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Synthesis of 2(1*H*)-Quinolinones *via* Pd-Catalyzed Oxidative Cyclocarbonylation of 2-Vinylanilines

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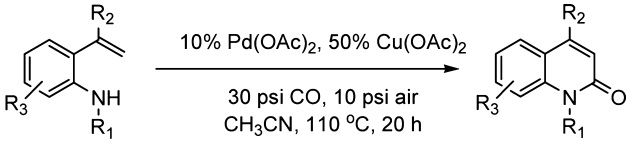
ABSTRACT



Palladium-catalyzed oxidative cyclocarbonylation of *N*-monosubstituted-2-vinylanilines constitutes a simple, direct, and selective method for the synthesis of 2(1*H*)-quinolinones. The reaction conditions are attractive in terms of environmental considerations and operational simplicity. 2(1*H*)-Quinolinones with a variety of functional groups were prepared in up to 97% yield.

Transition metal catalysis has become a powerful tool for the efficient syntheses of densely functionalized heterocycles from relatively simple starting compounds. Particularly in recent years, methods for catalytic C−H bond activation have emerged, resulting in the syntheses of numerous heterocycles, while avoiding the harsh reaction conditions and halogenated starting compounds that are necessary for many classic metal-catalyzed reactions.[1] Along these lines, we recently discovered a new route to coumarins, *via* the Pd-catalyzed oxidative cyclocarbonylation of 2-vinylphenols.[2] This was the first report of an intramolecular oxidative carbonylation, in which a nucleophile such as YH (Y = OR or NRR′) had been coupled directly with a terminal alkene. Extending this work, we have investigated the reaction to prepare an analogous nitrogen-containing heterocycle, i.e., the 2(1*H*)-quinolinone motif, starting from 2-vinylaniline. We were encouraged, not only by our work with 2-vinylphenols but also by the seminal 2004 report from Orito's group, demonstrating the preparation of benzolactams *via* Pd-catalyzed direct aromatic carbonylation of secondary amines.[3]

2-Quinolinones (as well as their 4-quinolinone isomers) are a naturally occurring class of compounds, which exhibit a broad spectrum of pharmacological activity, including antibiotic,[4] anticancer,[5] antiviral,[6] antihypertensive,[6] and other[7] activities. They may also serve as synthetic intermediates to 2-(pseudo)haloquinolines.[8] Understandably, the preparation of these valuable compounds has attracted a great deal of interest. Classic methods include the base-catalyzed Friedländer[9a] and acid-catalyzed Knorr[9b,4a] syntheses, while several other[9c−g] nonmetal-catalyzed syntheses have recently been reported. Metal-catalyzed methods[10] include inter-[10a−f] and intramolecular,[9g,10g−m] carbonylative[10b,c,f] and noncarbonylative[9g,10a,d,e,g−m] cyclizations, a few of which have employed C−H bond activation.[10g,h,m] To date, no reported single method has been demonstrated to prepare

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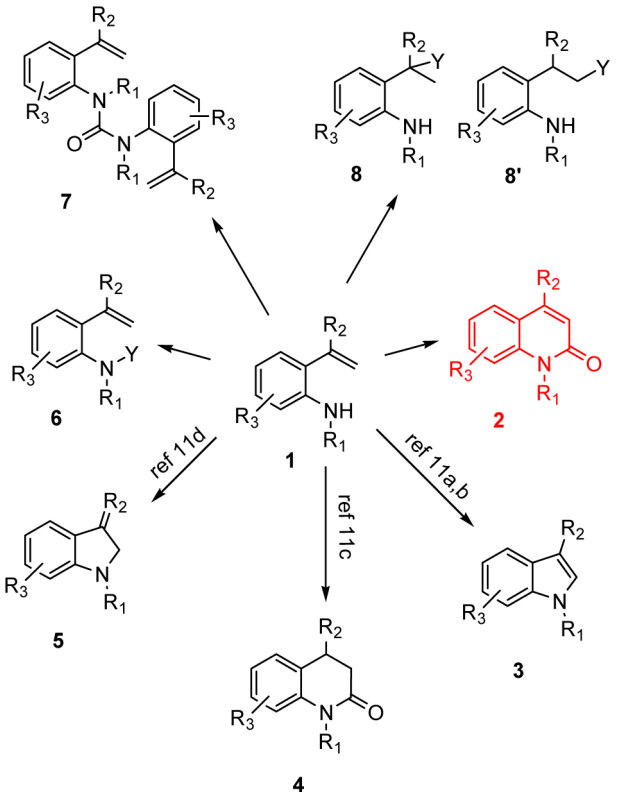
2-quinolinones with both electron-donating and -withdrawing substituents on the nitrogen.

