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Synthesis of Coumarins via Pd-Catalyzed Oxidative Cyclocarbonylation of 2-Vinylphenols

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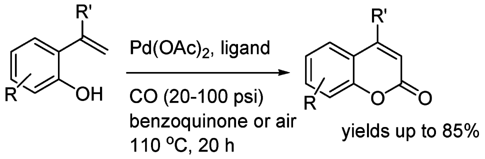
ABSTRACT



Palladium-catalyzed oxidative cyclocarbonylation of 2-vinylphenols constitutes a simple, direct method for the synthesis of coumarins. The reaction conditions, employing low pressures of CO, and air or 1,4- benzoquinone as the oxidant, are attractive in terms of environmental considerations and operational simplicity. Coumarins with a variety of functional groups were prepared in yields up to 85%.

Coumarins (compounds containing the 2*H*-chromen-2-one structure) are a ubiquitous class of natural products in plants, animals, and microbiota.[1] They show a broad variety of biological activities, such as anticoagulant,[2] antitumor,[3] anti-inflammatory,[4] antibiotic,[5] anti-HIV-1,[5] antidiabetic,[6] and antidepressant[6] activities. Consequently, coumarins are used as synthetic building blocks in the pharmaceutical, perfume, and agrochemical industries, as well as additives in food and cosmetics.[1] They can be extracted from plants—a tedious process—or synthesized by various means,[7] many involving the condensation of a carbonyl compound with a phenol derivative (e.g., the Pechmann condensation). These classical methods usually require harsh conditions (e.g., stoichiometric amounts of strong acids), are not highly regiospecific, and lead to difficult separations of product mixtures. Various catalytic routes[7] to coumarins include, for example, the Pd-catalyzed oxidative reactions of phenols with propargylic esters[8a] or ethyl acrylates;[8b] traditional Pd-catalyzed carbonylative cross-coupling of 2-iodophenols and alkynes;[8c] and Ru-catalyzed ring-closing metathesis of esterified 2-vinylphenols.[8d,e] Here, we report a route to coumarins *via* Pd-catalyzed oxidative cyclocarbonylation of 2-vinylphenols. This method is a new, oxidative example from within a class of transformations which are of genuine industrial relevance and well established in the literature, namely, the alkoxycarbonylation of unsaturated compounds.

Transition-metal-catalyzed oxidative carbonylation involves the connection of two components through a carbonyl group, with the assistance of an oxidant. It is synthetically simple and efficient, since it avoids the use of halogenated or otherwise activated substrates, is often accomplished under mild reaction conditions, and does not require an added

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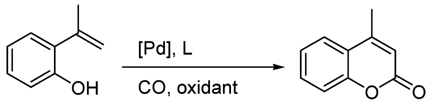
base or generate a stoichiometric HX byproduct. In fact, water is the only stoichiometric byproduct when oxygen is employed as the oxidant. Therefore, oxygen—and better yet, air—is a rather ideal oxidant. However, not all oxidative transformations are suited to using oxygen, and reagents such as quinones, peroxides, and salts of silver and copper are often employed.[9]

The oxidative alkoxycarbonylation of unsaturated compounds has been extensively investigated in the literature. There are many accounts of intramolecular oxidative alkoxycarbonylations, for example, whereby cyclized products are obtained from hydroxy-functionalized alkenes or alkynes.[10] These transformations generally do not require the activation of a C–H bond, since the product is formed with the concurrent loss of hydrogen from amine and/or alcohol nucleophiles. By contrast, the intermolecular Pd-catalyzed oxidative alkoxycarbonylation of terminal alkynes *does* involve sp C–H bond activation, and alkyl 2-alkynoate esters are easily obtained under mild conditions.[11] The corresponding oxidative alkoxycarbonylation of alkenes to α,*β*-unsaturated esters remains challenging, however, since the necessary reaction conditions typically transform the substrate into a complicated mixture of products.[12] In fact, very little has been published on the selective synthesis of α,*β*-unsaturated esters from alkenes and alcohols.[13] Bianchini and co-workers have made excellent contributions in this regard including the preparation of methyl cinnamate in good selectivity (up to 99%) from styrene and methanol, using Pd catalysts with 1,4-benzoquinone, diphosphine ligands, and a protic acid cocatalyst under high CO pressure (800 psi).[13d] A similar reaction was carried out by Jiang and co-workers, but with isomerization of the double bond.[14] They obtained alkyl-3-phenylbut-3-eneoates via Pd-catalyzed oxidative allylic C–H carbonylation of α-methylstyrene substrates, using a mixed quinone (BQ/DDQ) oxidant system.

