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A General Synthesis of Alkenyl-Substituted Benzofurans, Indoles, and Isoquinolones by Cascade Palladium-Catalyzed Heterocyclization/Oxidative Heck Coupling

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Dedicated to Professor José Barluenga on the occasion of his 70th birthday

Abstract: Structurally diverse C3-alkenylbenzofurans, C3-alkenylindoles, and C4-alkenylisoquinolones are efficiently prepared by using consecutive Sonogashira and cascade Pd-catalyzed heterocyclization/oxidative Heck couplings from readily available *ortho*-iodosubstituted phenol, aniline, and benzamide substrates, alkynes, and functionalized olefins. The cyclization of O- and N-heteronucleophiles follows regioselective 5-*endo-dig*- or 6-*endo-dig*-cyclization modes, whereas the subsequent Heck-type coupling with both mono- and disubstituted olefins takes place stereoselectively with exclusive formation of the *E* isomers in most cases.

Keywords: cyclization · Heck reaction · heterocycles · homogeneous catalysis · palladium

Introduction

Palladium-catalyzed cascade heterocyclization/Heck-type coupling reactions have found application in recent years in the synthesis of heterocyclic derivatives.[1] In these reactions Pd^{II} usually activates a C–C π bond toward nucleopalladation with a tethered nucleophile, and the resulting organopalladium intermediate then reacts with an alkene through carbopalladation and β-H elimination steps. External oxidants are required to render the reaction catalytic in Pd^{II} by oxidation of the Pd^0 species produced in the last step.[2] Different functionalities, both oxygen[1a,e,f,h–j] and nitrogen based[1b,c,g,k] have been documented as nucleophilic partners, usually of the NuH type,[3] whereas, in most cases, the participating π bond has been the constituent of a C=C double bond (either alkene or cumulene). In contrast, the use of C≡C triple bonds, as exemplified in Scheme 1, has been restricted to a limited use of carbamate or sulfonamide nitrogen nucleophiles.[1b,c]

We realized that the tactical combination of a Sonogashira reaction of 2-haloaryl heteroatom derivatives **1**–**3**, followed by an oxidative cyclization/Heck cascade, had the potential to become a general and practical approach to the preparation of alkenyl-substituted heterocyclic derivatives

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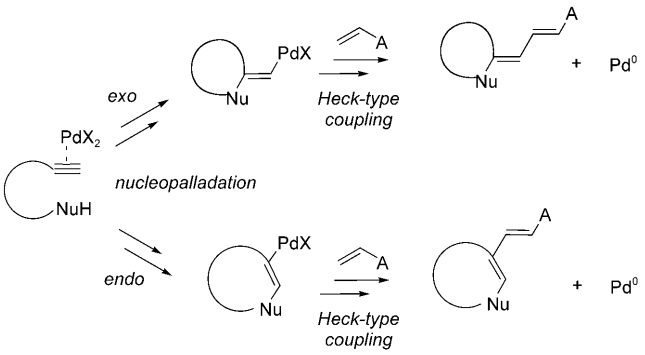
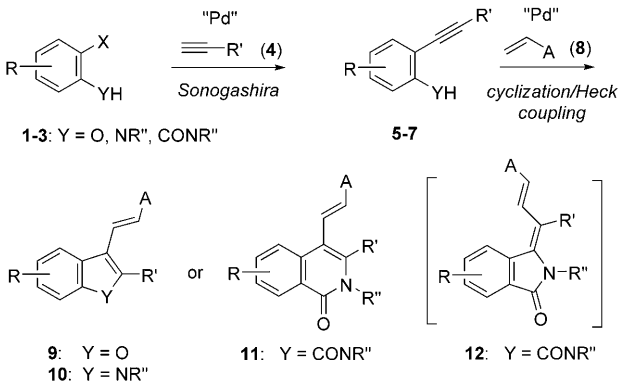


Scheme 1. A cyclization/Heck cascade.

9–12 (Scheme 2). An added benefit of this strategy would be structural diversity in products **9–12** emanating from variations in the starting halide- and alkyne-derivatives **1–3** and



Scheme 2. Strategy for the preparation of benzofurans **9**, indoles **10**, and isoquinolones **11**.

4, respectively, as well as from the use of a variety of alkene coupling partners **8**. To explore these possibilities, we targeted the corresponding reactions of 2-alkynylphenols (**5**; YH = OH), -anilines (**6**; YH = NHR″, R″ = H or alkyl) and -carboxyamides (**7**; YH = CONHR″), whereby formation of products **9–11** would involve either 5- or 6-*endo-dig* cyclizations, whereas the alternative 5-*exo-dig*-process (in the case of **7**) could lead to **12**. Because both 5-*exo*- and 6-*endo*-cyclizations have been reported for 2-alkynylbenzamides **7** (YH = CONHR″) under Pd-catalyzed conditions,[4–6] the control of the regiochemistry of cyclization became an additional challenge with these particular substrates.

