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Palladium-Catalyzed Sequential Oxidative Cyclization/Coupling of 2-Alkynylphenols and Alkenes: A Direct Entry into 3-Alkenylbenzofurans

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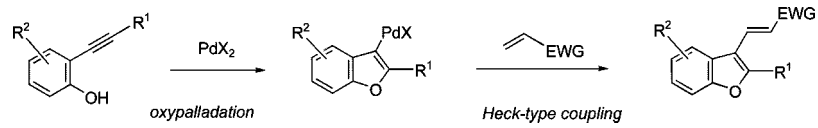
ABSTRACT



A new Pd-catalyzed tandem intramolecular oxypalladation/Heck-type coupling between 2-alkynylphenols and alkenes is reported, leading to 3-(1-alkenyl)benzofurans. Participating alkenes include those substituted with an electron-withdrawing group (ester, ketone, amide, nitrile, sulfone), as well as styrene. Remarkably, β-substituted-α,β-unsaturated carbonyl-type derivatives also participate effectively. The ready availability of substituted alkynylphenols, together with flexibility in the alkene choice, makes this simple strategy a versatile one for the synthesis of structurally diverse benzofuran derivatives.

Benzofurans are interesting compounds because of their natural occurrence and biological activities.[1] In particular, benzofurans substituted at C-3 with 3-oxoprop-2-enyl fragments (**6**) are endowed with significant pharmacological potential.[2] The synthesis of these compounds has been most often realized using either Wittig reactions from 3-formyl derivatives[2d] or Heck couplings from the corresponding 3-halobenzofurans.[2d,3] A more direct and potentially versatile route would involve the one-pot sequential palladium-catalyzed cyclization/Heck-coupling starting from 2-alkynylphenols **2** and α,β-unsaturated carbonyl compounds (Scheme 1), and this strategy would also benefit from the ready availability of substrates **2** via Sonogashira-type reactions.[4]

Always latent in these reactions is the potentially troublesome need for oxidation of the Pd(0) generated in the Heck coupling to the Pd(II) required for alkyne activation in the preceding cyclization step. This probably explains the scarcity of literature reports dealing with intramolecular

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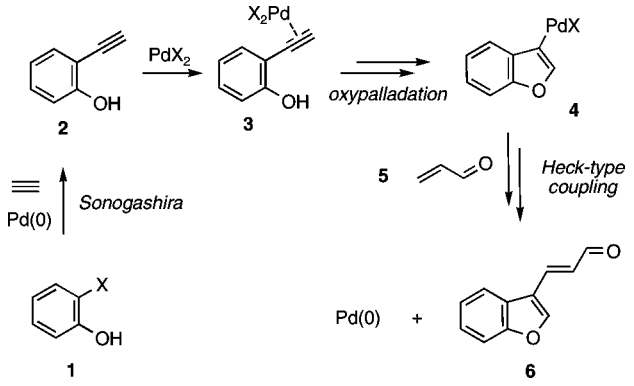
Scheme 1

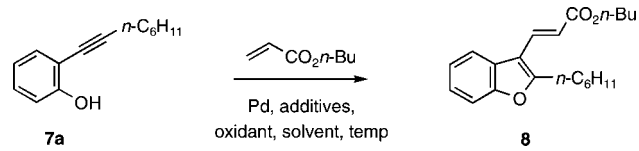


nucleopalladation followed by Heck reaction,[5,6] only one of them involving the preparation of a fully aromatic furan nucleus.[6] In that particular case, however, the buta-1,2,3-triene carbinol cyclization precursors had to be generated in situ for good yields, and the reactions of α,*β*-unsaturated ketones were complicated by the competing formation of conjugate addition (hydroarylation-type) products. A limitation was also found in that the coupling reaction did not tolerate substitution at the *β*-alkene position of the α,*β*-unsaturated carbonyl compound.[6]

With these precedents, we initiated a study directed at the efficient formation of benzofurans using the general ideas depicted in Scheme 1. At the outset, one of the foreseeable benefits of this strategy, besides simplicity, was the attainment of structural diversity, emanating from variations in the starting phenol (**1**) and alkyne components as well as from the use of a variety of alkene coupling partners. Reported below are the preliminary results of the successful realization of these ideas.