As shown in Scheme 1, many products may be derived from 2-vinylanilines under various conditions. We anticipated that the choice of the N-substituent (R_1) would greatly influence the nature of the NH nucleophile and, thus, the selectivity of this reaction. Our first attempt to prepare 2(1*H*)-quinolinone (**2**, Scheme 1) from 2-vinylaniline (**1**, $R_1 = R_2 = R_3 = H$), using the conditions optimized with 2-vinylphenols, produced only the urea dimer (**7**). We next examined 2-isopropenyl-*N*-tosylaniline (**1e**, R_1 = Ts, R_2 = Me, $R_3 = H$) as a model substrate. Under higher CO pressures, we obtained only the saturated lactam **4e** (Table 1, entries 1 and 2). By lowering the CO pressure to ≤30 psi, we could avoid the formation of **4e** and instead obtain mixtures of the desired 4-methyl-*N*-tosyl-2(1*H*)-quinolinone **2e**, along with indole **3e**. As shown in Table 1, when starting from this substrate, the selectivity between the 2(1*H*)-quinolinone and the indole was highly sensitive to reaction conditions. We probed the utility of different ligands, co-oxidants, and bases in the system. Eventually, the simple combination of $Pd(OAc)_2/Cu(OAc)_2$ in CH_3CN was found to be highly effective, although it could not suppress some formation of the indole (Table 1, entry 11).

Hoping we might avoid this side reaction by adjusting the R_1 group, we tested 2-isopropenyl-*N*-methylaniline

Scheme 1. Some Possible Products of 2-Vinylanilines[11a]



[a] Y represents any intermolecular coupling partner.

(**1a**) with $Pd(OAc)_2/Cu(OAc)_2$ in CH_3CN and were pleased to obtain 1,4-dimethylquinolin-2(1*H*)-one (**2a**) in 58% yield, with no indole formation (Table 1, entry 12). However, we did isolate 2-isopropenyl-*N*-acetyl-*N*-methylaniline (type **6**, Scheme 1) as a byproduct, under these and other conditions starting from **1a**, usually in about 10−20% yield. Even when copper(II) pivalate[12] was used with $Pd(OAc)_2$ instead of copper(II) acetate, the byproduct was 2-isopropenyl-*N*-acetyl-*N*-methylaniline, rather than 2-isopropenyl-*N*-pivalyl-*N*-methylaniline. It was also noted that the product mixtures from $Pd(OAc)_2/Cu(OAc)_2$ in CH_3CN contained acetic acid, observable in some product NMR spectra.

By adding a small amount of air to the system, the amount of $Cu(OAc)_2$ required could be reduced to 0.5 equiv (Table 1, entry 15). All other changes in our reaction parameters—the Pd precursor and loading [10% $Pd(OAc)_2$], solvent (CH_3CN), time (~20 h), temperature (110 °C), and pressures of CO (30 psi) or air (10 psi)—either decreased or did not improve the yield of **2a**. Completely ineffective for obtaining **2a** from **1a** (*ceteris paribus*) were the following oxidants and/or additives: air/dppb (20 psi/10%), air/BQ

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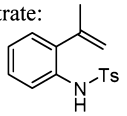
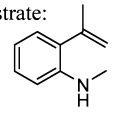
Table 1. Selected Optimization Experiments to Form 2(1*H*)-Quinolones (**2**), Starting with **1** (R_2 = Me, R_3 = H)