As a result of those studies,[1j] we now report a cascade nucleopalladation/Heck process, encompassing 5-*endo*- and 6-*endo-dig* cyclizations, leading to structurally diverse 3-alkenylbenzofurans (**9**), 3-alkenylindoles (**10**), and 4-alkenylisoquinolones (**11**) from Sonogashira products **5–7** and substituted alkenes **8**. Products **9–11** are related to compounds with interesting biological profiles[7] and, therefore, represent valuable targets. The synthesis of 3-(3-oxoprop-2-enyl)-benzofurans and corresponding 4-alkenylisoquinolones has often been realized by using either Wittig reactions from 3-formyl-derivatives[8,9] or Heck couplings from the appropriate halo-derivatives.[9,10] In comparison, the one-pot cascade palladium-catalyzed cyclization/Heck-coupling reported here (Scheme 2) is a more direct and potentially versatile route, and this strategy would also benefit from the ready availability of substrates **5–7**, which can be obtained from Sonogashira-type reactions.[11,12] This type of strategy has already been employed in the synthesis of 3-alkenylindoles, but the reported methodology was found to have important limitations.[1b,c] For example, the amino group had to be suitably protected as a carbamate (YH = NHCOR) or sulfonamide (YH = $NHSO_2R$) for successful cyclization and subsequent coupling reaction, and an elaborate synthetic route was needed for sulfonamide substrate preparation. Other important shortcomings included a limited scope, particularly for the alkene partner involved in the Heck coupling.[13–15]

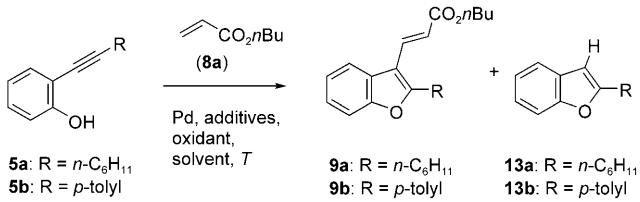
Results and Discussion

Representative substrates **5–7** were prepared straightforwardly, as indicated in Scheme 2, from the appropriate halide and alkyne precursors (**1–3** and **4**, respectively) under typical Sonogashira conditions (see the Supporting Information).

A survey of reaction conditions was then performed with representative 2-alkynylphenol substrates in couplings with *n*-butyl acrylate (Table 1). Initially, compound **5a** was used under a range of reaction conditions with a common base, which was thought to be useful as a trap for the acid released in the cyclization and Heck reactions (Table 1, entries 1–5).

Included here were conditions closely related to those previously found to be successful with buta-1,2,3-triene carbinols (Table 1, entry 1)[1i] and α-allenols (Table 1, entry 2).[1e] However, the yields of product **9a** with these and other combinations of solvent, catalyst, and base (Table 1, entries 3–5) were not satisfactory. In the last case (Table 1, entry 5), the use of $[Pd_2(dba)_3]$ resulted in efficient formation of benzofuran **13a**, the product of cycloisomerization of the starting alkynylphenol **5a**, and no coupling product **9a** was detected. On the other hand, inspired by conditions reported for allenoic acids in other oxidative coupling processes,[16] the use of $PdCl_2$/KI in dimethylformamide (DMF) proved successful, and benzofuran **9a** was obtained in good yield (Table 1, entry 6). The same reaction conditions worked well for alkynylphenol **5b**, which was converted cleanly into benzofuran **9b** in very high yield (Table 1, entry 7). This product was a more convenient model than **9a**, which decomposed partially upon purification, and further tests were conducted with **5b**. The use of KI was not mandatory for the cyclization/coupling reaction (Table 1, entry 9) but the yield was found to improve considerably in its presence (compare Table 1, entries 7 and 9). The alternative use of nBu_4NI as a nonmetallic iodide salt (Table 1, entry 8) also benefited the yield, albeit to a lesser extent, relative to yields obtained in the absence of iodide (Table 1, entry 9). The possible effect of iodide anions in these reactions is discussed below. Other palladium catalysts, such as $[PdCl_2(PPh_3)_2]$ and $Pd(OAc)_2$ (Table 1, entries 10 and 11) also proved useful, but yields were somewhat inferior to those obtained with $PdCl_2$. Under the new sets of conditions, the use of a base was again found to have deleterious effects on the coupling, as shown by the result summarized in Table 1, entry 12. On the other hand, Pd^0 catalysts were much less efficient (Table 1, entries 13 and 14). As expected, the use of oxidizing conditions was required for efficient catalysis. As a result, when the reaction was carried out under an Ar atmosphere, the yield of coupling product was considerably reduced (Table 1, entry 15). Excess acrylate was also

Table 1. Survey of reaction conditions for the preparation of benzofurans **9a** or **9b**.[a,b]



