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Facile Construction of the Benzofuran and Chromene Ring Systems via Pd^{II}-Catalyzed Oxidative Cyclization

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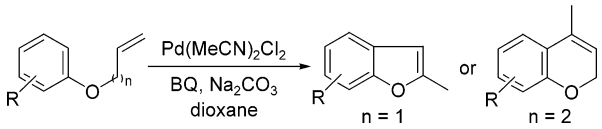
ABSTRACT



We herein report the development of one-pot procedures for the conversion of allyl aryl ethers to 2-methylbenzofurans (via sequential Claisen rearrangement and oxidative cyclization) and for the conversion of aryl homoallyl ethers to chromenes (via direct oxidative cyclization). It is likely that both reactions proceed via a common Pd-catalyzed pathway involving olefin activation, nucleophilic attack, and β-hydride elimination.

Benzofurans and chromenes have attracted considerable attention due to their biological activity and their presence in a variety of significant natural products.[1] Consequently, a number of synthetic strategies have been reported for the construction of benzofurans[2,3] and chromenes.[4] A common approach to the benzofuran ring system consists of Claisen rearrangement[5] of an allyl aryl ether followed by Pd-catalyzed intramolecular oxidative cyclization[3c−f] of the corresponding 2-allylphenol, accomplishing the overall transformation in two discrete reactions (Scheme 1). Chromenes are also constructed by a two-step sequence, typically involving prefunctionalization of the arene (e.g., halogenation at the 2-position) followed by Heck-type cyclization.[4d−f] We were interested in developing a one-pot synthesis of benzofurans from allyl aryl ethers whereby a single catalytic system would invoke sequential Claisen rearrangement and oxidative cyclization.[6] Similarly, we proposed that the direct oxidative coupling of unactivated arene and olefin components of aryl homoallyl ethers would be an efficient route to the chromene core, obviating the need for prehalogenation. Herein we report simple, convenient methods for the one-pot synthesis

(1) (a) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285. (b) Keay, B. A. *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 2. p 395. (c) Cagniant, P.; Cagniant, D. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1975; Vol.18, p 337. (d) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao. G. Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939.

(2) For recent examples, see: (a) Zhang, J.; Zhang, Y.; Zhang, Y.; Herndon, J. W. *Tetrahedron* **2003**, *59*, 5609. (b) Cruz, M. del C.; Tamariz, J. *Tetrahedron Lett.* **2004**, *45*, 2377. (c) Xie, X.; Chen, B.; Lu, J.; Han, J.; She, X.; Pan, X. *Tetrahedron Lett.* **2004**, *45*, 6235. (d) Konno, T.; Chae, J.; Ishihara, T.; Yamanaka, H. *Tetrahedron* **2004**, *60*, 11695. (e) Bellur, E.; Freifeld, I.; Langer, P. *Tetrahedron Lett.* **2005**, *46*, 2185.

(3) For a review, see: (a) Cacchi, S.; Fabrizi, G.; Goggiomani, A. *Heterocycles* **2002**, *56*, 613. For intramolecular oxidative arene-olefin cyclizations, see: (b) Zhang, H.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 6144 and references therein. For oxidative cyclizations of 2-allylphenols, see: (c) Hosokawa, T.; Maeda, K.; Koga, K.; Moritani, I. *Tetrahedron Lett.* **1973**, *14*, 739. (d) Hosokawa, T.; Ohkata, H.; Moritani, I. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 1533. (e) Hosokawa, T.; Murahashi, S.-I. *Acc. Chem. Res.* **1990**, *23*, 49. (f) Roshchin, A. I.; Kel'chevski, S. M.; Bumagin, N. A. *J. Organomet. Chem.* **1998**, *560*, 163 and references therein.

