Dramatic Base-Oriented Chemoselective Tandem Wacker Cyclizations: Synthesis of Bisbenzannelated Spiroketals and 2-Substituted Chromans

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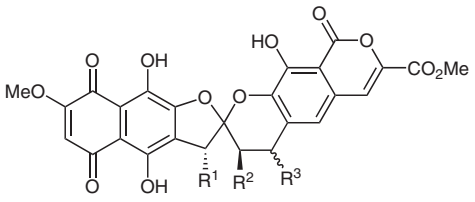
Received 7 March 2011

Abstract: A Pd(II)/Cu(II)-catalyzed chemoselective tandem aerobic cyclization of phenolic olefins leads to [5,6]-bisbenzannelated spiroketals or 2-substituted chromans, wherein it was interestingly found that the presence or absence of base could be responsible for the tunable selectivity. The [5,6]-bisbenzannelated spiroketals were achieved from tandem Wacker cyclization–aroxylation in moderate yields in the absence of base, and 2-substituted chromans were formed through base-mediated Pd(II)/Cu(II)-catalyzed tandem Wacker cyclization–Michael addition in good yields.

Key words: palladium, chemoselectivity, spiroketals, chromans, Wacker cyclization

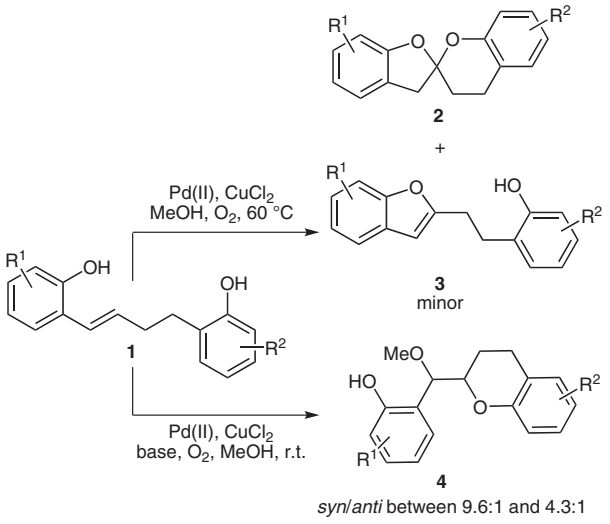
Palladium-catalyzed Wacker-type oxidative functionalization of alkenes is of great interest in the formation of various carbon–oxygen bonds in modern organic synthesis, and it has been proven to be one of the most versatile methods for rapid increase in molecular complexity. Among them, the intramolecular Wacker cyclization has shown to be extremely effective for the synthesis of furans,[1] pyrans,[2] benzofurans,[3] chromans,[4] and dioxabicyclic compounds.[5] In these reactions, palladium activates the double bond for nucleophilic attack. Nevertheless, to the best of our knowledge, there is no report on the synthesis of bisbenzannelated spiroketals by Pd(II)-catalyzed intramolecular Wacker cyclization so far. Very few intermolecular difunctionalization reactions and spiroketalization reactions of olefins have been reported using Pd (II)-catalyzed oxidations, especially those involving a nucleopalladation process.[6]

Importantly, the bisbenzannelated spiroketal cores exist widely in natural products, such as rubromycins and heliquinomycins (Figure 1) and play very important roles in their bioactivities.[7–12] At present, the synthetic methods[13–16] reported were mainly based on the acid-catalyzed spiroketalization of bisphenolic ketones,[14] haloetherification of a benzofuran,[13a] or cycloaddition type reaction.[15] The most recent work on metal-catalyzed spiroketalization of bisphenolic alkynes was reported by our group using gold reagents as catalysts.[16] The catalytic and efficient construction of such synthetically interesting bisbenzannelated spiroketal cores is still of high demand in modern organic synthesis of the structurally related natural products.[17]