5a: R = *n*-C_6H_{11}
5b: R = *p*-tolyl

9a: R = *n*-C_6H_{11}
9b: R = *p*-tolyl

13a: R = *n*-C_6H_{11}
13b: R = *p*-tolyl

	5	Catalyst [equiv]	Additive/Conditions[b]	Solvent	T [°C]	t [h]	9/13	Yield [%][c]
1	**5a**	$[Pd(PPh_3)_4]$	Et_3N (5), LiCl (4), air[d]	THF	60	20	**9a**	11
2	**5a**	$Pd(OAc)_2$ (0.1)	PPh_3 (0.2), LiCl (5), K_2CO_3 (7), air, $Cu(OAc)_2$ (2.1)[d]	DMF	RT	5	**9a**	20
3	**5a**	$[Pd(PPh_3)_4]$ (0.1)	Et_3N (10), air	DMF	RT	8	**9a**	10
4	**5a**	$[Pd(PPh_3)_4]$ (0.1)	Et_3N (10), air	toluene	RT	24	**9a**	34
5	**5a**	$[Pd_2(dba)_3]$	PPh_3 (0.2), Et_3N (10), air[d]	DMF	RT	11	**13a**	60
6	**5a**	$PdCl_2$	KI (0.5), air	DMF	80	20	**9a**	62
7	**5b**	$PdCl_2$	KI (0.5), air	DMF	80	20	**9b**	94
8	**5b**	$PdCl_2$	Bu_4NI (0.5), air	DMF	80	20	**9b**	82
9	**5b**	$PdCl_2$	air	DMF	80	20	**9b**	76
10	**5b**	$[PdCl_2(PPh_3)_2]$	KI (0.5), air	DMF	80	20	**9b**	81
11	**5b**	$Pd(OAc)_2$	KI (0.5), air	DMF	80	20	**9b**	72
12	**5b**	$Pd(OAc)_2$	Et_3N (5), air	DMF	80	20	–	–[e]
13	**5b**	$[Pd(PPh_3)_4]$	KI (0.5), air	DMF	80	20	**9b**	<50[f]
14	**5b**	$[Pd_2(dba)_3]$	PPh_3 (0.2), KI (0.5), air	DMF	80	20	**9b**	41[g]
15	**5b**	$PdCl_2$	KI (0.5), Ar	DMF	80	20	**9b**	20
16	**5b**	$PdCl_2$	KI (0.5), air[h]	DMF	80	20	**9b/13b**	45/20
17	**5b**	$PdCl_2$	KI (0.5), air[i]	DMF	80	20	**9b/13b**	42/14
18	**5b**	$PdCl_2$	KI (0.5), air[j]	DMF	80	20	**9b/13b**	47/20

[a] Unless otherwise stated, 5 mol % of Pd complex and 6 equiv of *n*-butyl acrylate were used relative to **5**. dba = dibenzylideneacetone. [b] Number of equivalents relative to **5** are given in parentheses. [c] Isolated yield. [d] *n*-Butyl acrylate (4 equiv) was used. [e] Degradation. [f] Product was not pure. [g] Starting material was recovered (56 %). [h] *n*-Butyl acrylate (1 equiv) was used. [i] *n*-Butyl acrylate (2 equiv) was used. [j] *n*-Butyl acrylate (3 equiv) was used.

found to be important, as shown by the effect of lowering the amount of olefin from 6 to 1–3 equivalents (Table 1, entries 16–18), which had the effect of reducing the yield of coupling product substantially while also leading to formation of the cycloisomerization product **13b** in moderate amounts.

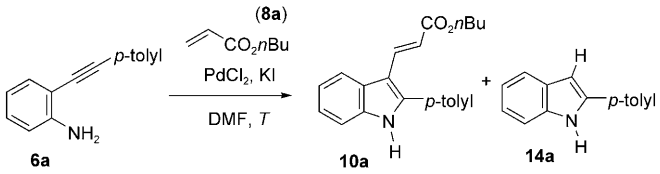
The reaction conditions summarized in Table 1, entries 6 and 7 were applied to representative 2-alkynylaniline and 2-alkynylbenzamide substrates to assess the generality of the reaction (Table 2). Aniline **6a** reacted at 80 °C with competing formation of cycloisomerization product **14a** (Table 2, entry 1). However, raising the temperature to 100 °C produced a much better yield of coupling product **10a**, without any observable cycloisomerization, under otherwise identical reaction conditions (Table 2, entry 2). On the other hand, under the standard conditions, formation of isoquinolones **11** from benzamides **7** took place without apparent interference from cycloisomerization, however, the yields were only moderate (Table 2, entries 11 and 12). In this case, the simple expedient of changing the catalyst was tried; among several palladium complexes that were tested, $[PdCl_2(PPh_3)_2]$ produced the desired improvement, and products **11** were obtained in much higher yields (Table 2, entries 13 and 14). The effect of KI was assessed with benzamide substrate **7a**, and found to be much more pronounced than in the benzofuran case. Thus, lowering the amount of KI from the standard 0.5 equivalents to just 0.2 equivalents was clearly detrimental to the yield of **11b** (Table 2, entry 15), whereas doubling the amount was inconsequential (Table 2, entry 16). Similar to the benzofuran case, control experiments performed with either variable amounts of alkene (Table 2, entries 3–6 and 17) or in an Ar atmosphere (Table 2, entries 8 and 18) confirmed the need for excess alkene and oxygen, respectively, whereas bases were again found to inhibit the reaction (Table 2, entries 9 and 10).

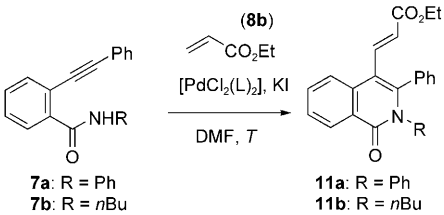
The conditions given in Table 2, entries 2, 13, and 14 were then taken as standard for aniline and benzamide substrates, respectively. It is interesting that, in line with the inhibitory effect of bases, the reaction of the aniline substrate **6a** required higher temperature than that of the less basic phenols **5**, and for those required for the benzamide **7** series. Reaction times for *N*-phenylbenzamides were consistently shorter than for the more basic *n*-butyl analogues (see also Table 3 below).