(4) (a) Pastine, S. J.; Youn, S. W.; Sames, D. *Org. Lett.* **2003**, *5*, 1055. (b) Youn, S. W.; Pastine, S. J.; Sames, D. *Tetrahedron* **2003**, *59*, 8859. (c) Hardouin, C.; Burgaud, L.; Valleix, A.; Doris, E. *Tetrahedron Lett.* **2003**, *44*, 435. (d) Caddick, S.; Kofie, W. *Tetrahedron Lett.* **2002**, *43*, 9347. (e) Shezad, N.; Clifford, A. A.; Rayner, C. M. *Tetrahedron Lett.* **2001**, *42*, 323. (f) Shi, L.; Narula, C. K.; Mak, K. T.; Kao, L.; Xu, Y.; Heck, R. F. *J. Org. Chem.* **1983**, *48*, 3894.

(5) For a review, see: (a) Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939. (b) Hiersemann, M.; Abraham, L. *Eur. J. Org. Chem.* **2002**, 1461. For Claisen rearrangement of allyl aryl ethers with catalytic amount of metal catalysts, see: (c) ($IrCl_3$/AgOTf) Grant, V. H.; Liu, B. *Tetrahedron Lett.* **2005**, *46*, 1237 and references therein. (d) ($Yb(OTf)_3$) Sharma, G. V. M.; Ilangovan, A.; Sreenivas, P.; Mahalingam, A. K. *Synlett* **2000**, 615. (e) ($Pd(MeCN)_2Cl_2$) Anjaneyulu, A. S. R.; Isaa, B. M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2089.

(6) For one-pot synthesis of benzofurans from β-haloallyl aryl ethers, see: (a) Tao, Z.-F.; Qian, X.; Fan, M. *Tetrahedron* **1997**, *53*, 13329. (b) Mali, R. S.; Pandhare, N. A.; Sindkhedkar, M. D. *Tetrahedron Lett.* **1995**, *36*, 7109. (c) Saisi, M. R. *Hetereocycles* **1982**, *19*, 1473.

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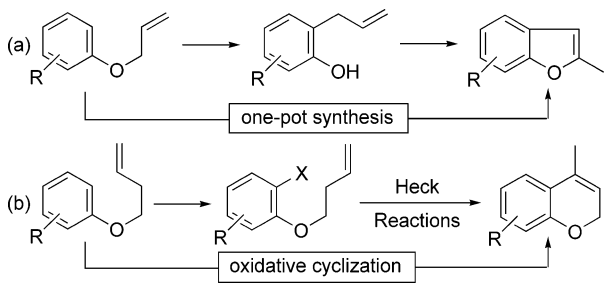
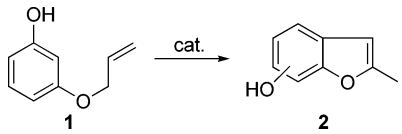
Scheme 1. General Methods for Synthesis of Benzofurans and Chromenes



of benzofurans by Claisen rearrangement and subsequent oxidative cyclization of allyl aryl ethers and for the synthesis of chromenes by direct oxidative cyclization of aryl homoallyl ethers.

We focused our initial efforts in this area on the one-pot synthesis of benzofuran **2** from allyl aryl ether **1**. Transition metal complexes that were previously reported to either promote Claisen rearrangement[5] or facilitate the oxidative cyclization of 2-allylphenols[3c−f] were included in the screen (Table 1; for complete data, see Supporting Information).

Table 1. Optimization Studies for the Cyclization of Compound **1**[a]