Application of the reaction conditions reported to be successful with buta-1,2,3-triene carbinols[6] to the coupling between alkynylphenol **7a** and *n*-butyl acrylate afforded the desired product **8**, but the yield was not satisfactory (Table 1, entry 1). Similarly, conditions inspired in those previously employed with α-allenols in a related process[5d] were also disappointing (entry 2), as were other combinations of solvent, catalyst, and base (entries 3−5). Interestingly, the use of $Pd_2(dba)_3$ resulted in efficient formation of benzofuran **9**, the product of cycloisomerization of the starting alkynylphenol **7a**, and no **8** was detected (Figure 1). Eventually, conditions reported for allenoic acids in other oxidative coupling processes[7] proved successful, and benzofuran **8** was obtained in good yield (entry 6).

Table 1. Survey of Reaction Conditions for the Preparation of Benzofuran **8**[a]



	conditions[b]	time (h)	yield[c]
1[d]	$Pd(PPh_3)_4$, Et_3N (5), LiCl (4), THF, air, 60 °C	20	11
2[d]	$Pd(OAc)_2$,[e] PPh_3,[f] LiCl (5), K_2CO_3 (7), DMF, air, $Cu(OAc)_2$ (2.1), rt	5	20
3	$Pd(PPh_3)_4$,[e] Et_3N (10), DMF, air, rt	8	10
4	$Pd(PPh_3)_4$,[e] Et_3N (10), toluene, air, rt	24	34
5[d]	$Pd_2(dba)_3$, PPh_3,[f] Et_3N (10), DMF, air, rt	11	60[g]
6	$PdCl_2$, KI (0.5), DMF, air, 80 °C	20	62

[a] Unless otherwise stated, 5 mol % of a Pd complex and 6 equiv of *n*-butyl acrylate were used relative to **7a**. [b] Within brackets, number of equivalents relative to **7a**. [c] Isolated yield (%). [d] 4 equiv of *n*-butyl acrylate. [e] 10 mol %. [f] Pd/PPh_3 ratio = 1:2. [g] Product was 2-hexylbenzofuran (**9**).

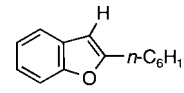


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Figure 1. Byproduct obtained in the preparation of **8**.

As shown in Table 2, the same conditions were applied successfully to other 2-alkynylphenols, incorporating variations at both the terminal alkynyl position (entries 3−5) and the phenol moiety (entries 2, 4, and 5). The data illustrate the use of both aryl- (entries 3−5) and alkyl-substituted alkynes (entries 1 and 2) as efficient precursors, as well as good tolerance to the presence of electron-withdrawing (entries 4 and 5) and electron-donating groups (entries 3−5) alike in the aryl groups at either alkyne termini.

Particular attention was paid to the possibility of applying this cyclization/coupling reaction to olefins other than *n*-butyl acrylate, as this would allow a significant increase in structural diversity (Table 3). In fact, a wide variety of olefins were found to participate efficiently, and this included α,*β*-

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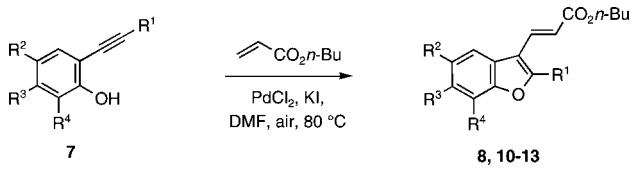
Table 2. Preparation of Benzofurans **8** and **10**−**13** from **7** and *n*-Butyl Acrylate[a]



7 8, 10-13

	R^1, R^2, R^3, R^4	time (h)	product	yield[b]
1	*n*-C_6H_{13}, H, H, H	20	**8**	62[d]
2	*n*-C_6H_{13}[c]	20	**10**	57[d]
3	*p*-Tolyl, H, H, H	20	**11a**	91
4	*p*-Tolyl, CO_2Me, H, H	7	**12**	99
5[e]	*p*-$(CO_2Et)C_6H_4$, ^{t}Bu, H, ^{t}Bu	20	**13**	75