γ-rubromycin $R^1 = R^2 = R^3 = H$
purpuromycin $R^1 = R^2 = H$, $R^3 = OH$
heliquinomycin R^1 = *O*-cymarose, $R^2 = OH$, $R^3 = H$

Figure 1 The natural bioactive rubromycin compounds



Scheme 1 $PdCl_2/CuCl_2$-catalyzed chemoselective tandem aerobic cyclization

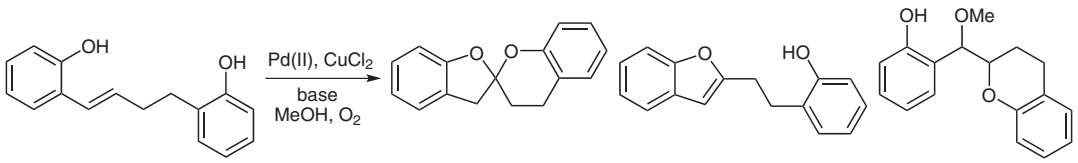
As a preliminary investigation on Pd(II)-catalyzed intramolecular oxidative difunctionalization of olefins as well as the continuing research on the synthesis of rubromycins, we wanted to integrate intramolecular Wacker oxidation and spontaneous ketalization in the synthetic realm of bisbenzannelated spiroketal chemistry, which is crucial for the synthesis of the corresponding natural products. Interestingly during such exploration, an unexpected reaction chemoselectivity was revealed for the palladium-catalyzed oxidative functionalization of alkenes. As shown in Scheme 1, the biscyclized spiroketal and 5-*endo*-trig cyclization products **2** and **3** or 6-*exo*-trig cyclization product **4**[6] could be individually afforded from the phenolic olefin **1** in the presence of oxygen under the catalysis of Pd(II)/Cu(II), wherein the selectivity is mainly dependent on the absence or presence of base. Notably,

SYNLETT 2011, No. 11, pp 1579–1584
Advanced online publication: 10.06.2011
DOI: 10.1055/s-0030-1260775; Art ID: W06711ST

this palladium-catalyzed Wacker-type oxidative cyclization provided a novel divergent route from phenolic olefins **1** to bisbenzannelated spiroketals **2** or functionalized chromans **4**.[6] Herein we wish to report our preliminary results on this topic.

Initially, the phenolic olefin **1a**, which was readily prepared from Julia olefination,[18] was treated with oxygen under the catalysis of $PdCl_2/CuCl_2$ in MeOH. The desired spiroketal **2a** was formed in 65% yield, along with 5-*endo*-trig cyclization product **3a** in 28% yield (Table 1, entry 1). In order to improve the efficiency, different palladium reagents, copper reagents, as well as solvents were screened in detail. In MeOH as solvent and without base, it was found that $PdCl_2/CuCl_2$ as catalyst gave the best result. While using catalytic $Pd(MeCN)_2Cl_2/CuCl_2$, the reaction provided **2a** in a slightly lower yield and took longer reaction time (Table 1, entry 2). Analogously, $Pd(OAc)_2$ as a co-catalyst also showed obviously lower efficiency (Table 1, entry 3). In addition to palladium catalyst, the employment of copper salt as a co-catalyst was vital to this oxidative transformation, and only trace amount of **2a** could be observed in the absence of $CuCl_2$ (Table 1, entry 4). Besides, CuCl instead of $CuCl_2$ was also examined in this reaction, but no positive improvement was observed in this case (Table 1, entry 5). To further investigate the solvent effect, the aprotic CH_2Cl_2, DME, DMF, or toluene as reaction media were also used in this model cyclization. However, no reaction happened or the reaction gave messy products. Interestingly, when a base was used as an additive to improve the recycling efficiency of catalyst, the chroman **4a** instead of **2a** and **3a** was unexpectedly formed via 6-*exo*-trig cyclization in high yield and in short reaction time. For example, using Cs_2CO_3 as a base, the reaction gave **4a** in 7.1:1 dr and 89% yield (Table 1, entry 6), in which the *syn* configuration of major product was determined by NMR spectral analysis as well as comparison with the literature data.[6c] Further investigations disclosed that other inorganic and organic bases, such as $KHCO_3$ and DABCO, were also effective for this cyclization (Table 1, entries 7 and 8). For this interesting 6-*exo*-trig cyclization, the catalyst $PdCl_2$ showed good result (Table 1, entry 9). Other palladium catalysts such as $Pd(MeCN)_2Cl_2$ (Table 1, entry 9) and $Pd(OAc)_2$ (Table 1, entry 10) proved to be less effective for this transformation. The co-catalyst $CuCl_2$ was also an indispensable reagent for this case (Table 1, entry 11), and de-