The standard set of reaction conditions in each case was then applied to different alkynyl-substituted phenol, aniline, and benzamide substrates **5**–**7** using an acrylate derivative as standard alkene partner. The results, which are collected in Table 3, show variations at the terminal alkynyl position (R^1), the alkynyl-substituted aryl ring (R^2–R^4) and the amino group (R^5), the latter only in the case of anilines and benzamides.

As shown in Table 3, substrates with different alkynyl R^1 substituents, such as aryl (both electron-poor and electron-rich) and alkyl groups, provided the expected products in high yields in most cases. A trimethylsilyl (TMS) group was also tolerated in the case of phenol and aniline substrates (Table 3, entries 6 and 12), but the corresponding benzamide failed to give the desired product (Table 3, entry 16). In the last case, the substrate was recovered largely unchanged under the standard conditions at 80 °C, and underwent decomposition at higher temperatures with loss of the TMS group and formation of unidentified products. It is likely that, in comparison to the phenol and aniline cases, the additional amide substituent R^5 provided a very crowded environment that contributed to the failure of the reaction. On the other hand, the coupling cascade was tolerant of additional substituents at the alkynyl-bearing aryl moiety (R^2–

Table 2. Test of the standard reaction conditions for aniline and benzamide substrates.[a]

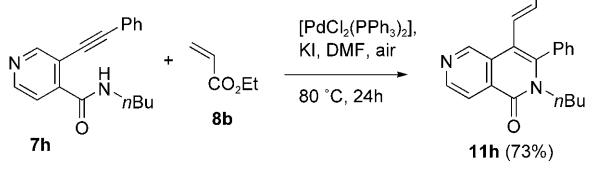




	6/7	L	T [°C]	Variables[b]	t [h]	Product	Yield [%][c]
1	**6a**	–	80	–	20	**10a/14a**	56/39
2	**6a**	–	100	–	20	**10a**	85
3	**6a**	–	100	**8a** (5)	20	**10a**	60
4	**6a**	–	100	**8a** (4)	20	**10a/14a**	58/30
5	**6a**	–	100	**8a** (2)	20	**10a/14a**	43/43
6	**6a**	–	100	**8a** (1)	20	**10a/14a**	20/80
8	**6a**	–	100	Ar	20	**14a**	60
9	**6a**	–	100	NaOAc (3)	20	**14a**	40[d]
10	**6a**	–	100	Et_3N (3)	4	–	–[e]
11	**7a**	–	80	–	15	**11a**	63
12	**7b**	–	80	–	23	**11b**	57
13	**7a**	PPh_3	80	–	16	**11a**	78
14	**7b**	PPh_3	80	–	23	**11b**	82
15	**7a**	PPh_3	80	KI (0.2)	14	**11a**	37
16	**7a**	PPh_3	80	KI (1)	14	**11a**	79
17	**7a**	PPh_3	80	KI (1), **8b** (1)	20	**11a**	61
18	**7a**	PPh_3	80	Ar	14	**11a**	21[f]

[a] Unless otherwise stated, 5 mol% of Pd complex, 0.5 equiv of KI and 6 equiv of **8a** or **8b** were used relative to **6** or **7** under an air atmosphere. [b] Variations with respect to the standard conditions. Number of equivalents relative to **6** or **7** are given in parentheses. [c] Isolated yield. [d] Starting material (60%) was recovered. [e] Starting material (100%) was recovered. [f] Starting material (77%) was recovered.

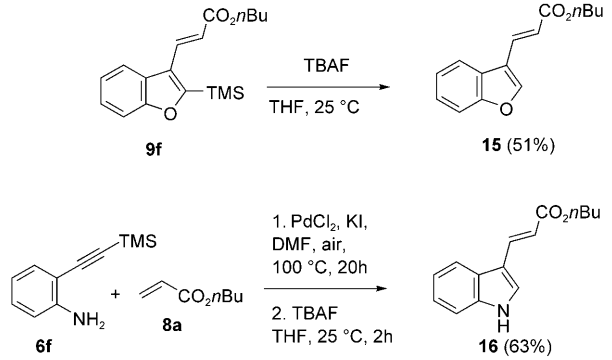
R^4), with both electron-donating and electron-withdrawing groups being well-represented (Table 3, entries 4, 5, 8, 9, and 20). In one case, a heteroaromatic alkynyl derivative was tested successfully (Scheme 3). Aniline and benzamide substrates also allowed additional variations at the amino group (R^5). Thus, besides the unprotected primary anilines displayed in Table 3, entries 7–12, a secondary amino group in aniline **6g** was also found to afford a similarly good yield (Table 3, entry 13); a result that considerably expands the scope of this reaction. As for the benzamide substrates, aryl,



Scheme 3. Preparation of 6-azaisoquinolone (a 2,6-naphthyridine-1-one) **11h**.

alkyl, and benzyl amino substituents (R^5) were all found to be successful (Table 3, entries 14–20). In one case (Table 3, entry 19), a potential protecting group (*p*-methoxyphenyl) was introduced at the amino group and the reaction proceeded with similar efficiency.

