem.* **2003**, *5*, 79.

(5) For recent selected papers on palladium-free synthesis of benzo[*b*]furans, see: (a) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L. *Synlett* **1999**, 1432 and references therein. (b) Bates, C. G.; Saejueng, P.; Murphy, J. M.; Venkataraman, D. *Org. Lett.* **2002**, *4*, 4727 and references therein. (c) Baker, S. R.; Cases, M.; Keenan, M.; Lewis, R. A.; Tan, P. *Tetrahedron Lett.* **2003**, *44*, 2995. (d) Dahlén, A.; Petersson, A.; Hilmersson, G. *Org. Biomol. Chem.* **2003**, *1*, 2423. (e) McKiernan, G. J.; Hartley, R. C. *Org. Lett.* **2003**, *5*, 4389. (f) Serra, S.; Fuganti, C. *Synlett* **2003**, 2005. (g) Miyata, O.; Takeda, N.; Naito, T. *Org. Lett.* **2004**, *6*, 1761. (h) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 10292. (i) Yao, T.; Yue, D.; Larock, R. C. *J. Comb. Chem.* **2005**, *7*, 809. (j) Kao, C.-L.; Chern, J.-W. *J. Org. Chem.* **2002**, *67*, 6772.

(6) 2-Alkynylphenols **1a**−**d** were prepared from the reactions of the corresponding 2-iodophenols with terminal alkynes directly, and substrates **1e**−**g** were obtained via three steps including O-protection, Sonogashira coupling, and O-deprotecting by known procedures, see: refs 3a and 4a.

Table 2. Synthesis of Benzo[*b*]furans via Palladium-Catalyzed Annulation of 2-Alkynylphenols (**1**) in the Presence of HEt$_3$NI[a]



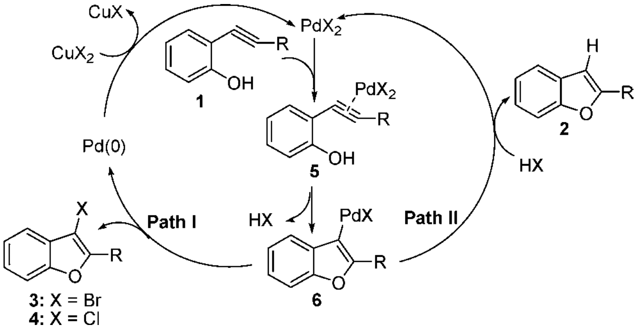
Entry	Substrate	Conditions	Time (h)	Isolated yield (%) 2	3 or 4
1	 R = *n*-C_8H_{17} (**1a**)	B	8	12 (**2a**)	60 (**4a**)
2	R = Ph (**1b**)	A	8	0 (**2b**)	92 (**3b**)
3	R = Ph (**1b**)	B	8	17 (**2b**)	70 (**4b**)
4	R = *p*-MeC$_6$H$_4$ (**1c**)	A	6	0 (**2c**)	91(**3c**)
5	R = *p*-MeC$_6$H$_4$ (**1c**)	B	7	25 (**2c**)	65 (**4c**)
6	R = *t*-Bu (**1d**)	A	9	10 (**2d**)	69 (**3d**)
7	R = *t*-Bu (**1d**)	B	10	13 (**2d**)	65 (**4d**)
8[b]	 (**1e**)	A	16	0 (**2e**)	78 (**3e**)
9[b]	(**1e**)	B	24	46 (**2e**)	51(**4e**)
10[bc]	 (**1f**)	A	12	0 (**2f**)	92 (**3f**)
11[bd]	(**1f**)	B	24	42 (**2f**)	45 (**4f**)
12[bc]	 (**1g**)	A	24	58 (**2g**)	37 (**3g**)

[a] Reaction conditions: (A) **1** (0.3 mmol), PdBr$_2$ (5 mol %), CuBr$_2$ (3 equiv), and HEt$_3$NI (0.2 equiv) in DCE (5 mL) at room temperature; (B) **1** (0.3 mmol), PdCl$_2$ (5 mol %), CuCl$_2$ (3 equiv), and HEt$_3$NI (0.2 equiv) in DCE at room temperature. [b] PdX$_2$ (10 mol %) at 60 °C. [c] HEt$_3$NBr (0.2 equiv) instead of HEt$_3$NI. [d] HEt$_3$NCl (0.2 equiv) instead of HEt$_3$NI.

mobenzo[*b*]furans (**3b**) exclusively (entry 2). When 5 mol % of PdCl$_2$, 3 equiv of CuCl$_2$, and 0.2 equiv of HEt$_3$NI were added, a 70% yield of 2-phenyl 3-chlorobenzo[*b*]furans (**4b**) was obtained together with a 17% yield of **2b** (entry 3). However, both higher loading of PdX$_2$ and higher reaction temperature were required for the reaction of other substituted substrates **1e**,**f** to produce satisfactory yields (entries 8−12). The results showed that electron-donating groups in the aromatic ring favored the desired reaction, but an electron-withdrawing group suppressed it. For example, the substrate **1e** bearing a methyl group gave the target product **3e** exclusively in the presence of PdBr$_2$ and CuBr$_2$ (entry 8), whereas 2-alkynylphenol **1e** bearing a nitro group provided the desired product **3g** as a minor product (37% yield; entry 12).