Table 1 Optimization of the Palladium-Catalyzed Cyclization of **1a**[a]



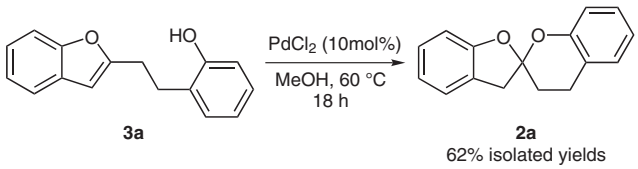
1a **2a** **3a** **4a**

Entry	Catalyst	Base	Time (h)	Yield of **2a** (%)[b]	Yield of **3a** (%)[b]	Yield of **2a** (%)[b]	*syn*/*anti*[c]
1	$PdCl_2$	none	10	65	28	trace	
2	$Pd(MeCN)_2Cl_2$	none	12	60	25	trace	
3	$Pd(OAc)_2$	none	16	33	31	0	
4[d]	$PdCl_2$	none	10	4	trace	0	
5[e]	$PdCl_2$	none	10	35	30	trace	
6	$PdCl_2$	Cs_2CO_3	5	0	0	89	7.1:1
7	$PdCl_2$	$KHCO_3$	7	0	0	72	7:1
8	$PdCl_2$	DABCO	10	0	0	60	6.3:1
9	$Pd(MeCN)_2Cl_2$	Cs_2CO_3	5	0	0	87	7:1
10	$Pd(OAc)_2$	Cs_2CO_3	10	0	0	56	7:1
11[d]	$PdCl_2$	Cs_2CO_3	8	0	0	7	7:1
12[e]	$PdCl_2$	Cs_2CO_3	12	0	0	60	6.5:1

[a] Reactions were carried out using **1a** (0.2 mmol, 1.0 equiv), Pd(II) (0.02 mmol, 0.1 equiv), $CuCl_2$ (0.04 mmol, 0.2 equiv), and base (0.04 mmol, 0.2 equiv) in solvent (2.0 mL) under an ambient atmosphere of O_2.
[b] Isolated yields.
[c] The dr of **4a** was measured by ^1H NMR and the relative configurations were determined by comparison with the data of literature.[6c] See Supporting Information for details.
[d] Without $CuCl_2$ in the reactions.
[e] CuCl was used in place of $CuCl_2$.

creased yield was observed when using CuCl instead of $CuCl_2$ (Table 1, entry 12). In terms of the investigations mentioned above, $PdCl_2/CuCl_2$ as catalyst and MeOH as solvent in the presence or absence of Cs_2CO_3 was finally identified as optimal reaction conditions for this chemoselective divergent oxidative cyclization.

In order to understand more about this spiroketalization, benzofuran **3a** was isolated and treated with $PdCl_2$ in MeOH at 60 °C. As shown in Equation 1, the desired spiroketal **2a** was formed after 18 hours in 62% yield, followed by the recovery of **3a** in 30% yield. This control experiment clearly demonstrated that 5-*endo*-trig cyclization product **3a** was the precursor of biscyclized spiroketal **2a**, to some extent giving a mechanistic insight into this Pd(II)/Cu(II)-catalyzed Wacker-type oxidative cyclization.

