Palladium-Catalyzed Cyclization/Heck- and Cyclization/Conjugate-Addition-Type Sequences in the Preparation of Polysubstituted Furans

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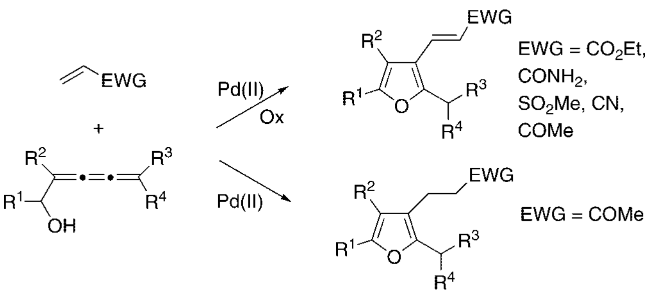
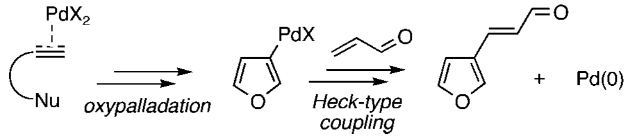


Palladium-catalyzed heterocyclization-coupling sequences have been developed starting from buta-1,2,3-trienyl carbinols and electron-deficient alkenes. Polysubstituted furans are formed where the heterocyclic ring originates from the elements of the butatrienyl carbinol while the electron-deficient olefin is incorporated as a C-3 substituent. In most cases, the reaction proceeds via a Heck-type pathway leading to the efficient formation of 3-vinylfurans. However, couplings with methyl vinyl ketone display a divergent behavior to afford selectively either Heck- or hydroarylation-type products depending on reaction conditions.

Furans substituted at C-3 with a 3-oxopropenyl unit (ketone, ester, or amide) have attracted recent attention because of their applications as active ingredients in pharmaceutical or agrochemical formulations, besides being useful synthetic intermediates.[1] The simple 2,4,5-unsubstituted derivatives are readily available from 3-furfural[2] or 3-lithiofuran[3] by using conventional chemistry, but for more substituted derivatives the synthesis is not as straightforward.[1b] The Pd(0)-catalyzed coupling between organic halides or triflates (R−X) and acyclic unsaturated substrates bearing an internal nucleophile is a practical method for the preparation of a variety of substituted heterocyclic structures incorporating the organic fragment (R).[4] While the preparation of 3-(3-oxopropenyl)furan derivatives by using this strategy has been described starting from 3-iodoacrylates and either allenyl carboxylic acids[5] or α-allenones,[6] this approach is nevertheless limited by the availability of the required iododerivatives. An attractive alternative would involve the use of simple α,β-unsaturated carbonyl derivatives in Pd(II)-catalyzed intramolecular oxypalladation/Heck-type coupling sequences (Scheme 1), and this may also allow the general introduction of other vinyl units. However, in this particular approach Pd(0) is released in the Heck coupling[7] whereas Pd(II) is needed to activate the unsaturated system toward cyclization. In fact, the difficulties associated with reoxidation of Pd(0) to the Pd(II) needed to maintain the catalytic cycle probably explain the scarcity of literature reports on intramolecular nucleopalladation followed by Heck reaction.[8] In the only reported case utilizing alcohol nucleophiles, the use of hydroxyalkenes provided an entry into saturated oxygen heterocycles of the tetrahydrofuran type,[8d] but in these examples the new vinyl unit was necessarily incorporated at the exocyclic carbon located at the furan C-2 rather than directly at C-3, as required for 3-vinylfuran synthesis.

SCHEME 1. Oxypalladation/Heck Strategy for 3-Vinylfuran Synthesis



Pd(0)-catalyzed cyclization/couplings of penta-2,3,4-trien-1-ols **3** with organic halides, on the other hand, have been shown to incorporate aryl-[9a] and allylic[9b] groups at C-3 of the newly formed furan ring. Notably, alcohols **3** are easily generated in situ from readily available epoxypropargyl ester substrates **1** and have the appropriate oxidation state needed to lead directly to the fully aromatic furan system. With these precedents, we

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SCHEME 2. Epoxypropargyl Ester Route to Polysubstituted Furans