Compared with the previous work,[2−5] the present reaction did not require any bases, which suggested a different mechanism. A possible mechanism for the palladium-catalyzed selective annulation reaction is proposed as outlined in Scheme 2.[2,3,5] First, attack of the active palladium species with the substrate resulted in the formation of intermediate **5**, followed by the addition of the phenolic oxide nucleophile to the PdX$_2$-activated intermediate **5** affording intermediate **6** and HX. Then two pathways might proceed: (i) With the aid of CuX$_2$, the cleavage of the C−Pd σ-bond of intermediate **6** can take place readily to form 2-substituted 3-halobenzo[*b*]furans **3**/**4** and the Pd(0) species.[7] The active Pd(II) species can be regenerated by the oxidation reaction of Pd(0) with CuX$_2$ to start a new catalytic cycle. (ii) Protonolysis of intermediate **6** formed 2-substituted benzo[*b*]furans **2** and regenerated the active Pd(II) species.[8]

Scheme 2. Possible Mechanism



We inferred that the role of HEt$_3$NX may be to complex with Pd(0) readily to favor the generation of Pd(0); in other words, HEt$_3$NX might labilize the palladium−carbon σ-bond, thereby converting palladium into a good leaving group.[9,10] As a result, nucleophilic substitution of the metal may take place readily to limit the involvement as pathway II.[7,9,10] Study of the accurate roles of HEt$_3$NX is in progress.

In summary, a novel and selective method for the synthesis of 2-disubstituted 3-halobenzo[*b*]furans has been developed. Furthermore, HEt$_3$NX was found as a switch to shift the

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(7) It has been reported that Cu(II) as an oxidant could cleave the C−Pd σ-bond, see: (a) Bäckvall, J. E.; Nordberg, R. E. *J. Am. Chem. Soc.* **1980**, *102*, 393. (b) Ji, J.; Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 1160. (c) Zhu, G.; Ma, S.; Lu, X.; Huang, Q. *J. Chem. Soc., Chem. Commun.* **1995**, 271. (d) Li, J.-H.; Jiang, H.-F.; Feng, A.-Q.; Jia, L.-Q. *J. Org. Chem.* **1999**, *64*, 5984. (e) Li, J.-H.; Jiang, H.-F.; Chen, M.-C. *J. Org. Chem.* **2001**, *66*, 3627. (f) Li, J.-H.; Liang, Y.; Xie, Y.-X. *J. Org. Chem.* **2004**, *69*, 8125. (g) Li, J.-H.; Tang, S.; Xie, Y.-X. *J. Org. Chem.* **2005**, *70*, 477. (h) Ma, S.; Lu, X. *J. Org. Chem.* **1993**, *58*, 1245.

(8) For recent representative papers on protonolysis of the Pd complex to regenerate the active Pd(II) species by HCl, see: (a) Pei, T.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2001**, *123*, 11290. (b) Yang, D.; Li, J.-H.; Gao, Q.; Yan, Y.-L. *Org. Lett.* **2003**, *5*, 2869. (c) Wang, X.; Pei, T.; Han, X.; Widenhoefer, R. A. *Org. Lett.* **2003**, *5*, 2699. (d) Han, X.; Wang, X.; Pei, T.; Widenhoefer, R. A. *Chem.—Eur. J.* **2004**, *10*, 6333 and references therein.

(9) The other additives were used to labilize the palladium−carbon σ-bond, see: Zhu, G.; Lu, X. *J Organomet. Chem.* **1996**, *508*, 83 and references therein.

(10) Et$_3$NHI might complex with Pd(0) readily to generate L$_2$Pd(I)H in situ, see: Jeevanandam, A.; Narkunan, K.; Ling, Y.-C. *J. Org. Chem.* **2001**, *66*, 614.

selectivity. In the presence of PdX_2, 2-substituted benzo[*b*]furans were obtained in good yields (entry 1 in Table 1), whereas in the presence of 5−10 mol % of PdX_2, 3 equiv of CuX_2, and 0.2 equiv of HEt_3NI, 2-disubstituted 3-halobenzo[*b*]furans were selectively produced as the major products. Further efforts to study the mechanism and extend the application of these additives in other palladium-catalyzed transformations are underway in our laboratory.

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Supporting Information Available: Analytical data and spectra (^1H and ^{13}C NMR) for all the products **2**−**4**; typical procedure for the palladium-catalyzed annulation reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

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