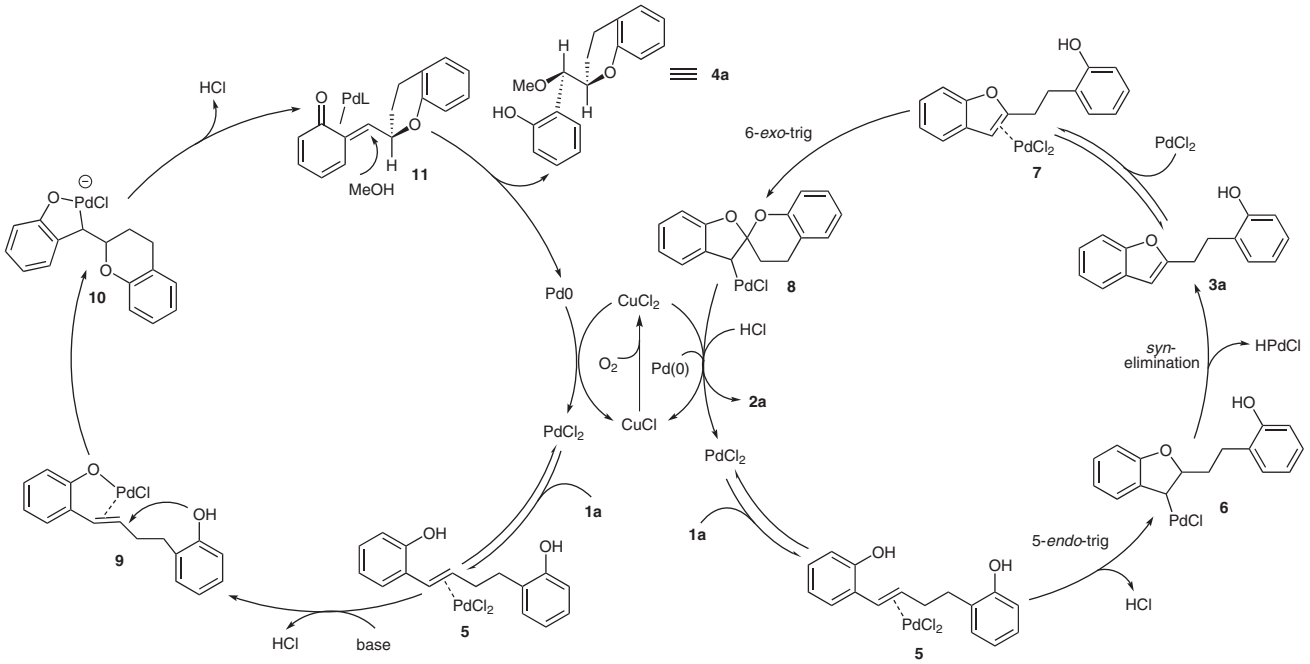


Equation 1 The conversion of **3a** into **2a**

Hosokawa and co-workers have reported an analogous catalytic cycle, which proceeded through an intermolecular Wacker reaction and led to the formation of acetals.[19] Based on the above results, the mechanism for the formation of **2a** was proposed in Scheme 2. The catalytic process mainly included two stages. In the first stage, Pd(II) combined with the double bond and activated it. Then the phenolic hydroxyl group attacked the double bond, leading to the formation of five-membered ring **6**. Through β-hydride elimination, intermediate **3a** was formed. This Wacker cyclization is a dynamic kinetic reaction, and the two OH groups have similar nucleophility. Generally, the preferential formation of five-membered ring resulted from the left phenolic OH group which was more close to the activated double bond. As the second stage, the further conversion of **3a** to **2a** could happen in the second cycle of palladium catalysis involving aroxylation cyclization.