entry	solvent	additives (equiv)	CO/air (psi)	% 2	% 3
substrate: **1e** 					
1	NEt_3	BQ[a] (1.5), dppb (0.1)	450/0	0	0[b]
2	NEt_3	BQ (1.5), dppb (0.1)	100/0	0	0[c]
3	NEt_3	BQ (1.5), dppb (0.1)	20/0	19	25
4	NEt_3	BQ (1.5), dppb (0.1)	20/20	24	43
5	NEt_3	BQ (1.5), dppb (0.1)	30/30	<10	41
6	NEt_3	dppb (0.1)	20/20	7	0
7	CH_3CN	BQ (1.5), dppb (0.1)	20/20	16	0
8	CH_3CN	AgOAc (2), BQ (0.01)	30/0	42	10
9	CH_3CN	AgOAc (2), $CuCl_2$ (1.5)	30/0	32	13
10	CH_3CN	$CuCl_2$ (1.5)	30/0	0	n.d.[d]
11	CH_3CN	$Cu(OAc)_2$ (2)	30/0	43	n.d.
substrate: **1a** 					
12	CH_3CN	$Cu(OAc)_2$ (2)	30/0	58	0
13	NEt_3	$Cu(OAc)_2$ (2)	30/0	18	0
14	CH_3CN	BQ (1.5)	30/0	7	0
15	CH_3CN	$Cu(OAc)_2$ (0.5)	30/10	61	0
16	CH_3CN	$Cu(OAc)_2$ (0.5)	55/20	44	0
17	CH_3CN	$Cu(OAc)_2$ (0.5)	30/20	55	0
18	CH_3CN	$Cu(OAc)_2$ (0.5)	10/10	53	0
19	CH_3CN	$Cu(OAc)_2$ (0.15)	30/10	50	0
20	CH_3CN	$Cu(OAc)_2$ (0.5), K_2HPO_4 (1)	30/10	56	0
21	CH_3CN	$[Cu_2(pivalate)_4]_n$ (0.5)	30/10	33	0
22[e]	4:1 CH_3CN: HOAc	$Cu(OAc)_2$ (0.5)	30/10	21	0

Reaction conditions: 0.75 mmol of **1**, 10% $Pd(OAc)_2$, 110 °C, 20 h. [a] BQ = 1,4-benzoquinone. [b] Obtained 39% of **4e**. [c] Obtained 25% of **4e**. [d] Product was detected by TLC, but yield was not determined. [e] T = 75 °C.

(10 psi/1%), air/BQ/dppb (10 psi/1%/10%), $PhI(OAc)_2$ (1.5 equiv), AgOAc (2 equiv), $CuCl_2$ (2 equiv), $Cu(CF_3SO_3)_2$ (2 equiv), and $Cu(OAc)_2$ alone [without $Pd(OAc)_2$]. Also ineffective were the following solvents: THF, toluene, dioxane, and DMSO. With the optimized conditions in hand, we explored the generality of this reaction toward other *N*-monosubstituted-2-vinylanilines (Table 2).

It was necessary for the aniline to be a secondary amine, and the yields were clearly higher with electron-donating R_1 groups than with electron-withdrawing groups. The most favorable R_1 group tested was isopropyl (Table 2, **2c**, **2h-2j**). It is likely that the steric demand, very near to the nitrogen, deterred the side reaction that produced 2-isopropenyl-*N*-acetyl-*N*-methylaniline from **1a**. The analogous type **6** byproduct was not observed with substrate **1f** or **1g**.

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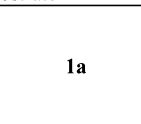
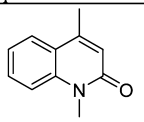
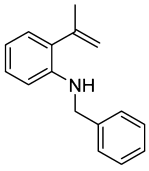
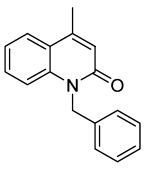
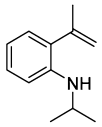
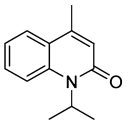
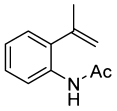
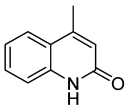
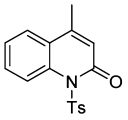
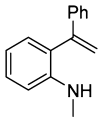
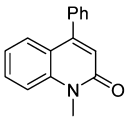
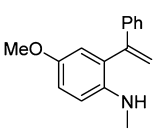
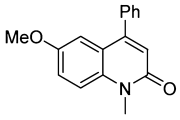
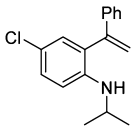
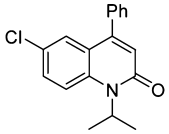
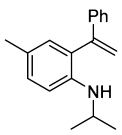
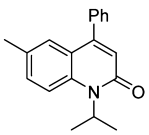
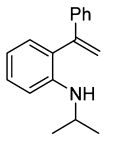
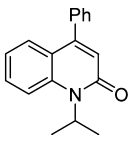
Table 2. Optimized Oxidative Cyclocarbonylation of 2-Vinylanilines to 2(1*H*)-Quinolinones[a]

substrate		product		% yield
1a 	**2a**			61
1b 	**2b**			77
1c 	**2c**			97
1d 	**2d***			15
1e	**2e**			49
1f 	**2f**			82
1g 	**2g**			0
1h 	**2h**			92
1i 	**2i**			83
1j 	**2j**			90

[a] Isolated yields using the following experimental conditions: **1** (0.75 mmol), $Pd(OAc)_2$ (0.075 mmol), $Cu(OAc)_2$ (0.375 mmol), CH_3CN (5 mL), CO (30 psi), air (10 psi), 110 °C, 20 h.