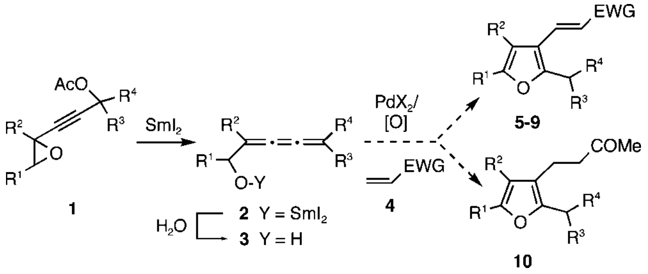
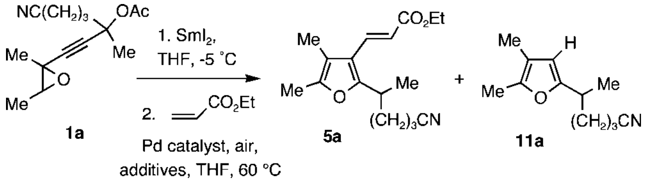


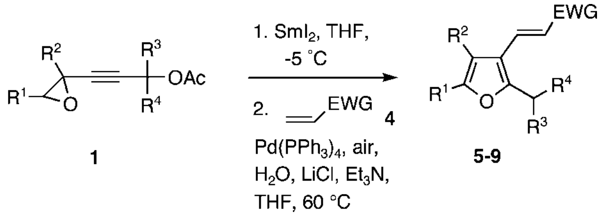
TABLE 1. Survey of Reaction Conditions for the Palladium-Catalyzed Step[a]



	Pd	additives (*n*)[b]	**5a**[c]	**11a**[c]
1	$Pd(OAc)_2$	H_2O (1)/LiCl (4)	52 (52)	8 (5)
2	$Pd(PPh_3)_4$	H_2O (1)/LiCl (4)	39	29
3	$Pd(OAc)_2$	H_2O (1)/LiCl (4)/Et_3N (1)	(41)	(2)
4	$Pd(PPh_3)_4$	H_2O (1)/LiCl (4)/Et_3N (5)	74	
5	$Pd_2(dba)_3$	H_2O (1)/LiCl (4)/Et_3N (5)	<30	
6	$Pd(PPh_3)_4$	H_2O (1)/Et_3N (5)	46	
7	$Pd(PPh_3)_4$	LiCl (4)/Et_3N (5)		
8[d]	$Pd(PPh_3)_4$	H_2O (1)/LiCl (4)/Et_3N (5)	63	
9[e]	$Pd(PPh_3)_4$	H_2O (1)/LiCl (4)/Et_3N (5)	61	
10[f]	$Pd(PPh_3)_4$	H_2O (1)/LiCl (4)/Et_3N (5)	59	
11[g]	$Pd(PPh_3)_4$	H_2O (1)/LiCl (4)/Et_3N (5)	48	18
12[h]	$Pd(PPh_3)_4$	LiCl (4)/Et_3N (5)	21	

[a] Unless otherwise indicated, 5 mol % of Pd complex and 15 equiv of ethyl acrylate. [b] *n* = number of equivalents. [c] Isolated yield (%) of pure product. Alternatively, within parentheses, yield calculated by ^1H NMR with 3,4-dimethoxybenzonitrile as internal standard. [d] Ten equivalents of ethyl acrylate was used. [e] Five equivalents of ethyl acrylate was used. [f] Two equivalents of ethyl acrylate was used. [g] Reaction run under Ar. [h] Reaction run from isolated **3a**.

TABLE 2. Preparation of Furans 5–9 from Epoxides 1 and Electron-Deficient Alkenes 4[a]