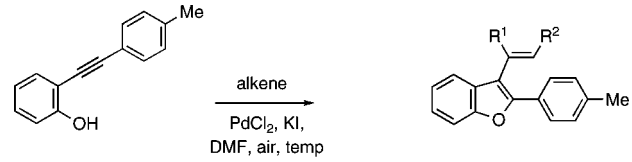
[a] Conditions: $PdCl_2$ (5 mol %), KI (50 mol %), *n*-butyl acrylate (6 equiv). [b] Isolated yield (%). [c] R^2, R^3 = $-C(Me)_2-CH_2CH_2-C(Me)_2-$; R^4 = H. [d] Product decomposes partially upon purification. [e] Reaction run at 100 °C.

unsaturated esters (entries 1 and 2), ketones (entries 3−6), amides (entries 7 and 8), nitriles (entries 9 and 10), and sulfones (entry 11), as well as styrene (entry 12). Products derived from conjugate addition-type (hydroarylation) processes[8] were not detected in the case of α,β-unsaturated ketones. Particularly remarkable is the participation of β-substituted α,β-unsaturated carbonyl-type derivatives (entries 2, 4−6, 8, and 10), as Heck reactions with 1,2-disubstituted olefins have been often limited by their low reactivity under typical conditions. With the advent of oxidative conditions and the use of boronic acids or siloxanes in place of organic halides,[9] this problem was solved, but the use of those alkenes in cyclization/Heck-type couplings remained so far unreported. In two cases (entries 2 and 8), competitive formation of a regioisomer of type **14** (Figure 2), the result of double bond migration, was observed. This is likely the result of hydropalladation/dehydropalladation processes promoted by the HPdX released in the Heck coupling and triggered by the congested nature of these conjugated products.

Tables 1−3 also attest to the high stereoselectivity of this reaction. Thus, exclusive formation of the (*E*)-isomer of 3-alkenylbenzofurans **8** and **10**−**13** was observed in most cases. The exception was acrylonitrile (entry 9), which afforded the product as an *E*/*Z* mixture, a result which is in line with related precedents.[9b,f]

Some control experiments were also run to gain further insight into the mechanistic details of this sequential process. When the reaction between **7c** and *n*-butyl acrylate was run under Ar, the coupling product **11a** was obtained in only 20% yield, confirming that oxygen was needed for effective

Table 3. Formation of Benzofurans from **7c** and Alkenes[a]



7c 11

	alkene	temp (°C)	11	R^1, R^2	yield[b]
1	*n*-butyl acrylate	80	**11a**	H, CO_2n-Bu	91
2	methyl (*E*)-but-2-enoate	80	**11b**	Me, CO_2Me	71[c]
3	methyl vinyl ketone	80	**11c**	H, COMe	91
4	(*E*)-pent-3-en-2-one	80	**11d**	Me, COMe	56
5	cyclohexenone	100	**11e**	$(CH_2)_3C(O)$	31
6	cyclopentenone	100	**11f**	$(CH_2)_2C(O)$	36
7	acrylamide	100	**11g**	H, $CONH_2$	50
8	(*E*)-but-2-enamide	100	**11h**	Me, $CONH_2$	40[d]
9[e]	acrylonitrile	100	**11i**	H, CN	60[f]
10[g]	but-2-enenitrile	80	**11j**	Me, CN	57[h]
11	methyl vinyl sulfone	100	**11k**	H, SO_2Me	57
12	styrene	80	**11l**	H, Ph	57

[a] Conditions: $PdCl_2$ (5 mol %), KI (50 mol %), alkene (6 equiv), 20 h. [b] Isolated yield (%). [c] A 1:1 mixture of **11b** and **14a** was obtained. [d] A 1:1.5 mixture of **11h** and **14b** was obtained. [e] Reaction run in a sealed tube. [f] A 3:1 *E*/*Z* mixture was obtained. [g] The starting alkene was a 1:1 *E*/*Z* mixture. [h] A 1.2:1 *E*/*Z* mixture was obtained