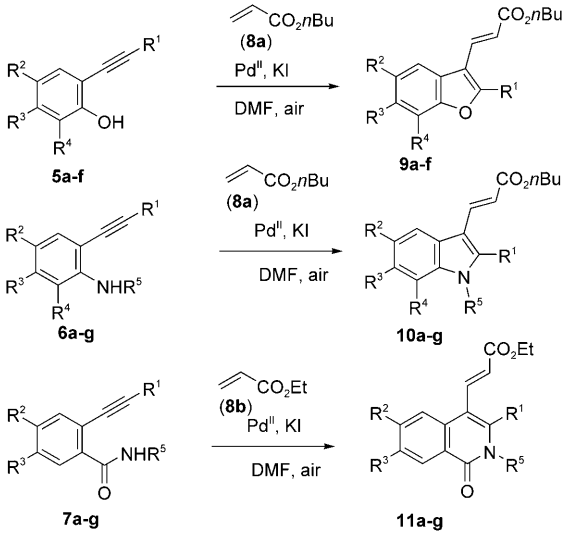
Trimethylsilyl-substituted products **9f** and **10f** are precursors of the corresponding 2-unsubstituted benzofuran **15** and indole **16**, which can be generated by protodesilylation (Scheme 4), offering a convenient alternative to the hypothetical use of acetylene as the alkyne component in the Sonogashira coupling. In the case of the TMS-derivative **10f**, the synthetic approach described above (Table 3, entry 12) was, in fact, accompanied by competing formation of the desilylated product **16** upon reaction of **6f** with **8a**. By introducing treatment with TBAF into the workup procedure, exclusive formation of **16** was realized (Scheme 4).



Scheme 4. Preparation of 2-unsubstituted benzofuran **15** and indole **16**. TBAF = tetrabutylammonium fluoride.

Even more structural diversity could be gained with variations of the olefin substituents. A very extensive study has been performed by using phenol substrates **5**, whereas the application to anilines **6** and benzamides **7** was more selective. As shown in Table 4 and Scheme 5, a wide variety of functional groups were incorporated with the olefin component, including carbonyls of different types, such as ester (**8c** and **8d**), ketone (**8e–h**), and amide (**8i** and **8j**), as well as cyano (**8k** and **8l**), sulfonyl (**8m**), and phenyl groups (**8n**). Application of the standard reaction conditions was straightforward for most monosubstituted alkenes ($R^2 = R^3 = H$; Table 4, entries 6, 8, 10, 11, and 14–20). One exception was the reaction of aniline **6a** with methyl vinyl sulfone **8m** for which, under the standard conditions, competing formation of cycloisomerization product **14** (see Table 2) was observed (34% yield, in addition to 48% of the expected product **10m**). Interestingly, changing the catalyst to $[PdCl_2(PPh_3)_2]$ (Table 4, entry 17) completely suppressed formation of **14**, and the desired product **10m** was obtained in excellent yield. In the case of α,β-unsaturated ketones (Table 4, entries 2–5, 14, and 18), the alternative conjugate addition type (hydroarylation) product[17] **18** (Scheme 5) was only observed with the benzamide **7b** (Table 4, entry 18), albeit in minor amounts, and even in this case the yield of the Heck product was high.

Table 3. General preparation of 3-alkenylbenzofurans, 3-alkenylindoles, and 4-alkenylisoquinolones from alkynyl substrates **5–7** and *n*-butyl (**8a**) or ethyl acrylate (**8b**).[a]



