

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

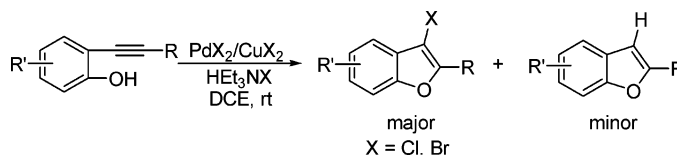
Yun Liang, Shi Tang, Xu-Dong Zhang, Li-Qiu Mao, Ye-Xiang Xie, and Jin-Heng Li\*

Key Laboratory of Chemical Biology & Traditional Chinese Medicine Research,  
College of Chemistry and Chemical Engineering, Hunan Normal University,  
Changsha 410081, People's Republic of China

jhli@hunnu.edu.cn

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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  $\text{PdX}_2$ ,  $\text{CuX}_2$ , and  $\text{HEt}_3\text{NX}$ , 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.<sup>1</sup> For these reasons, a number of efficient and selective methods have been developed for their synthesis.<sup>1c,2–5</sup> Among these transformations, the palladium-catalyzed annulations of *o*-hydroxylarylacetylenes is considered to be one of the most effective strategies.<sup>2–4</sup> Generally, benzo[*b*]furans are prepared by either palladium-catalyzed one-pot annulations of 2-hy-

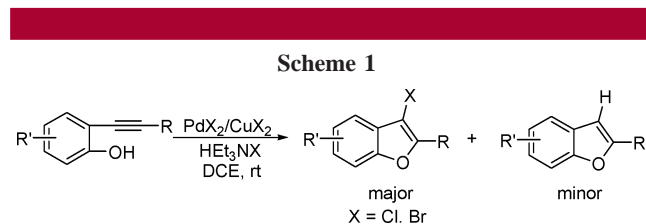
droxyaryl iodides with alkynes<sup>3</sup> or palladium-catalyzed annulations of 2-hydroxyaryl iodides with electrophilic reagents (unsaturated halides<sup>4a–d</sup> or  $\text{CO}^{4e–l}$  etc.). In the latter transformations, however, the competition between the attack of electrophilic reagents and 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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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.<sup>5a,h,i</sup> 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).



As shown in Table 1, 2-(2-*n*-octylethynyl)phenol (**1a**) was

**Table 1.** Screening the Effect of Additives on the Palladium Bromide-Catalyzed Annulation of 2-(2-*n*-Octylethynyl)phenol (**1a**)<sup>a</sup>

entry	additive (equiv)	yield (%) <sup>b</sup>	
		2a	3a
1 <sup>c</sup>		97 (91)	0
2 <sup>d</sup>		50	4
3		84 (81)	10
4 <sup>e</sup>		85	8
5 <sup>f</sup>		0	0
6 <sup>g</sup>		95 (90)	5 ( <b>4a</b> )
7	HEt <sub>3</sub> NI (0.1)	40	43
8	HEt <sub>3</sub> NI (0.2)	10	77 (75)
9	HEt <sub>3</sub> NI (0.5)	0	0
10	HEt <sub>3</sub> NCl (0.2)	75	14
11	HEt <sub>3</sub> NBr (0.2)	69	17
12	TBAB (0.2)	83 (80)	8
13	KI (0.2)	81	10
14	PPh <sub>3</sub> (0.2)	81	9
15	Et <sub>3</sub> N (1.0)	78	12

<sup>a</sup> Reaction conditions: **1** (0.3 mmol), PdBr<sub>2</sub> (5 mol %), and CuBr<sub>2</sub> (3 equiv) in DCE (5 mL) at room temperature for 5 h. <sup>b</sup> GC yield. Isolated yield is given in parentheses. <sup>c</sup> Without CuBr<sub>2</sub>. <sup>d</sup> CuBr<sub>2</sub> (1 equiv). Conversion of **1a** was 60% as determined by GC analysis. <sup>e</sup> CuBr<sub>2</sub> (5 equiv). <sup>f</sup> Without PdBr<sub>2</sub>. 2-(1,2-Dibromo-2-phenylvinyl)phenol was isolated in 10% yield. <sup>g</sup> PdCl<sub>2</sub> (5 mol %) and CuCl<sub>2</sub> (3 equiv) instead of both PdBr<sub>2</sub> and CuBr<sub>2</sub>.

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<sub>2</sub> (entry 1). It is noteworthy that the presence of CuBr<sub>2</sub> 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<sub>2</sub>, 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<sub>2</sub> 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<sub>2</sub> was further increased to 5 equiv (entry 4). The results also demonstrated that PdBr<sub>2</sub> played a crucial role in the reaction (entry 5). Without PdBr<sub>2</sub>, no benzo[*b*]furans were observed. Another catalytic system (PdCl<sub>2</sub>/CuCl<sub>2</sub>) was also tested (entry 6). It was found that PdCl<sub>2</sub> was also effective for the annulation reaction of **1a**. The addition of PdCl<sub>2</sub> and CuCl<sub>2</sub> 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<sub>3</sub>NI 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<sub>2</sub>, 3 equiv of CuBr<sub>2</sub>, and 0.1 equiv of HEt<sub>3</sub>NI, 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<sub>3</sub>NI, 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<sub>3</sub>NI to 0.5 equiv led to no reaction (entry 9). Other reagents, including HEt<sub>3</sub>NCl, HEt<sub>3</sub>NBr, TBAB, KI, Et<sub>3</sub>N, and PPh<sub>3</sub>, 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**<sup>6</sup> 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<sub>2</sub>, 3 equiv of CuBr<sub>2</sub>, and 0.2 equiv of HEt<sub>3</sub>NI afforded a 92% isolated yield of 2-phenyl 3-bro-