	1	R^1	R^2	R^3	R^4	EWG	*t* (h)[b]	**5**	yield[c]
1	**1a**	Me	Me	Me	$(CH_2)_3CN$	CO_2Et	17	**5a**	74
2	**1a**	Me	Me	Me	$(CH_2)_3CN$	CO_2NH_2	18	**6a**	58
3	**1a**	Me	Me	Me	$(CH_2)_3CN$	SO_2Me	18	**7a**	54
4	**1a**	Me	Me	Me	$(CH_2)_3CN$	CN	28	**8a**	53[d]
5	**1a**	Me	Me	Me	$(CH_2)_3CN$	COMe	4	**9a**	20[e]
6	**1b**	Me	Me	Me	$(CH_2)_2Ph$	CO_2Et	17	**5b**	83
7	**1b**	Me	Me	Me	$(CH_2)_2Ph$	$CONH_2$	20	**6b**	80
8	**1b**	Me	Me	Me	$(CH_2)_2Ph$	SO_2Me	20	**7b**	69
9	**1c**	^iPr	^iBu	Me	$(CH_2)_2Ph$	CO_2Et	20	**5c**	76
10	**1c**	^iPr	^iBu	Me	$(CH_2)_2Ph$	$CONH_2$	16	**6c**	72
11	**1c**	^iPr	^iBu	Me	$(CH_2)_2Ph$	SO_2Me	43	**7c**	61
12	**1d**	^iPr	^iBu	H	$(CH_2)_2Ar^f$	CO_2Et	18	**5d**	73
13	**1d**	^iPr	^iBu	H	$(CH_2)_2Ar^f$	$CONH_2$	24	**6d**	72
14	**1d**	^iPr	^iBu	H	$(CH_2)_2Ar^f$	SO_2Me	50	**7d**	70
15	**1e**	Me	Me	H	$(CH_2)_2Ph$	CO_2Et	4	**5e**	45
16	**1e**	Me	Me	H	$(CH_2)_2Ph$	$CONH_2$	20	**6e**	56
17	**1e**	Me	Me	H	$(CH_2)_2Ph$	SO_2Me	20	**7e**	51
18	**1f**	Me	Me	$(CH_2)_5$		CO_2Et	4	**5f**	80
19	**1f**	Me	Me	$(CH_2)_5$		$CONH_2$	5	**6f**	71
20	**1f**	Me	Me	$(CH_2)_5$		SO_2Me	20	**7f**	66

[a] Amounts of reagents relative to **1**: SmI_2 (2.25 equiv), $Pd(PPh_3)_4$ (5 mol %), H_2O (1 equiv), LiCl (4 equiv), Et_3N (5 equiv), and alkene (15 equiv). [b] Reaction time for the Pd-catalyzed step. [c] Isolated yield (%) of pure product. [d] Based on recovered triene **3a** (37%). [e] Also obtained in 39% yield was ketone **10a** [R^1 = R^2 = R^3 = Me, R^4 = $(CH_2)_3CN$, Scheme 2]. [f] Ar = 3,4-dimethoxyphenyl.

have now studied an alternative cyclization/oxidative Heck-type sequence between alcohols **3** and electron-deficient alkenes **4** as an entry into 3-vinylfurans **5**–**9**. As will be shown below, in a particular case the reaction can also be steered to the formation of products of type **10**, the formal result of an alternative conjugate addition to the electron-deficient alkene (Scheme 2).

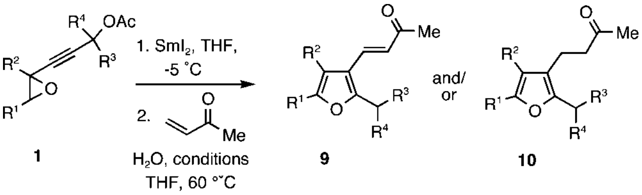
Epoxide **1a** and ethyl acrylate (**4a**) were selected as model substrates for a survey of reaction conditions (Table 1). Reduction of **1a** generated a samarium alkoxide (**2a**) that was directly treated with a Pd catalyst and ethyl acrylate under various conditions. After an initial screening, suitable starting conditions for formation of the Heck product **5a** were found in the form of $Pd(OAc)_2$ as catalyst, with H_2O and LiCl as additives, in THF at 60 °C under an air atmosphere (entry 1). In these initial experiments, the desired furan **5a** was invariably accompanied by **11a**, the result of cycloisomerization of alcohol **3a**.[9a] For catalyst reoxidation the simple and mild protocol of allowing air to diffuse through a $CaCl_2$ tube, as in entry 1, was of comparable efficiency to the use of a pure oxygen atmosphere. However, other oxidants or cooxidants, such as $Cu(OAc)_2$ or benzoquinone, gave poorer results. Under the foregoing oxidizing conditions, a Pd(0) complex also promoted the reaction but with concomitant substantial formation of **11a** (entry 2). The additional use of Et_3N had the effect of decreasing the amount of **11a** relative to **5a** (entries 3 and 4). This beneficial effect of Et_3N was particularly noticeable with $Pd(PPh_3)_4$ as catalyst whereupon formation of **11a** was completely suppressed and the yield of **5a** increased significantly (entry 4). The presence of phosphines in this last catalyst appeared to be important too, as $Pd_2(dba)_3$ afforded a poor yield of **5a** under otherwise identical conditions (entry 5). Further control experiments served to establish the need for both H_2O and LiCl under $Pd(PPh_3)_4$ catalysis (entries 6 and 7) as well as the convenience of using a large excess of ethyl acrylate for optimum yields (entries 8–10). A very significant reaction was observed under strict Ar conditions (entry 11) suggesting the presence of alternative internal oxidants.[8d–h] Finally, the need for running the reaction without isolation of alcohol **3a** was shown by the experiment in entry 12 where the application of the reaction conditions of entry 1 to a purified sample of **3a** (prepared in 85% isolated yield from **1a**)[9a] resulted in a comparatively much lower yield of **5a**. These observations hint at the involvement of Sm(III) salts at the Pd-oxidation and/or some other stage of the coupling.