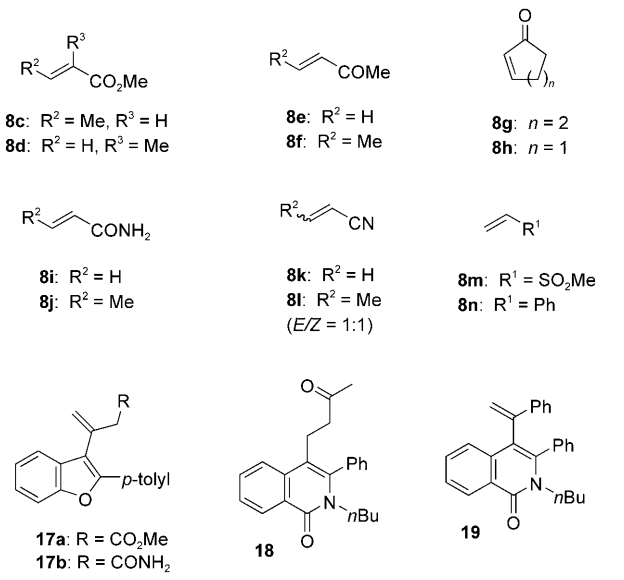
	5–7	R^1	R^2	R^3	R^4	R^5	Conditions[a]	9–11	Yield [%][b]
1	**5a**	*n*-C_6H_{13}	H	H	H	–	A	**9a**	62[c]
2	**5b**	*p*-Tolyl	H	H	H	–	A	**9b**	91
3	**5c**	*n*-C_6H_{13}	–[d]		H	–	A	**9c**	57[c]
4	**5d**	*p*-Tolyl	CO_2Me	H	H	–	A[e]	**9d**	99
5	**5e**	*p*-(CO_2Et)C_6H_4	*t*Bu	H	*t*Bu	–	A[f]	**9e**	75
6	**5f**	TMS	H	H	H	–	A	**9f**	79
7	**6a**	*p*-Tolyl	H	H	H	H	B	**10a**	85
8	**6b**	*p*-Tolyl	CO_2Me	H	H	H	B	**10b**	76
9	**6c**	*p*-Tolyl	Me	H	H	H	B	**10c**	57
10	**6d**	*n*-C_6H_{13}	H	H	H	H	B	**10d**	76
11	**6e**	$(CH_2)_4OH$	H	H	H	H	B	**10e**	32
12	**6f**	TMS	H	H	H	H	B	**10f**	72[g]
13	**6g**	*p*-Tolyl	H	H	H	Me	B	**10g**	74
14	**7a**	Ph	H	H	–	Ph	C	**11a**	78
15	**7b**	Ph	H	H	–	*n*Bu	C	**11b**	82
16	**7c**	TMS	H	H	–	Ph	C[h]	–	–[i]
17	**7d**	*n*-C_6H_{13}	H	H	–	Ph	C	**11d**	77
18	**7e**	Ph	H	H	–	CH_2Ph	C	**11e**	85
19	**7f**	Ph	H	H	–	(*p*-MeO)C_6H_4	C	**11f**	72
20	**7g**	Ph	MeO	MeO	–	*n*Bu	C	**11g**	83

[a] Unless otherwise indicated, reactions were conducted with Pd^{II} complex (5 mol%), KI (50 mol%), and acrylate ester (6 equiv) in DMF under an air atmosphere for the indicated time. Conditions A: $PdCl_2$, 80°C, 20 h. Conditions B: $PdCl_2$, 100°C, 20 h. Conditions C: $[PdCl_2(PPh_3)_2]$, 80°C, 21–25 h (R^4 = *n*Bu or Bn) or 15–16 h (R^4 = Ar). [b] Isolated yield. [c] Product decomposes partially upon purification. [d] R^2, R^3 = -$C(Me)_2CH_2CH_2C(Me)_2$-. [e] Reaction time was 7 h. [f] Reaction conducted at 100°C. [g] Yield of a 1:1 mixture of **10f** and **16** (see Scheme 4). [h] Reaction conducted at 120°C for 21 h. [i] Degradation.

Besides monosubstituted alkenes, a range of disubstituted α,β-unsaturated carbonyl-type derivatives (R^2 or $R^3 \neq H$) was also found to participate effectively (Table 4, entries 1, 3–5, 7, 9, 12, and 13). This is remarkable, because the use of disubstituted alkenes has often been problematic in Heck reactions due to low reactivity,[18] and, in fact, remained almost unreported in oxidative cyclization/Heck-type couplings prior to our work.[1h] In the present case, these alkenes have often shown a tendency to react with extensive degradation, and this has led to the need for some adjustment of the reaction conditions. As a result, in some cases it was found advantageous to increase the amount of olefin (Table 4, entry 12) or to change the catalyst (Table 4, entry 13). In a few instances, some disubstituted alkenes required increased temperatures, and this had a negative impact on yields (Table 4, entries 4, 5, and 7). This was particularly noticeable with the benzamide substrate **7b**, which led mainly to cycloisomerization and degradation products.

Interestingly, in two instances, formation of a regioisomer of type **17** (Scheme 5) was observed in reactions of phenol **5b** with β-substituted α,β-unsaturated carbonyl derivatives (Table 4, entries 1 and 7). Isomers **17** are probably generated as a result of double-bond migration from products **9g** and **9m** through hydropalladation/dehydropalladation processes promoted by HPdX. This palladium species is released in the Heck coupling and is normally expected to undergo base-promoted elimination of HX to form Pd^0, which then undergoes oxidation back to the Pd^{II} needed to initiate the cyclization/coupling process. However, the reaction conditions involved here are base-free and that pathway is not functional, thus making it more likely that HPdX could be available. In any case, isomerization is probably triggered by the congested nature of the trisubstituted, conjugated products.

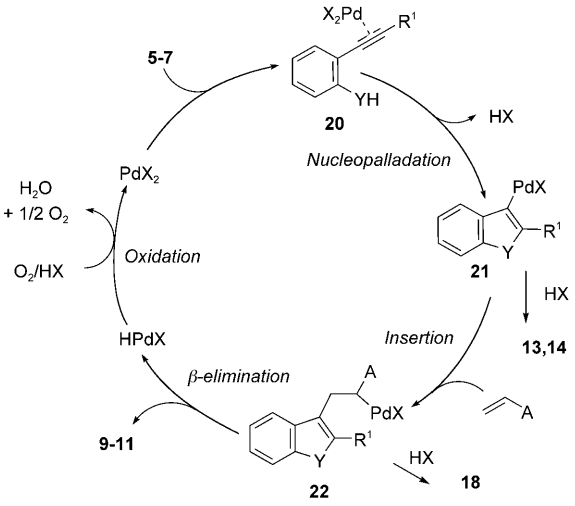
The results shown in Tables 3 and 4 also attest to the high regio- and stereoselectivity of formation of products **9–11**. High isolated yields of isoquinolone products **11** were realized without apparent formation of the alternative isoindolone-type products **12** (see Scheme 2). Furthermore, exclusive formation of the *E* isomers was observed in most cases. The exception was acrylonitrile (Table 4, entries 8 and 16), which afforded the products as *E*/*Z* mixtures, a result that is in line with related precedents.[18b,f] No stereochemical conclusions can be drawn from the reactions of but-2-enenitrile (Table 4, entry 9), because the starting alkene was already an *E*/*Z* mixture.