However, when a base was involved in this catalytic reaction, an intramolecular phenolic anion exchange happened, leading to the formation of **9** from **5**. A similar mechanism has been depicted by Sigman and co-workers.[6] Following the intramolecular nucleophilic attack of right phenolic OH group in **9**, the benzopyran intermediate **10** was formed. After the elimination of HCl under base, a Pd(0) complex with methide quinine, **11**, was generated in situ. Then further intermolecular attack of MeOH resulted in the formation of the chroman **4a**. During the addition of MeOH to the methide quinone complex, notably, the nucleophilic attack of the hydroxyl group of MeOH mainly took place from the less hindered *Re* face, giving the major product with *syn* stereochemistry.[6] In the above-mentioned two catalytic cycles, the selectivity between 5-*endo*-trig cyclization and 6-*exo*-trig cyclization in **5** was mainly controlled by phenolic anion exchange at Pd(II) center in the presence of base or a direct nucleophilic addition of phenol hydroxy group to Pd(II)-activated double bond in the absence of base.

To extend the generality of this Wacker-type oxidative cyclization reaction, various substrates were treated with the above optimized conditions, and the results are summarized in Table 2. All cases showed significant base-oriented chemoselectivity. And the substituents on the phenol ring had obvious effects on this Wacker cyclization. When the substituents at *para* position of phenolic hydroxyl in the left phenyl ring A were the electron-donating



Scheme 2 Proposed mechanism of Pd-catalyzed Wacker cyclization and conjugated addition of phenolic olefins

groups, such as methyl or *tert*-butyl group, the reactions gave the corresponding bisbenzannelated spiroketals **2b**,**c** in moderate yields along with low yields of the benzofuran side products **3b**,**c** (Table 2, entries 2 and 3). In contrast, electron-withdrawing groups on the same position, such as phenyl, chlorine, or ester group, caused longer reaction time, lower yields of the bisbenzannelated spiroketals **2d**–**f**, and higher yields of the benzofuran side product **3d**–**f** (Table 2, entries 4–6). When using substrate **1g** with a methoxyl group *ortho* to the phenol ring A, the Wacker-type oxidative cyclization smoothly proceeded, and **2g** was formed in higher yield (Table 2, entry 7). From these results, it may conclude that the electron-rich phenyl ring A might benefit the formation of spiroketal product **2**, as the electron-donating group on ring A will increase the Pd(II)-involved nucleophilic activation of the double bonds in benzofuran **3**, which will make acceleration for the further aroxylation of the second phenolic OH group.

But the electron-withdrawing groups on ring A will reduce the reactivity of the double bond as donor for Pd(II)-mediated olefin activation, giving the decreased ratios of **2**/**3**. Otherwise, **1h** gave mainly **3h** along with messy product, which may be responsible to the steric hindrance of the methoxyl group.

According to the preliminary investigation of base-oriented chemoselectivity, the phenolic olefins **1a**–**g**, in the presence of Cs_2CO_3 (20 mol%) together with $PdCl_2$ (10 mol%) and $CuCl_2$ (20 mol%) in MeOH, underwent the expected 6-*exo*-trig cyclization to give the corresponding 2-substituted chromans **4** in good yields (Table 3). Similar to the spiroketalization, these difunctionalization reactions of olefins with election-donating groups at the *para* position of phenolic hydroxyl group of phenyl ring A gave better yields (entries 2, 3, and 7) than that with electron-withdrawing groups (Table 3, entries 4–6). The reaction using the substrate with methoxyl group at *ortho* position of the phenol ring A (R^2 = OMe) or at *ortho* position of the phenol ring B (R^3 = OMe) was also investigated, and the desired chromans **4g** (Table 3, entry 7) was obtained in 95%. Compared with the aforementioned spiroketalization (Table 2), this chroman-forming difunctionalization reaction mostly took shorter time and gave higher yields (Table 3).