By using the conditions found optimal for formation of **5a** as standard (entry 4, Table 1), a survey of alkenes was conducted to determine the scope of this reaction (Table 2). Thus, acrylamide (**4b**), methyl vinyl sulfone (**4c**), and acrylonitrile (**4d**) were also suitable partners for the cyclization/coupling sequence, providing good yields of the corresponding products **6a**−**8a** (entries 2–4). However, the reaction with methyl vinyl ketone (**4e**) was complicated by competition between Heck- and hydroarylation-type pathways with the latter predominating (entry 5). Other alkenes, such as acrylaldehyde, cyclohexenone, ethyl crotonate, *tert*-butyl methacrylate, styrene, cyclohexene, or 3,4-dihydro-2*H*-pyran, were not successful.

The corresponding reactions with other epoxides **1** and electron-deficient alkenes **4a**−**c** provided uniformly good yields of 3-vinylfuran derivatives **5**–**7** (entries 6–20), which display structural diversity stemming from the choice of the olefin activating group as well as from the convergent assembly of the starting esters.[9] Therefore, in common with other Pd-catalyzed applications of intermediates **3**, this cyclization/Heck-type coupling sequence succeeds in the formation of densely substituted functionalized furans[10] in a highly efficient manner, with complete regiocontrol, and without interference from the competing Pd(II)-catalyzed cycloisomerization process.

As noticed above, under the standard cyclization/coupling conditions, the reaction with methyl vinyl ketone departed from the general trend in that it provided **10a** as major product in addition to the expected **9a** (entry 5, Table 2). The tendency of α,β-unsaturated ketones (and aldehydes) to give unwanted hydroarylation (conjugate addition) products with aryl halides or triflates, under typical Pd(0)-catalyzed Heck reaction conditions, is well-known.[11,12] In fact, that particular reactivity of methyl vinyl ketone (and related conjugated ketones and aldehydes) has already been exploited with nucleophile-tethered (oxygen- or nitrogen-based) unsaturated derivatives in Pd(II)-catalyzed cyclization/conjugate-addition reactions.[8c,13] However, in the reported cases a relatively high acidity of the nucleophile (pH ≤ 5) has been found to be a requirement for adequate reactivity, whereas the use of relatively nonacidic alcohol nucleophiles has not been described so far.[14] Therefore, the possibility of taking synthetic advantage of this divergent behavior to perform alternatively Heck- or conjugate-addition-type coupling sequences in the context of furan synthesis was explored next. The corresponding results are displayed in Table 3. It was found that performing the reaction with $Pd(OAc)_2$ as catalyst in the absence of Et_3N, under either air or Ar atmospheres, completely suppressed the formation of Heck products **9** (entries 1–6). On the other hand, a high Heck selectivity was restored by using Ag_2CO_3 in place of LiCl under otherwise standard conditions (entries 7–9). Again, running the reactions without isolation of alcohols **3** proved advantageous, as shown by the experiment in entry 10 where an isolated alcohol **3f** was submitted to the conditions of entry 1 (expected to give **10f** selectively), resulting in a mixture of **9f** and **10f** with no selectivity. Therefore, a simple switch of reaction conditions provides access to either series of products **9** or **10** selectively. Furthermore, ethyl acrylate and methyl vinyl ketone give noticeably different results under identical reaction conditions (compare entry 1 of Table 1 with entry 1 of Table 3). Thus, the former follows the Heck pathway exclusively whereas the latter affords only a conjugate-addition product.