To our knowledge, our current work is the first report of an intramolecular oxidative alkoxycarbonylation with net sp^2 C–H bond activation, whereby α,*β*-unsaturated lactones (coumarins) are selectively formed from adjacent vinyl and phenol groups on an aromatic ring. We discovered this reaction while exploring alternative reaction conditions to form saturated lactones from 2-vinylphenols, *via* the Pd-catalyzed cyclocarbonylation we reported earlier.[15] The α,*β*-unsaturated lactone was formed in low yields under

Table 1. Optimization of the Oxidative Cyclocarbonylation of 2-Isopropenylphenol (**1a**)[a]



1a **2a**

entry	(co)oxidant	ligand	CO/O_2 (psi)	solvent	% **2a**
1[b]	1,4-BQ	dppb	300/0	toluene	38
2	1,4-BQ		300/0	toluene	<7
3	$Cu(OAc)_2$		300/0	toluene	10
4	1,4-BQ	dppb	300/0	toluene	47
5	1,4-BQ	dppb	100/0	toluene	63
6	1,4-BQ	dppb	100/0	THF	68
7	1,4-BQ	dppb	100/0	CH_3CN	75
8[c]	1,4-BQ	dppb	100/0	CH_3CN	60
9	1,4-BQ[d]	dppb	100/0	CH_3CN	41
10	1,4-BQ	dppe	100/0	CH_3CN	69
11	1,4-BQ	phen	100/0	CH_3CN	75[e]
12	1,4-BQ	phen	100/0	DCE	67
13	1,4-BQ	dppf	100/0	CH_3CN	54
14	1,4-BQ	TMEDA	100/0	CH_3CN	61
15	1,4-BQ	TMBDA	100/0	CH_3CN	0
16	1,4-BQ	PR_3[f]	100/0	CH_3CN	21
17	1,4-BQ	dppb	30/0	CH_3CN	57
18[g]	1,4-BQ	dppb	100/0	CH_3CN	71
19[h]	1,4-BQ	dppb	100/0	CH_3CN	0
20		dppb	100/100	CH_3CN	41
21		dppb	20/20	CH_3CN	43
22		phen	100/100	CH_3CN	63
23		phen	100/20	CH_3CN	45
24	1,4-BQ[i]	phen	100/20	CH_3CN	64
25	$Cu(OAc)_2$[i]	phen	100/20	CH_3CN	54
26[j]	$CuCl_2$[i]	phen	100/20	CH_3CN	25[j]
27		phen	20/20	CH_3CN	65
28[k]		phen	15/30	CH_3CN	55
29		phen	20/20 air	CH_3CN	74
30[c]		PPh_3	20/20 air	CH_3CN	41
31[c]		Cytop292[l]	20/20 air	CH_3CN	37

[a] All reactions were performed at 1 mmol (**1a**) scale. Unless otherwise indicated, the reaction conditions were as follows: $Pd(OAc)_2$ (10%), ligand (10%), (co)oxidant (1.5 equiv), 110 °C, 20 h. Yields are isolated yields. [b] 4% Pd loading. [c] 20% ligand loading. [d] 3 equiv of oxidant. [e] **2a** was obtained in 60% isolated yield, plus a further 15% yield in a mixture with the oxidized dimer **3**. [f] A monophosphine heterocycle: 1-butyl-2,2,6,6-tetramethylphosphinane. [g] The precatalyst was $Pd(TFA)_2$ (10%). [h] The reaction mixture contained *p*-toluenesulfonic acid (2 equiv). [i] 0.5 equiv of co-oxidant. [j] The precatalyst was $PdCl_2$ (10%). From this reaction, **4** was also obtained in 48% yield. [k] T = 140 °C. [l] 1,3,5,7-Tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane.

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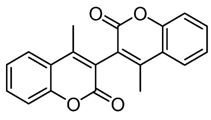
certain conditions, sometimes as the main or only product, even in the absence of an external oxidant. The addition of an oxidant greatly improved yields, however, and several were investigated in the course of optimizations.