1 **2**

entry	catalyst (mol %)	oxidant	base	temp (°C)	time (h)	yield (%)[b]
1	$Pd(MeCN)_2Cl_2$ (100)	–	–	rt	4	30
2	$Pd(MeCN)_2Cl_2$ (20)	–	–	rt	24	18
3	$Pd(MeCN)_2Cl_2$ (20)	BQ	–	rt	5	54
4	$Pd(PhCN)_2Cl_2$ (20)	BQ	–	rt	5	50
5	$Pd(OAc)_2$ (20)	BQ	–	rt	5	–
6	$Pd(PPh_3)_2Cl_2$ (20)	BQ	–	rt	5	–
7	$PdCl_2$ (20)	BQ	–	rt	5	trace
8	$PtCl_2$ (20)	BQ	–	rt	5	–
9	$RuCl_3$ (20)	BQ	–	rt	5	–
10	$Pd(MeCN)_2Cl_2$ (20)	BQ	Na_2CO_3	rt	5	60
11	$Pd(MeCN)_2Cl_2$ (20)	$CuCl_2$	Na_2CO_3	rt	5	trace
12	$Pd(MeCN)_2Cl_2$ (20)	$Cu(OAc)_2$	Na_2CO_3	rt	5	5
13	$Pd(MeCN)_2Cl_2$ (10)	BQ	Na_2CO_3	80	0.5	52
14	$Pd(MeCN)_2Cl_2$ (5)	BQ	Na_2CO_3	65	5	66
15	$Pd(MeCN)_2Cl_2$ (2)	BQ	Na_2CO_3	80	12	trace

[a] All reactions were carried out with catalyst, base (1 equiv), and oxidant (1 equiv) in dioxane (0.015 M). [b] Determined by ^1H NMR using trichloroethylene as an internal standard.

Metal complexes were examined in a variety of solvents, and the effects of oxidants and bases were studied. When the reaction was carried out with a stoichiometric amount of $Pd(CH_3CN)_2Cl_2$ at room temperature, **1** was completely consumed in 4 h and benzofuran **2** was formed in 30% yield, presumably as a result of Pd-catalyzed Claisen rearrangement followed by oxidative cyclization (Table 1, entry 1). Analysis of the crude reaction mixture by ^1H NMR showed the remainder of the material to be either products of ether cleavage or uncyclized Claisen products, reaffirming our initial worries that these side reactions would be problematic. The formation of benzofuran instead of dihydrobenzofuran suggested that β-hydride elimination had occurred, followed by isomerization of the initially formed exocyclic olefin to the thermodynamically preferred benzofuran. This indicated that a stoichiometric oxidant would be required for the catalytic conversion of **1** to **2**. In accord with this hypothesis, treatment of **1** with a catalytic amount of $Pd(CH_3CN)_2Cl_2$ and a stoichiometric amount of 1,4-benzoquinone in 1,4-dioxane at room temperature for 5 h led to **2** in 54% yield (Table 1, entry 3). In addition to $Pd(CH_3CN)_2Cl_2$, $Pd(PhCN)_2Cl_2$ served as an effective catalyst for this reaction (Table 1, entry 4). Conversely, $PtCl_2$, $RuCl_3$, and other Pd(II) sources were not effective (Table 1, entries 5−9). It was also found that 1,4-benzoquinone was the optimal oxidant in this reaction system. We supposed that the addition of base would promote the cyclization of the Claisen-derived intermediate allylphenol, since the phenolic hydroxyl should be deprotonated in order to act as nucleophile toward the olefin fragment, either directly or through coordination to Pd.[3b−f,7] As expected, the inclusion of Na_2CO_3 provided increased yield (Table 1, entry 10). Finally, increasing the temperature to 65 °C led to the optimal result in the presence of 5 mol % $Pd(CH_3CN)_2Cl_2$, 1,4-benzoquinone, and Na_2CO_3, providing benzofuran **2** in 66% yield (Table 1, entry 14).