Scheme 5. Olefins **8c–n** used in the oxidative Heck coupling reactions and side-products **17–19** obtained in the cyclization/coupling reactions (Table 4).

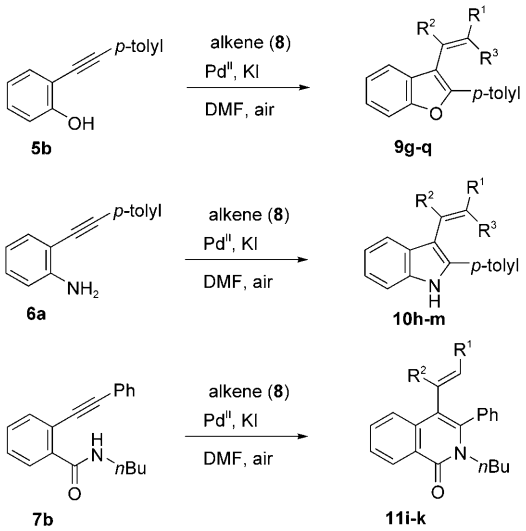
A plausible mechanism for this Pd-catalyzed cyclization/Heck coupling is depicted in Scheme 6. After Pd^{II}-promoted cyclization, intermediate **21** undergoes alkene insertion, followed by β-H elimination with release of products **9–11** and a palladium hydride. Oxidation of the latter then regenerates the catalytic PdX_2 species.[19] Alternatively, protonation of intermediates **21** or **22** affords cycloisomerization products **13** or **14**, or hydroarylation adduct **18**, respectively.

Several observations lend support to this mechanistic interpretation. As discussed earlier, formation of regioisomers **17** in reactions of β-substituted α,β-unsaturated carbonyl derivatives (Table 4, entries 1 and 7) suggests that HPdX is involved in hydropalladation/dehydropalladation processes with products **9g** or **9m** and, presumably, also with excess



Scheme 6. A plausible mechanism for the Pd-catalyzed cyclization/Heck coupling.

Table 4. General preparation of 3-alkenylbenzofurans, 3-alkenylindoles, and 4-alkenylisoquinolones from alkynyl substrates **5–7** and alkenes **8c–n** (Scheme 5).[a]



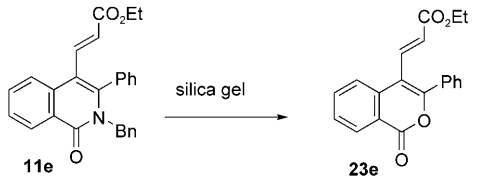
	8	5–7	Conditions[a]	9–11	R^1	R^2	R^3	Yield [%][b]
1	**8c**	**5b**	A	**9g**	CO_2Me	Me	H	70[c]
2	**8e**	**5b**	A	**9h**	COMe	H	H	91
3	**8f**	**5b**	A	**9i**	COMe	Me	H	56
4	**8g**	**5b**	A[d]	**9j**	$(CH_2)_3CO$		H	31
5	**8h**	**5b**	A[d]	**9k**	$(CH_2)_2CO$		H	36
6	**8i**	**5b**	A[d]	**9l**	$CONH_2$	H	H	50
7	**8j**	**5b**	A[d]	**9m**	$CONH_2$	Me	H	43[e]
8	**8k**	**5b**	A[f]	**9n**	CN	H	H	60[g]
9	**8l**	**5b**	A	**9o**	CN	Me	H	57[h]
10	**8m**	**5b**	A[d]	**9p**	SO_2Me	H	H	57
11	**8n**	**5b**	A	**9q**	Ph	H	H	60
12	**8c**	**6a**	B[i,j]	**10h**	CO_2Me	Me	H	51
13	**8d**	**6a**	B[k,l]	**10i**	CO_2Me	H	Me	67
14	**8e**	**6a**	B	**10j**	COMe	H	H	79
15	**8i**	**6a**	B	**10k**	$CONH_2$	H	H	95
16	**8k**	**6a**	B[f,i]	**10l**	CN	H	H	77[m]
17	**8m**	**6a**	B[k]	**10m**	SO_2Me	H	H	87
18	**8e**	**7b**	C[j]	**11i**	COMe	H	H	71[n]
19	**8i**	**7b**	C	**11j**	$CONH_2$	H	H	78
20	**8n**	**7b**	C[d]	**11k**	Ph	H	H	**39**[o]