We chose 2-isopropenylphenol (**1a**) as a model substrate to optimize the oxidative Pd-catalyzed cyclocarbonylation of **1a** to **2a**. Table 1 shows some of the conditions that were tried. Acceptable yields of **2a** were obtained with palladium(II) acetate at a 10% catalyst loading. No reaction took place in the absence of a palladium source. The reaction was not enhanced by the use of a less coordinating anion in the precatalyst (Table 1, entry 18) or by addition of *p*-toluenesulfonic acid (Table 1, entry 19). A range of solvents were tolerated, but best results were obtained in acetonitrile (Table 1, entries 5–7, 11, 12). The optimal pressure of CO depended upon the choice of oxidant. For example, with 1,4-benzoquinone, 100 psi of CO appeared to be the optimal pressure, whereas, with O_2 or air, the optimal CO pressure was around 1 or 2 atm.

The reaction requires a ligand, since essentially no product is formed in the absence of one (Table 1, entries 2 and 3). An equimolar ratio of Pd/L worked best. In fact, excess ligand actually appeared detrimental (Table 1, entry 8). Monodentate phosphines performed rather poorly (Table 1, entries 16, 30, and 31), and a longer chain dinitrogen ligand, *N,N,N′,N′*-tetramethyldiaminobutane, was completely ineffective (Table 1, entry 15). In contrast, diphosphine or short-chain dinitrogen bidentate ligands all worked fairly well (Table 1, entries 7, 10–14). When using 1,10-phenanthroline (phen) as the ligand in acetonitrile, with 1,4-benzoquinone as the oxidant, **2a** was obtained in 60% isolated yield after column chromatography, plus a further 15% yield that eluted in a 1:1 mixture with the oxidized dimer **3** (Table 1, entry 11). Dimer **3** was only observed in this particular solvent/ligand/oxidant combination.



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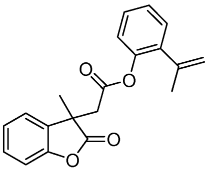

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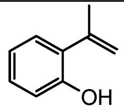
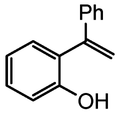
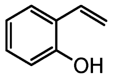
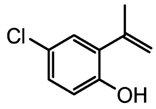
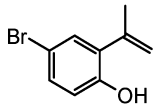
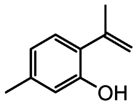
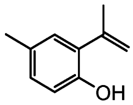
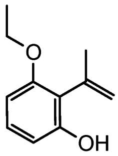
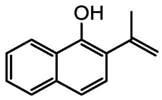
Another interesting outcome was found using $PdCl_2$/$CuCl_2$ with CO/O_2 (Table 1, entry 26), where the dimeric diester **4** was formed in 48% yield, along with the expected coumarin in 25% yield. This result seems to follow the argument of Bianchini and co-workers[13d] that the presence of a more strongly coordinating counteranion (i.e., chloride) would hinder β-hydride elimination from the Pd-alkyl intermediate and favor CO coordination to Pd, leading to double carbonylation, followed by nucleophilic attack by the phenol group of a second molecule of **1a**.

We tried a range of oxidants and co-oxidants for the reactions, and initially, it appeared that nothing could surpass the results obtained with a slight excess of 1,4-benzoquinone and moderate CO pressure. Therefore, we explored the substrate scope under those conditions (Table 2). Obviously, though, the use of oxygen and lower CO pressures would be more ideal and green. Therefore, we were delighted to discover that this reaction worked as well or better under low pressures of CO and without 1,4-benzoquinone, when we replaced low pressures of O_2 with air (Table 1, entry 29, and Table 2). We tried all substrates under these lower-pressure, aerobic conditions for comparison.

Table 2. Optimized Oxidative Cyclocarbonylation of 2-Vinylphenols to Coumarins

	substrate	product	% yield with 1,4-BQ^a	% yield with air^b
1a		**2a**	75	74
1b		**2b**	85	54^c
1c		**2c**	58	85
1d		**2d**	56	80
1e		**2e**	49	63
1f		**2f**	67	57
1g		**2g**	70	73
1h		**2h**	52	79
1i:		**2i**	34	22

[a] Isolated yields using the following experimental conditions: **1** (1 mmol), 1,4-benzoquinone (1.5 mmol), $Pd(OAc)_2$ (0.1 mmol), dppb (0.1 mmol), CH_3CN (5 mL), CO (100 psi), 110 °C, 20 h. [b] Isolated yields from the following experimental conditions: **1** (1 mmol), $Pd(OAc)_2$ (0.1 mmol), 1,10-phenanthroline (0.1 mmol), CH_3CN (5 mL), air (20 psi), CO (20 psi), 110 °C, 20 h. [c] The experiment was repeated once and gave the same result.