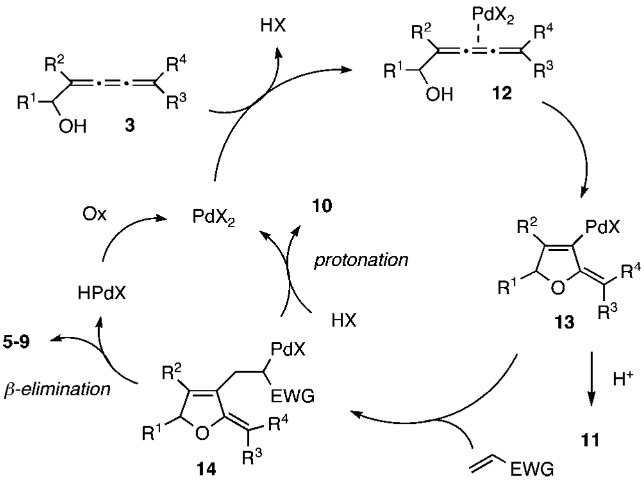
TABLE 3. Preparation of Furans 9 and 10 from 1 and Methyl Vinyl Ketone[a]



	1	conditions[b]	*t* (h)[b]	9, 10[c]	yield[d]
1	**1a**	$Pd(OAc)_2$, LiCl, air	2	**10a**	53
2	**1a**	$Pd(OAc)_2$, LiCl, Ar	5	**10a**	52
3	**1b**	$Pd(OAc)_2$, LiCl, Ar	2	**10b**	65
4	**1c**	$Pd(OAc)_2$, LiCl, Ar	22	**10c**	50
5	**1d**	$Pd(OAc)_2$, LiCl, Ar	2	**10d**	70
6	**1f**	$Pd(OAc)_2$, LiCl, Ar	23	**10f**	52
7	**1a**	$Pd(PPh_3)_4$, Ag_2CO_3, Et_3N, air	26	**9a**	60
8	**1c**	$Pd(PPh_3)_4$, Ag_2CO_3, Et_3N, air	52	**9c**	57
9	**1f**	$Pd(PPh_3)_4$, Ag_2CO_3, Et_3N, air	40	**9f**, **10f**	66, 18
10[e]	**1f**	$Pd(OAc)_2$, LiCl, air	3	**9f**, **10f**	(21), (21)

[a] Amounts of reagents relative to **1**: SmI_2 (2.25 equiv), palladium catalyst (5 mol%), H_2O (1 equiv), LiCl (4 equiv), Et_3N (5 equiv), Ag_2CO_3 (2 equiv), methyl vinyl ketone (15 equiv). [b] Conditions and reaction time for the Pd-catalyzed step. [c] Cycloisomerization products **11** were also obtained (<10% yield) in entries 1–6. [d] Isolated yield (%) of pure product. Alternatively, within parentheses, yield calculated by ^1H NMR with 3,4-dimethoxyphenylacetonitrile as internal standard. [e] Reaction run from isolated **3f**.

SCHEME 3. Catalytic Cycle for Formation of 5−10 from 3



A mechanistic rationale for formation of **5**–**10** is provided in Scheme 3. Thus, after the initial Pd(II)-promoted cyclization, intermediate **13** undergoes carbopalladation followed by either Pd−H elimination (eventually leading to **5**–**9**) or protonation

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(14) For a related Ru-catalyzed reaction, see: (a) Trost, B. M.; Pinkerton, A. B. *J. Am. Chem. Soc.* **2002**, *124*, 7376–7389. For a mechanistic variant in a similarly Ru-catalyzed reaction, see: (b) Trost, B. M.; Pinkerton, A. B. *J. Am. Chem. Soc.* **1999**, *121*, 10842–10843. (c) Trost, B. M.; Pinkerton, A. B.; Seidel, M. *J. Am. Chem. Soc.* **2001**, *123*, 12466–12476.

(to afford **10**). In contrast to the Heck-type pathway forming **5–9**, formation of **10** directly regenerates the catalytic Pd(II) species and no oxidation is needed in that case. The formation of **10** from **3** and methyl vinyl ketone was initially thought to be also associated to the well-known effect of LiCl to inhibit β-H elimination from palladium complexes.[8c,13] However, the formation of equivalent amounts of **9** and **10** when the reaction was performed from an isolated alcohol **3** under typical conjugate-addition conditions (entry 10) indicates that Sm(III) species, usually carried over from the preceding reduction step but absent in this particular case, are also at least partially responsible for the formation of **10** in our reaction. It is further suggested that the oxophilicity of Sm(III) may promote a ligand exchange with Pd(II) (at the stage of **14**) with formation of a Sm(III) enolate, which then undergoes protonation. On the other hand, the precise role of Ag_2CO_3 in these reactions is unclear.[15] Nevertheless, it is noted that it may act both as base and oxidant,[16] and that it has been previously used in Heck-type reactions.[16,17]