[a] Unless otherwise indicated, reactions were conducted with Pd^{II} complex (5 mol%), KI (0.5 equiv), and alkene (6 equiv) in DMF under an air atmosphere for the indicated time. Conditions A: $PdCl_2$, 80°C, 20 h. Conditions B: $PdCl_2$, 100°C, 20 h. Conditions C: $[PdCl_2(PPh_3)_2]$, 80°C, 21–23 h. [b] Isolated yield. [c] A 1:1 mixture of **9g** and **17a** (Scheme 5) was obtained. [d] Reaction conducted at 100°C. [e] A 1:1.5 mixture of **9m** and **17b** (Scheme 5) was obtained. [f] Reaction conducted in a sealed tube. [g] A 3:1 *E*/*Z* mixture was obtained. [h] A 1.2:1 *E*/*Z* mixture was obtained. [i] Reaction conducted with 12 equiv of olefin. [j] Reaction time: 8 h. [k] $[PdCl_2(PPh_3)_2]$ was used as catalyst. [l] Reaction conducted at 60°C. [m] A 13:1 *E*/*Z* mixture was obtained. [n] The conjugate addition product **18** (20%) was also obtained (Scheme 5). [o] A 5:1 mixture of regioisomers **11k** and **19** (Scheme 5) was obtained.

alkene reagent. In fact, addition of HPdX to *n*-butyl acrylate has been reported to be involved in regeneration of a catalytically active Pd^{II} species in the absence of oxygen, and *n*-butyl propionate was found as a byproduct in such "oxidative Heck" reactions.[18f,20] In our reactions, however, oxygen is required for efficient catalysis and in no case was *n*-butyl propionate (or related products) formation observed, there-

fore, ruling out the involvement of excess alkene as a practical "oxidizing agent". Nevertheless, excess alkene is important in our reactions and could provide, through the same hydropalladation/dehydropalladation equilibria, control of the effective concentration of HPdX, as suggested by the results presented in Tables 1 (entries 16–18) and 2 (entries 4–6) with reduced amounts of alkene, whereupon cycloisomerization products were formed, presumably by either [HPdX] or HX promoted cyclization.[21]

Regeneration of an active Pd^{II} species is thus likely to proceed by oxidation of Pd^0 released from HPdX, in a process that is reported to require the presence of acid.[19,22,23] In fact, acid is released in both the initial Pd^{II}-promoted nucleopalladation and the final product-forming β-hydride elimination steps. Therefore, the inhibitory effect displayed by bases in these reactions (evidenced in Tables 1 and 2) is probably associated with a reduction in the concentration of acid available for catalyst regeneration; indeed, some indirect evidence indicates that acid is actually consumed in our reactions. For example, isoquinolones **11** are acid-sensitive materials, which tend to decompose upon silica gel chromatography (unless this is deactivated with Et_3N). In one case, the decomposition product has been identified as **23e**[24] (Scheme 7), and the conversion of amides **11** into lactones



Scheme 7. Formation of lactone **23e** from amide **11e**.

23 under GC–MS conditions has also been inferred in other cases. Nevertheless, high yields of products **11** are obtained under preparative conditions, after prolonged heating, without detectable formation of **23**, indicating a relative lack of acid. In this context, the additional beneficial effect of iodide anions in these reactions could also be ascribed to its participation in the Pd^0 oxidation step. Thus, in the presence of iodide salts under an oxygen atmosphere, iodine would be formed,[22] and this has been documented as being an oxidizing agent for Pd^0.[16]

Conclusion

The cascade, intramolecular alkyne nucleopalladation/intermolecular Heck-type coupling under oxidative conditions is an effective methodology for the preparation of benzofuran-, indole-, and isoquinolone-type derivatives, starting from readily available phenol, aniline, or benzamide substrates and functionalized alkenes. Furthermore, a combination of consecutive Sonogashira (in substrate preparation) and oxidative couplings conveniently sidesteps the preparation of haloaryl or β-halo-α,β-unsaturated carbonyl derivatives, and obviates the need for protection–deprotection steps required with alternative procedures. The cyclization step preceding oxidative coupling is shown to be effective for 5-*endo-dig*- and 6-*endo-dig*-cyclization modes, is compatible with O- and N-heteronucleophilic partners, and proceeds with excellent regioselectivity. The subsequent Heck-type coupling takes place stereoselectively with exclusive formation of *E* isomers in most cases, and allows the use of both mono- and disubstituted alkene partners. Finally, a very high degree of structural diversity is attainable through simple variations of the Sonogashira and Heck coupling partners, which also allows the introduction of useful functionality in the final products.

Experimental Section

General procedure for the cascade cyclization/Heck coupling: The Pd complex (0.012 mmol), KI (0.02 g, 0.120 mmol), and alkene **8** (1.44 mmol), were added to a solution of **5**–**7** (0.24 mmol) in DMF (2 mL), and the mixture was stirred in an air atmosphere under the conditions given in Tables 3 and 4. The mixture was allowed to cool to 25 °C and water (in the case of **5**–**6**) or a saturated aqueous solution of $NaHCO_3$ (in the case of **7**) was added. The mixture was extracted with EtOAc (×3), the combined organic layers were dried (Na_2SO_4), and the solvent was removed. The residue was purified by flash column chromatography under the conditions indicated in the Supporting Information for the individual cases.

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