14a R^2 = CO_2Me
14b R^2 = $CONH_2$

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Figure 2. Benzofuran isomerization products (**14**) and substrate for mechanistic exploration (**15**).

oxidation of Pd(0) to Pd(II).[9b−e,10] In this regard, the use of KI could provide another possibility for a Pd(0) oxidant. Thus, in related oxidative couplings, it has been suggested that iodine formed from the aerobic oxidation of iodide anions could be the actual oxidazing agent for Pd(0).[7] Interestingly, the presence of iodine in the reaction also offers a second plausible mechanism for formation of 3-alkenylbenzofurans. Indeed, iodination of 2-alkynylphenols has been reported to afford 3-iodobenzofuran derivatives **15** (Figure 2),[3] and the Heck chemistry of these aryl iodides is also known.[3] Therefore, an experiment was conducted whereupon iodobenzofuran **15** (R = *p*-tolyl) was subjected to the same reaction conditions that afforded **11a** from alkynylphenol **7c**. This resulted only in recovered starting material, effectively ruling out an iodination/Heck coupling sequence as the

(8) See ref 6 and references cited therein. See also: Fall, Y.; Doucet, H.; Santelli, M. *Tetrahedron* **2009**, *65*, 489–495.

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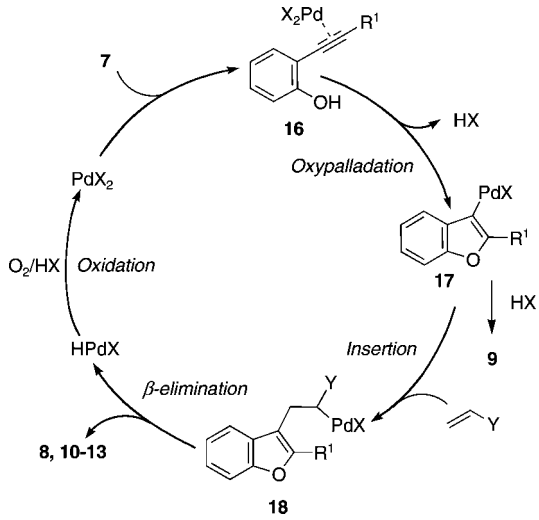
(10) Alternatively, excess acrylate has been reported to be involved in the regeneration of Pd(II) in some intermolecular oxidative Heck reactions. See ref 9f.

Scheme 2



mechanism of formation of benzofurans **8** and **10**−**13**. Furthermore, in the absence of KI, the coupling between phenol **7c** and *n*-butyl acrylate still afforded benzofuran **11a** in 76% yield (down from 91%, entry 1, Table 3), showing that, while the use of KI is clearly beneficial,[11] significant amounts of product are formed in its absence. This provides further support for the oxypalladation/Heck pathway depicted in Scheme 2. Thus, after Pd(II)-promoted cyclization, intermediate **17** undergoes alkene insertion, followed by Pd−H elimination with release of products **8**, **10**−**13**, and a palladium hydride. Oxidation of the latter regenerates the catalytic PdX_2 species. Alternatively, protonation of **17** affords side product **9**.

In conclusion, a variety of 2-alkynylphenols and substituted alkenes are effective partners in the one-pot palladium-catalyzed oxidative cyclization/Heck sequence leading to 3-alkenylbenzofurans.[12] This procedure conveniently sidesteps the preparation of the 3-halobenzofuran- or β-halo-α,β-unsaturated carbonyl derivatives required with other alternative procedures. Other particularly attractive features of this reaction include (i) the high degree of structural diversity attainable, (ii) effective participation of ketone derivatives without unwanted hydroarylation-type side reactions, and (iii) tolerance of substitution at the electron-deficient olefin β-position.

Efforts toward the development of intramolecular versions of this reaction en route to benzofuran natural products, as well as its extension to other types of coupling partners, are in progress and will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization of new compunds. This material is available free of charge via the Internet at http://pubs.acs.org.

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