In summary, the sequential one-pot reduction/coupling starting from alkynyloxiranes **1** and electron-deficient olefins provides an expeditious entry into functionalized furans **5–10**. The formation of either Heck- or conjugate-addition-type products is in part dictated by the choice of electron-withdrawing group on the alkene. Thus, ester, amide, nitrile, and sulfone activating groups cause the reaction to follow exclusively the Heck pathway, whereas the acetyl group gives alternative access to both types of products depending on the particular reaction conditions. This work introduces unsaturated alcohols as new substrates for Pd-catalyzed cyclization/conjugate additions sequences.

Experimental Section

General Procedure for Reduction/Oxypalladation/Heck Coupling of Epoxides 1 and Alkenes. A solution of SmI_2 (0.1 M, 9 mL, 0.9 mmol) was added to a solution of epoxide **1** (0.40 mmol) in THF (2 mL) at −5 °C under Ar, and the mixture was stirred for 3 h. Excess SmI_2 was destroyed by allowing air into the system through a $CaCl_2$ guard tube, which was maintained in place throughout the remainder of the procedure. After allowing the mixture to reach room temperature, H_2O (0.14 mL of a 2.8 M solution in THF, 0.40 mmol) was added, followed by the appropriate alkene (6.00 mmol), LiCl (68 mg, 1.60 mmol, previously maintained at 0.5 mmHg and 350 °C for 45 min) [or Ag_2CO_3 (220 mg, 0.80 mmol) in the case of methyl vinyl ketone], Et_3N (0.28 mL, 2.00 mmol), and $Pd(PPh_3)_4$ (23 mg, 0.02 mmol). The resulting mixture was placed in an oil bath at 60 °C and stirred until consumption of alcohol **3**, as judged by TLC. After cooling, the reaction mixture was poured over saturated K_2CO_3 (15 mL), and the layers were separated. The aqueous phase was extracted with EtOAc (3 × 15 mL), and the combined organic layers were washed with H_2O (2 × 10 mL) and dried (Na_2SO_4). For reactions run with acrylamide and methyl vinyl sulfone, the combined organic layers were washed with saturated K_2CO_3 (2 × 10 mL), H_2O (2 × 10 mL), and brine (2 × 10 mL) before drying with Na_2SO_4. The crude after evaporation was purified as indicated in the Supporting Information for the individual cases.

General Procedure for Reduction/Oxypalladation/Conjugate-Addition Coupling of Epoxides 1 and Methyl Vinyl Ketone. A solution of SmI_2 (0.1 M, 9 mL, 0.9 mmol) was added to a solution of epoxide **1** (0.40 mmol) in THF (2 mL) at −5 °C under Ar, and the mixture was stirred for 3 h. Dry air was bubbled through the solution to destroy excess SmI_2, and the mixture was purged with Ar for 15 min. After the mixture was allowed to reach room temperature, H_2O (0.14 mL of a 2.8 M solution in THF, 0.40 mmol) was added, followed by methyl vinyl ketone (0.50 mL, 6.0 mmol), LiCl (0.068 g, 1.60 mmol, previously maintained at 0.5 mmHg and 350 °C for 45 min), and $Pd(OAc)_2$ (4.5 mg, 0.02 mmol). The resulting mixture was placed in an oil bath at 60 °C and stirred until TLC indicated total consumption of triene **3**. After cooling, the reaction mixture was poured over saturated K_2CO_3 (15 mL), and the layers were separated. The aqueous phase was extracted with EtOAc (3 × 15 mL), and the combined organic layers were washed with H_2O (2 × 10 mL) and dried (Na_2SO_4). The crude after evaporation was purified as indicated in the Supporting Information for the individual cases.

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Supporting Information Available: Details of preparation and characterization data for **1c**, **1f**, and **5–10**, and copies of ^{1}H NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) A possible role for Ag^+ as Lewis acid cyclization promoter, with subsequent transmetalation to Pd(II),[5] is unlikely because in independent studies Ag^+ was shown not to promote cycloisomerization of **3** to **11**. M. Solay, Ph.D. Thesis, Universidad del País Vasco, Bilbao, Spain, 1997.

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