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Tandem Dehydrogenation/Oxidation/Oxidative Cyclization Approach to Wrightiadione and Its Derivatives

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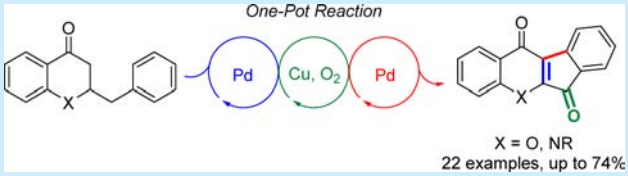
Supporting Information

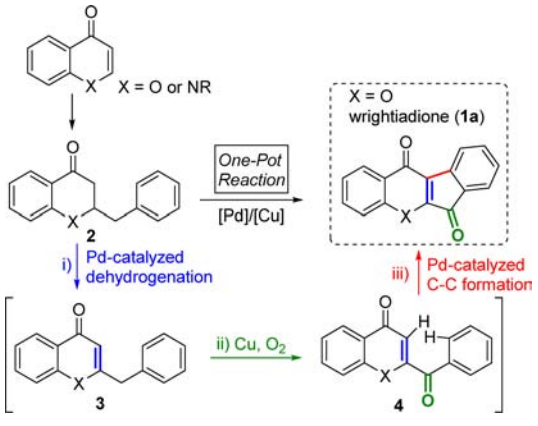
ABSTRACT: Wrightiadione contains a unique tetracyclic isoflavone moiety and has been shown to exhibit a broad range of biological activities. An efficient and straightforward synthetic method for generating the molecular complexity of wrightiadione was developed through three-step tandem dehydrogenation/oxidation/oxidative cyclization reactions with a Pd/Cu catalytic system. This unprecedented one-pot route utilizes a broad range of substrates, providing a convenient and powerful synthetic tool for accessing naturally occurring tetracyclic isoflavone wrightiadione and its nitrogen-containing derivatives.



Wrightiadione (**1a**), isolated from dried bark of *Wrightia tomentosa* is a unique tetracyclic isoflavone used medicinally in Thailand. This natural product exhibits a broad range of biological activities, including cytotoxicity against leukemia cell lines.[1] Consequently, the development of efficient methods for the synthesis of the wrightiadione scaffold is a topic of considerable importance.[2] Driven by the need for a more efficient synthetic route to wrightiadione derivatives, we were particularly interested in exploring an efficient, one-pot approach starting from simple starting materials such as readily available chromones and enaminones.[3a]

The transformations could be achieved via a multistep sequence (Scheme 1): (i) Pd-catalyzed dehydrogenation of 2-benzyl-substituted ketones **2** to α,β-unsaturated system **3**, (ii) Cu-catalyzed oxidation of the C−C bond at the γ-position of the α,β-unsaturated carbonyl system of **3** to afford the ketone intermediate **4**, and then (iii) subsequent Pd-catalyzed oxidative cyclization via direct intramolecular C−C bond formation of **4**. The starting materials, 2-benzyl-substituted chromanones or enaminones **2**, can be readily prepared by 1,4-addition of chromones using various organocuprates.[3b] The design of tandem processes can provide an opportunity for the direct construction of molecular complexity from simple starting materials. In addition, one-pot procedures are synthetically and environmentally advantageous for carrying out sequential catalytic operations in a single reaction vessel, thereby reducing synthesis time, undesired waste, and costs.[4,5] Therefore, we were interested in exploring one-pot sequential transformations that would enable facile synthesis of wrightiadione scaffolds by tandem catalysis. Herein, we present the first example of a tandem dehydrogenation/oxidation/oxidative cyclization process from readily available 2-benzylchromanones or dihydroquinolinones, which provides an efficient and straightforward protocol for the preparation of the tetracyclic isoflavones and their nitrogen-containing derivatives.