Yields of 2(1*H*)-quinolinones were reduced substantially when R_1 = acetyl or tosyl. Interestingly, the acetylated substrate **1d** produced the deprotected 2(1*H*)-quinolinone **2d***, albeit in low yield. We also noted, with the benzylated substrate **1b**, that no competing reaction took place between the nitrogen and its benzyl substituent, as might be expected, based on Orito et al.'s preparation of benzolactams *via*

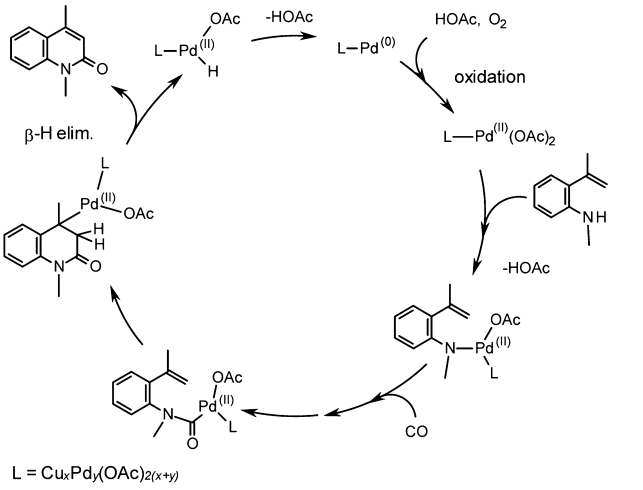
intramolecular aromatic carbonylation under nearly identical conditions.[3]

Regarding R_2 substitution, both methyl and phenyl groups worked well. 4-Phenyl-2(1*H*)-quinolinones could be obtained in as few as two steps, since the substrates were prepared simply by heating the appropriate aniline and phenylacetylene at 140 °C with montmorillonite KSF (acidic) resin.[13] Some compounds belonging to this class of 2-quinolones have already shown promise in clinical trials.[7a,e,f,14]

Finally, substitutions on the aniline aromatic ring met with mixed results. Chloro (**1h**) and methyl (**1i**) substituents *para* to the nitrogen did not strongly affect the reaction outcome, whereas substrate **1g**, with *p*-methoxy substitution, completely decomposed or polymerized under the reaction conditions into an unknown, highly polar product.

Based on there being no need for additional P or N ligands, and the performance of copper(II) salts in the order of $Cu(OAc)_2 > [Cu_2(pivalate)_4]_n \gg CuCl_2$, we reasoned that the active catalytic species in this reaction is a multinuclear cluster of type $Cu_mPd_n(OAc)_{2(n+m)}$, with acetate bridges between Cu and Pd.[15] That is, $Cu(OAc)_2$ acts as both an oxidant and a ligand, similar to its role in the Pd-catalyzed direct aromatic carbonylation with secondary amines.[3] The mechanism we propose, with **1a** as the model substrate (Scheme 2), is based on these considerations and on our proposed mechanism for coumarin synthesis. To begin the cycle, the aniline nitrogen adds to the active Pd^{II} species to form a Pd−N bond, with elimination of acetic acid. Coordination and insertion of CO leads to a Pd−carbamoyl species. Alkene insertion of the vinyl group into the Pd−CO bond then could generate an alkylpalladium intermediate. The 2(1*H*)-quinolinone product is finally released by β-hydride elimination, and the resulting palladium(II) hydride, $LPd^{II}HOAc$, may be reduced to a Pd^0 species through the loss of acetic acid. Pd^{II} is regenerated by Cu^{II} or O_2 to complete the catalytic cycle.

Scheme 2. Possible Mechanism of Oxidative Cyclocarbonylation



An alternative pathway may involve attack by the electron-rich alkene to palladium(II) to form a pallacycle intermediate, which could then undergo reductive elimination to give the product. Carbon monoxide insertion could take place before, or after, palladacycle formation.

In conclusion, we have developed an efficient Pd-catalyzed oxidative cyclocarbonylation of 2-vinylanilines to prepare (1*H*)-quinolinones in high yields, using simple and mild conditions. This reaction constitutes a new route to a highly important class of natural compounds. It is also, to our knowledge, the first oxidative carbonylation in which an aniline has been coupled directly with a terminal alkene. These results add value to the scope of Pd-catalyzed oxidative carbonylation reactions.

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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.

The authors declare no competing financial interest.

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