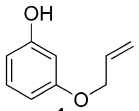
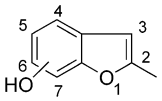
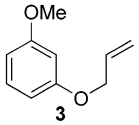
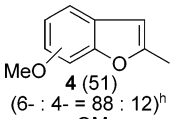
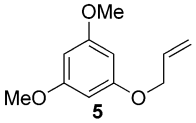
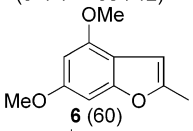
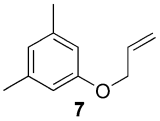
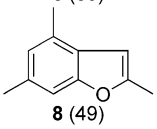
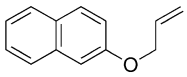
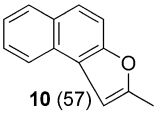
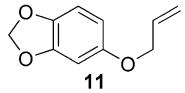
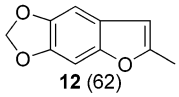
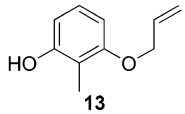
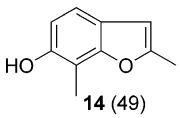
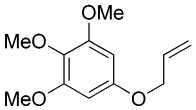
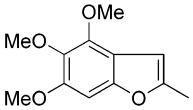
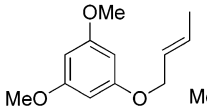
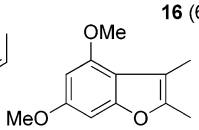
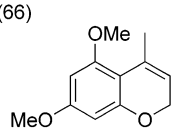
With the establishment of a viable one-pot reaction system, we set out to explore the scope of this sequential process. As shown in Table 2, a variety of allyl aryl ethers underwent tandem Claisen rearrangement/oxidative cyclization in the presence of $Pd(CH_3CN)_2Cl_2$ to form the corresponding benzofurans.

This method was compatible with functional groups such as methoxy, methylenedioxy, and free hydroxyl. While reactions of electron-rich arenes were facile, higher catalyst loading and increased temperatures were required for relatively electron-deficient arenes (Table 2, entry 2 and entries 4 and 5). It should be noted that in addition to producing the desired benzofuran product **18**, aryl crotyl ether **17** yielded a small amount of chromene product **19**, which could have formed through either direct oxidative coupling of the arene to the alkene or 6-*endo* cyclization of the Claisen-derived 2-(α-methylallyl)phenol. The former seems more plausible, since 5-*exo* cyclization occurs predominantly over 6-*endo* in the Pd^{II}-catalyzed oxidative cyclization of 2-allylphenols.[3c−f,8] This result prompted us to extend the application of our catalytic system to the formation of chromenes from aryl homoallyl ethers via direct oxidative cyclization.

(7) (a) Trend, R. M.; Ramtohul, Y. K.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2892. (b) Beccalli, E. M.; Broggini, G.; Paladino, G.; Pennoni, A.; Zoni, C. *J. Org. Chem.* **2004**, *69*, 5627.

(8) For a specific example of a 6-*endo* cyclization of 2-allylphenols, see: Larock, R. C.; Wei, L.; Hightower, T. R. *Synlett* **1998**, 522.

Table 2. Pd-Catalyzed Benzofuran Synthesis[a]

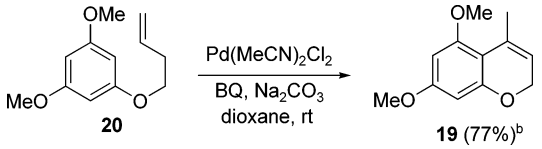
entry	substrate	product (%)[b]
1[c]	 **1**	 **2** (54) (6- : 4- = 84 : 16)[h]
2[d]	 **3**	 **4** (51) (6- : 4- = 88 : 12)[h]
3[c]	 **5**	 **6** (60)
4[e]	 **7**	 **8** (49)
5[d]	 **9**	 **10** (57)
6[f]	 **11**	 **12** (62)
7[g]	 **13**	 **14** (49)
8[c]	 **15**	 **16** (66)
9[e]	 **17**	 **18** (31)  **19** (12)

[a] All reactions were performed with $Pd(MeCN)_2Cl_2$, Na_2CO_3 (1 equiv), and BQ (1 equiv) in dioxane (0.015 M) for 1−5 h. [b] Isolated yields. [c] Performed with 5 mol % $Pd(MeCN)_2Cl_2$ at 65 °C. [d] Performed with 20 mol % $Pd(MeCN)_2Cl_2$ at 80 °C. [e] Performed with 25 mol % $Pd(MeCN)_2Cl_2$ at 80 °C. [f] Performed with 10 mol % $Pd(MeCN)_2Cl_2$ at 80 °C. [g] Performed with 10 mol % $Pd(MeCN)_2Cl_2$ at 65 °C. [h] The ratios were determined by ^1H NMR of the mixture.