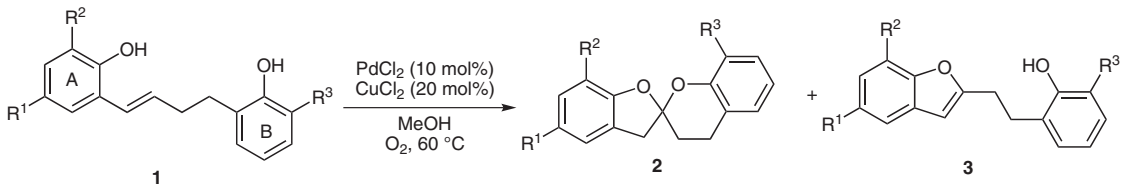
In summary, an efficient and highly chemoselective synthesis of [5,6]-bisbenzannelated spiroketals and 2-substitued chromans has been developed by using Pd(II)/Cu(II)-catalyzed heteroatom difunctionalization of phenolic olefins. This base-oriented selective Wacker-type oxidative cyclization was unprecedented, and the high chemoselectivity was drastically controlled by the presence or absence of base. This divergent synthetic protocol could serve as a good complement to the existing methodologies, and will be potentially useful in the synthesis of nature products with such spiro and chroman skeletons.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

We are grateful for the financial support of the National Natural Science Foundation of China (Grant No. 20802028).

Table 2 Wacker Cyclization of Phenolic Olefins[a]

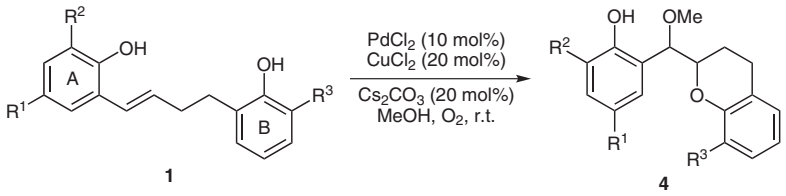


1 2 3

Entry	Substrate	Time (h)	Yield of **2** (%)[b]	Yield **3** (%)[b]
1	**1a** $R^1 = R^2 = R^3 = H$	10	**2a** 65	**3a** 28
2	**1b** R^1 = Me, $R^2 = R^3 = H$	10	**2b** 63	**3b** 27
3	**1c** R^1 = *t*-Bu, $R^2 = R^3 = H$	11	**2c** 60	**3c** 25
4	**1d** R^1 = Ph, $R^2 = R^3 = H$	14	**2d** 50	**3d** 32
5	**1e** R^1 = Cl, $R^2 = R^3 = H$	16	**2e** 45	**3e** 42
6	**1f** R^1 = EtOOC, $R^2 = R^3 = H$	22	**2f** 36	**3f** 28
7	**1g** $R^1 = R^3 = H$, R^2 = MeO	8	**2g** 71	**3g** 22
8	**1h** $R^1 = R^2 = H$, R^3 = MeO	13	**2h** messy	**3h** 47

[a] All reactions were performed on a 0.2 mmol scale.
[b] Isolated yields.

Table 3 Palladium-Catalyzed Cyclization and Conjugated Addition of Phenolic Olefins[a]



1 4

Entry	Substrate	Time (h)	Yield of **4** (%)[b]	*syn*/*anti*[c]
1	**1a** $R^1 = R^2 = R^3 = H$	5	**4a** 89	7.1:1
2	**1b** R^1 = Me, $R^2 = R^3 = H$	4	**4b** 90	7.7:1
3	**1c** R^1 = *t*-Bu, $R^2 = R^3 = H$	5	**4c** 89	4.3:1
4	**1d** R^1 = Ph, $R^2 = R^3 = H$	6	**4d** 85	9.1:1
5	**1e** R^1 = Cl, $R^2 = R^3 = H$	8	**4e** 88	6.2:1
6	**1f** R^1 = EtOOC, $R^2 = R^3 = H$	10	**4f** 56	6:1
7	**1g** $R^1 = R^3 = H$, R^2 = MeO	3	**4g** 95	9.6:1
8	**1h** $R^1 = R^2 = H$, R^3 = MeO	4	**4h** messy	

[a] All reactions were performed on a 0.2 mmol scale.
[b] Average isolated yield of two reactions.
[c] Measured by ^{1}H NMR.

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