Scheme 1. Approach to Wrightiadione Scaffold Involving Tandem Dehydrogenation/Oxidation/Oxidative Cyclization



In line with our hypothesis, we studied the feasibility of each step of the tandem process to determine the most compatible conditions. We initially explored the possibility of applying our recently reported Pd-catalyzed dehydrogenation reaction to this process.[6] Because Pd(II) catalyst, which promotes the dehydrogenation of saturated ketones,[7−9] could also be used to catalyze oxidative C−C bond formation, it seems to be feasible to conduct both types of reactions as one-pot reactions. We also speculated that the intermediates **3** generated in situ from Pd(II)-catalyzed dehydrogenation of **2** might undergo further copper-catalyzed oxidation of the benzylic C−H bond with molecular oxygen[10−12] because of the increased acidity of the

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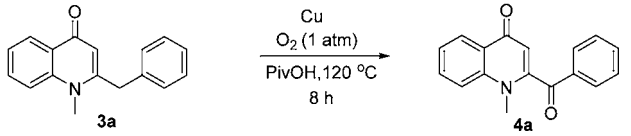
resulting methylene γ-hydrogens of the α,β-enolone system. In the overall tandem process, Cu(II) was employed not only as the oxidative trigger to regenerate Pd(0) to Pd(II) but also as a catalyst to promote the oxidation of the benzylic C−H bond.

To test the feasibility of converting intermediate **3** to the ketone intermediate **4**, our efforts began by exploring possible conditions for selective oxidation of enaminone **3a**. Recent advances in Cu-catalyzed oxidation provide useful starting points for our investigation of reactions.[12] Because the dehydrogenation event is highly solvent dependent, enaminone **3a** was subjected to the various reaction conditions in pivalic acid.[6a] To our delight, pivalic acid was found to be the optimal solvent in the oxidation step. Among the Cu species screened, $Cu(OAc)_2$ under 1 atm of O_2 was most effective, allowing the isolation of ketone intermediate **4a** in 65% yield (Table 1). Further screening

Table 1. Cu-Catalyzed Oxidation



entry[a]	Cu (5 mol %)	additive (equiv)	yield[b] (%)
1	$Cu(OAc)_2$		65
2	$Cu(OAc)_2$	NaOAc (0.5)	85
3	$Cu(OAc)_2$	Ag_2O (1.5)	79
4	CuI	NaOAc (0.5)	69
5	$CuBr_2$	NaOAc (0.5)	80
6	$CuCl_2$	NaOAc (0.5)	75
7	$Cu(OAc)_2$	NaOAc (0.5)/Ag_2O (1.5)	84

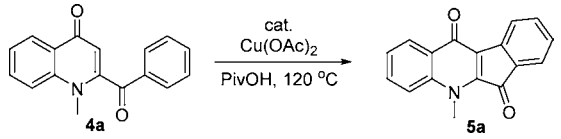
[a]Reaction conditions: **3a** (0.05 mmol), Cu (5 mol %), additive in PivOH (0.5 mL) under O_2 at 120 °C for 8 h. [b]^{1}H NMR yield.

studies revealed that the optimal result could be obtained with the addition of NaOAc (0.5 equiv), producing **4a** in the highest yield (85%). NaOAc appears to facilitate the reaction by removing a proton generated in the process of radical formation.

Next, we investigated direct intramolecular C−C bond formation through Pd-catalyzed oxidative cyclization of the resulting ketone intermediate **4a**.[13,14] After surveying some potential catalytic systems, we found that the combination of $Pd(OAc)_2$, $Cu(OAc)_2$, and NaOAc in PivOH, which were employed in either the dehydrogenation or oxidation steps, could enable the intramolecular oxidative coupling reaction, but with only 15% yield of the desired product **5a**. Further screening studies revealed that the optimal result could be obtained with the addition of Ag_2O, indicating the important role of Ag_2O in the oxidative coupling reaction (Table 2, entry 1).[13] Other silver sources were less effective in this reaction (entries 2−4). Under the optimized reaction conditions, the oxidative cyclization of **4a** proceeded to provide the best yield of 86%. Notably, control experiments verified that no reaction occurred without Pd catalyst, which indicated that Lewis acid catalyzed Nazarov-type cyclization was unlikely to be operative in this system (entries 5 and 6).