Since palladium dichloride complexes are known to catalyze olefin isomerization,[9] we worried that, upon exposure to the catalytic system we had developed for the tandem Claisen rearrangement/oxidative cyclization, an aryl homoallyl ether such as **20** might simply isomerize to the aryl crotyl ether **17** and then undergo conversion to a similar mixture of products **18** and **19**. To our delight, cyclization of **20** at room temperature in the presence of $Pd(CH_3CN)_2Cl_2$ gave chromene **19** in 77% yield without any detectable amount of benzofuran **18** (Scheme 2).

(9) (a) Han, X.; Widenhoefer, R. A. *J. Org. Chem.* **2004**, *69*, 1738 and references therein. (b) Reference 3d and references therein.

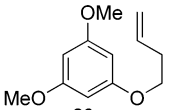
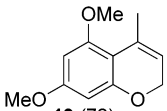
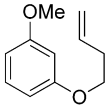
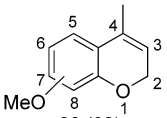
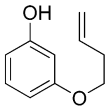
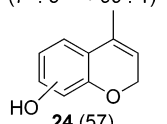
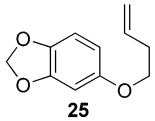
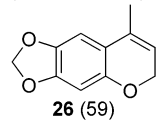
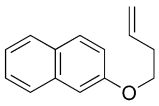
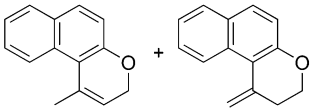
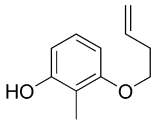
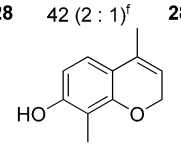
Scheme 2. Direct Oxidative Cyclization of **20**[a]



[a] $Pd(MeCN)_2Cl_2$ (5 mol %), Na_2CO_3 (1 equiv), and BQ (1 equiv) in dioxane (0.015 M) at room temperature. [b]Determined by ^1H NMR using trichloroethylene as an internal standard.

We proceeded to explore the substrate scope of this new method (Table 3). Several chromene derivatives could be prepared from their corresponding aryl homoallyl ethers. Higher catalyst loadings were required in similarly substituted systems relative to the analogous benzofuran formation; variations in the nucleophilicity of the arenes are reflected in the catalytic demands, with less nucleophilic arenes requiring higher catalyst loadings (Table 3, entries 2−6). The

Table 3. Pd-Catalyzed Chromene Synthesis[a]

entry	substrate	product (%)[b]
1[c]	 **20**	 **19** (72)
2[d]	 **21**	 **22** (62) (7- : 5- = >99 : 1)[f]
3[e]	 **23**	 **24** (57) (7- : 5- = 94 : 6)[f]
4[e]	 **25**	 **26** (59)
5[d]	 **27**	 **28** 42 (2 : 1)[f] **28'**
6[e]	 **29**	 **30** (39)

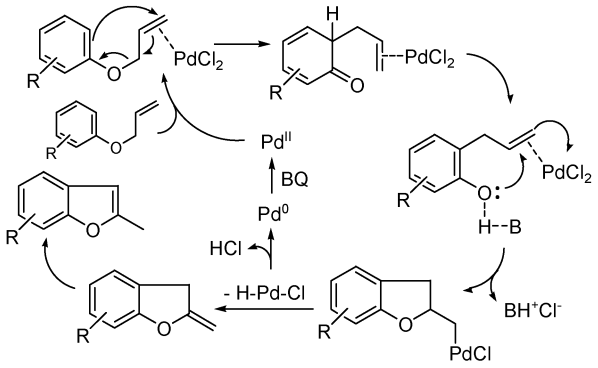
[a] All reactions were performed with $Pd(MeCN)_2Cl_2$, Na_2CO_3 (1 equiv), and BQ (1 equiv) in dioxane (0.015 M) for 1−5 h. [b] Isolated yields. [c] Performed with 5 mol % $Pd(MeCN)_2Cl_2$ at room temperature. [d] Performed with 25 mol % $Pd(MeCN)_2Cl_2$ at 80 °C. [e] Performed with 20 mol % $Pd(MeCN)_2Cl_2$ at 80 °C. [f] The ratios were determined by ^1H NMR of the mixture.