(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  $\text{HEt}_3\text{NI}^a$

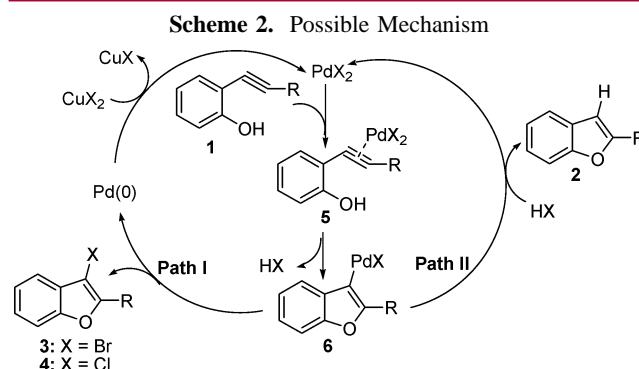
Entry	Substrate	Conditions	Time (h)	Isolated yield (%)	
				2	3 or 4
1		B	8	12 ( <b>2a</b> )	60 ( <b>4a</b> )
2	R = Ph ( <b>1b</b> )	A	8	0 ( <b>2b</b> )	92 ( <b>3b</b> )
3	R = Ph ( <b>1b</b> )	B	8	17 ( <b>2b</b> )	70 ( <b>4b</b> )
4	R = <i>p</i> -MeC <sub>6</sub> H <sub>4</sub> ( <b>1c</b> )	A	6	0 ( <b>2c</b> )	91 ( <b>3c</b> )
5	R = <i>p</i> -MeC <sub>6</sub> H <sub>4</sub> ( <b>1c</b> )	B	7	25 ( <b>2c</b> )	65 ( <b>4c</b> )
6	R = <i>t</i> -Bu ( <b>1d</b> )	A	9	10 ( <b>2d</b> )	69 ( <b>3d</b> )
7	R = <i>t</i> -Bu ( <b>1d</b> )	B	10	13 ( <b>2d</b> )	65 ( <b>4d</b> )
8 <sup>b</sup>		A	16	0 ( <b>2e</b> )	78 ( <b>3e</b> )
9 <sup>b</sup>	( <b>1e</b> )	B	24	46 ( <b>2e</b> )	51 ( <b>4e</b> )
10 <sup>bc</sup>		A	12	0 ( <b>2f</b> )	92 ( <b>3f</b> )
11 <sup>bd</sup>	( <b>1f</b> )	B	24	42 ( <b>2f</b> )	45 ( <b>4f</b> )
12 <sup>bc</sup>		A	24	58 ( <b>2g</b> )	37 ( <b>3g</b> )

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

mobenzo[*b*]furans (**3b**) exclusively (entry 2). When 5 mol % of  $\text{PdCl}_2$ , 3 equiv of  $\text{CuCl}_2$ , and 0.2 equiv of  $\text{HEt}_3\text{NI}$  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  $\text{PdX}_2$  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  $\text{PdBr}_2$  and  $\text{CuBr}_2$  (entry 8), whereas 2-alkynylphenol **1e** bearing a nitro group provided the desired product **3g** as a minor product (37% yield; entry 12).

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Compared with the previous work,<sup>2–5</sup> 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.<sup>2,3,5</sup> 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  $\text{PdX}_2$ -activated intermediate **5** affording intermediate **6** and  $\text{HX}$ . Then two pathways might proceed: (i) With the aid of  $\text{CuX}_2$ , the cleavage of the C–Pd  $\sigma$ -bond of intermediate **6** can take place readily to form 2-substituted 3-halobenzo[*b*]furans **3/4** and the  $\text{Pd}(0)$  species.<sup>7</sup> The active  $\text{Pd}(\text{II})$  species can be regenerated by the oxidation reaction of  $\text{Pd}(0)$  with  $\text{CuX}_2$  to start a new catalytic cycle. (ii) Protonolysis of intermediate **6** formed 2-substituted benzo[*b*]furans **2** and regenerated the active  $\text{Pd}(\text{II})$  species.<sup>8</sup>

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

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

(7) It has been reported that  $\text{Cu}(\text{II})$  as an oxidant could cleave the C–Pd  $\sigma$ -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  $\text{Pd}(\text{II})$  species by  $\text{HCl}$ , 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  $\sigma$ -bond, see: Zhu, G.; Lu, X. *J. Organomet. Chem.* **1996**, *508*, 83 and references therein.

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

selectivity. In the presence of PdX<sub>2</sub>, 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<sub>2</sub>, 3 equiv of CuX<sub>2</sub>, and 0.2 equiv of HEt<sub>3</sub>NI, 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 (<sup>1</sup>H and <sup>13</sup>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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