As demonstrated in Table 2, 2-vinylphenolic substrates with a variety of substitutions on the aromatic ring or vinyl group could be transformed into the corresponding coumarins. Substituents at the 3-, 4-, and 5-positions were well tolerated, especially under the optimized aerobic conditions. However, steric crowding, by introduction of a fused ring *ortho* to the hydroxyl group (**1i**), caused yields to fall sharply for the transformation of **1i** to **2i**, using either 1,4-benzoquinone or air as the oxidant.

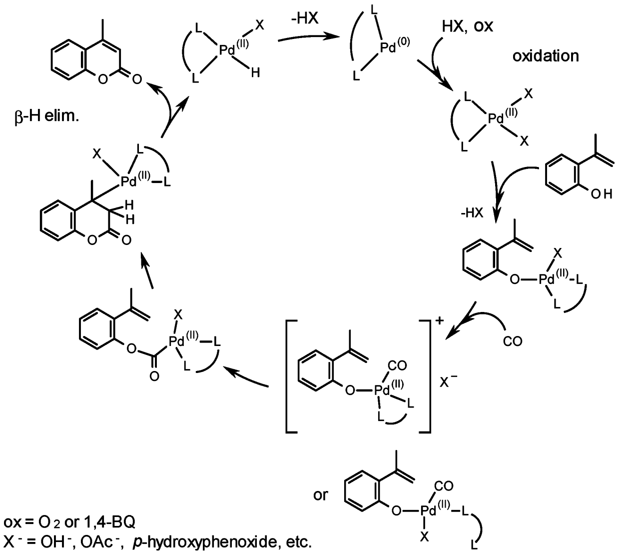
There were marked similarities, as well as clear differences, in the behavior of the two oxidative systems, as illustrated in Table 2. In both systems, a chloro-substituent (**1d**) was better tolerated than bromo- (**1e**) in the 4-position of the substrate. Also in both systems, methyl substitution was better tolerated in the 4-position (**1g**) than in the 5-position (**1f**). However, very different results were seen regarding substitution at the α-position of the vinyl group. When 1,4-benzoquinone was used as the oxidant, α-phenyl substituted **2b** was obtained in 85% yield, whereas the yield dropped to 58% for the unsubstituted **2c**. Under aerobic conditions, this trend was reversed: **2b** was obtained in just 54% yield, while **2c** was obtained in 85% yield. The reason for this is unclear.

Related substrates, 2-allylphenol and 2-vinylaniline, were each also subjected to the optimized reaction conditions with 1,4-benzoquinone. None of the desired seven-membered α,*β*-unsaturated lactone or six-membered α,*β*-unsaturated lactam, respectively, was obtained. 2-Vinylaniline did form the urea dimer in low (7%) yield.

A possible mechanism for the Pd-catalyzed intramolecular oxidative carbonylation of 2-vinylphenols is outlined in Scheme 1. This pathway is analogous in a number of respects to that proposed by Bianchini and co-workers for the oxidative carbonylation of styrene in methanol.[13d]

To begin the catalysis, a palladium phenoxide species is generated by ligand exchange with an anionic ligand, with the loss of HX. CO insertion into the Pd−O bond affords a phenoxycarbonyl palladium species. Alkene insertion of the vinyl group into the Pd−CO bond then generates an alkylpalladium intermediate. The coumarin product is finally released by *β*-hydride elimination, and the resulting palladium(II) hydride, $L_2Pd^{II}HX$, may be reduced to a palladium(0) species through the loss of HX. Palladium(II) is regenerated by the oxidant, either 1,4-benzoquinone or molecular oxygen, to complete the catalytic cycle.

Scheme 1. Possible Mechanism of Oxidative Cyclocarbonylation



ox = O_2 or 1,4-BQ
X^- = OH^-, OAc^-, *p*-hydroxyphenoxide, etc.

In conclusion, we have developed an efficient Pd-catalyzed oxidative cyclocarbonylation of 2-vinylphenols to prepare coumarins in high yields, using simple and mild conditions (CO $\leq$ 100 psi) with air or 1,4-benzoquinone as the oxidant. This reaction constitutes a new route to a highly important class of natural compounds. It is also, to our knowledge, the first intramolecular oxidative carbonylation in which a phenol has been coupled directly with a terminal alkene. These results add value to the scope of Pd-catalyzed oxidative carbonylations.

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