oxidative cyclization occurred with excellent regioselectivity for unsymmetrically substituted substrates (Table 3, entries 2−5), and only the homoallyl naphthyl ether **27** gave a significant amount of the regioisomeric *exo*-olefin.

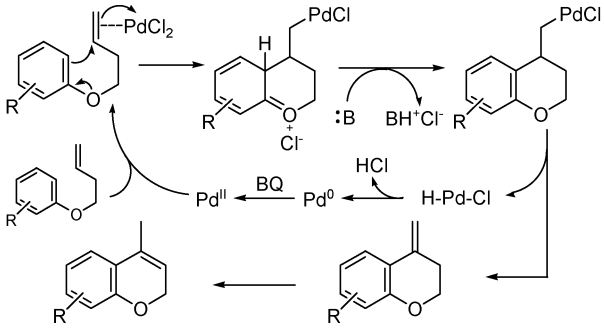
Plausible mechanisms for both Pd-catalyzed cyclizations presented herein are outlined in Scheme 3 and are based on the Wacker oxidation mechanism.[10] For allyl aryl ethers, the Pd-complexed olefin first undergoes Claisen rearrangement[5] to form the corresponding 2-allylphenol intermediate. Subsequently, intramolecular cyclization proceeds via oxypalladation.[3c−f] Coordination of the C−C π-bond by palladium activates the olefin toward intramolecular nucleophilic attack[3] by the phenolic oxygen, which is readily deprotonated by the stoichiometric quantity of base.[3b−f,7] Subsequent β-hydride elimination produces Pd(H)Cl and the 2,3-dihydro-2-methylene benzofuran, which isomerizes to the thermodynamically stable 2-methylbenzofuran.[3] Pd(H)Cl eliminates HCl and forms Pd^0, which is reoxidized by BQ to regenerate the catalytically active Pd(II) species (Scheme 3a).

Scheme 3. Possible Mechanism for the Pd-Catalyzed Cyclizations

(a) For Allyl Aryl Ethers : Claisen Rearrangement and Subsequent Intramolecular Oxidative Cyclizations



(b) For Aryl Homoallyl Ethers



Cyclization of the aryl homoallyl ether most likely proceeds via carbopalladation, wherein activation of the olefin by coordination to Pd(II) is followed by intramolecular nucleophilic attack by the arene. Subsequent β-hydride elimination forms Pd(H)Cl and the 4-methylenechromane, which isomerizes to the thermodynamically favored 4-methylchromene.[4e] Since no products derived from initial olefin isomerization were detected in any of the reactions in Table 3, it is likely that attack of the arene on the Pd-complexed olefin is fast relative to Pd-mediated olefin isomerization[9] (Scheme 3b).

In summary, we have developed both a one-pot procedure for the conversion of allyl aryl ethers to 2-methylbenzofurans and a direct oxidative cyclization of aryl homoallyl ethers to afford chromenes. Because a diverse range of allyl and homoallyl aryl ethers can be easily prepared, these Pd-catalyzed oxidative cyclizations represent an attractive means for the facile construction of benzofuran and chromene ring systems, which are pervasive motifs in biologically active natural products and pharmaceutical drug targets. Although the method is currently limited to electron-rich substrates, we are exploring ways to broaden the scope of the reaction to include other arenes, as well as acyclic substrates for the synthesis of monocyclic heterocycles.

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Supporting Information Available: Full experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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