Encouraged by the above results, we next evaluated the potential of the proposed tandem process by investigating the reactivity of 2-benzyl-1-methyl-2,3-dihydroquinolin-4(1*H*)-one (**2a**) as a model substrate for optimization (Table 3). After much experimentation, we were pleased to find that the desired product **5a** was formed with the combined catalytic systems, proving that the tandem process was indeed operating. As

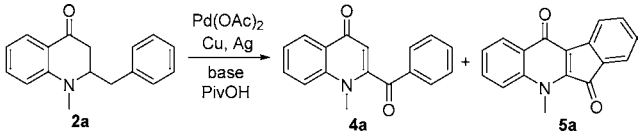
Table 2. Studies for Pd(II)-Catalyzed Intramolecular Oxidative Coupling[a]



entry	cat. (10 mol %)	additive (equiv)	oxidant (equiv)	yield[b] (%)
1	$Pd(OAc)_2$	NaOAc (0.5)	Ag_2O (1.5)	86
2	$Pd(OAc)_2$	NaOAc (0.5)	AgOAc (1.5)	76
3	$Pd(OAc)_2$	NaOAc (0.5)	Ag_2CO_3 (1.5)	75
4	$Pd(OAc)_2$	NaOAc (0.5)	AgTFA (1.5)	68
5		NaOAc (0.5)	Ag_2O (1.5)	0
6		$AlCl_3$ (3)	Ag_2O (1.5)	0
7	$Pd(OAc)_2$			12
8	$Pd(OAc)_2$		Ag_2O (1.5)	53
9[c]	$Pd(OAc)_2$	NaOAc (0.5)	Ag_2O (1.5)	35

[a]Reaction conditions: **4a** (0.05 mmol), $Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2$ (3 equiv), Ag_2O (1.5 equiv), NaOAc (0.5 equiv), PivOH (0.5 mL) under O at 120 °C for 8 h, Schlenk flask. [b]^{1}H NMR yield. [c]Without $Cu(OAc)_2$.

Table 3. Optimized Studies for Pd(II)-Catalyzed Tandem Dehydrogenation/Oxidation/Oxidative Cyclization Reactions of β-Substituted Cyclic Ketone[a]



entry	Cu (equiv)	Ag (equiv)	base (equiv)	yield[b] (%) (**4a**/**5a**)
1	$Cu(OAc)_2$ (3)	Ag_2O (1.5)		64 (40:60)
2	$Cu(OAc)_2$ (3)		NaOAc (0.5)	61 (66:34)
3		Ag_2O (1.5)	NaOAc (0.5)	7 (100:0)
4	$Cu(OAc)_2$ (3)	Ag_2O (1.5)	NaOAc (2)	60 (3:97)
5	$Cu(OAc)_2$ (3)	Ag_2O (1.5)	CsOAc (2)	60 (31:69)
6	$Cu(OAc)_2$ (3)	Ag_2O (1.5)	NaOAc (0.5)	78 (14:86)
7[c]	$Cu(OAc)_2$ (3)	Ag_2O (1.5)	NaOAc (0.5)	83 (10:90)
8[d]	$Cu(OAc)_2$ (3)	Ag_2O (1.5)	NaOAc (0.5)	70 (12:88)

[a]Reaction conditions: **2a** (0.05 mmol), $Cu(OAc)_2$ (3 equiv), catalyst (20 mol %), base, Ag_2O (1.5 equiv) in PivOH (0.5 mL) under O_2 at 120 °C for 8 h. [b]^{1}H NMR yield. [c]*t*-BuOAc/PivOH = 1:10 (v/v). [d]$Pd(OAc)_2$ (10 mol %).

predicted, optimization studies disclosed that the addition of Ag_2O was crucial for cyclizing the resulting intermediate **4a**. The solvent choice was also crucial, and other solvents including acetic acid, trifluoroacetic acid, or organic solvent were less effective. Among the bases screened, NaOAc (0.5 equiv) was most effective in this process in terms of overall conversion (entry 7). Notably, a lower isolated yield of product was obtained with increased amounts of NaOAc, although the **4a**/**5a** mixture ratio was improved up to 3:97 (entry 4). The reaction of substrate **2a** was found to best proceed with the use of a ^{t}BuOAc/PivOH (1:9 v/v) cosolvent system.

To get more mechanistic insight, the overall tandem process of **2a** was monitored under the standard reaction conditions (Figure 1). Approximately 50% of intermediate **3a** was produced within 30 min and then disappeared quickly with concomitant appearance of ketone **4a** and tetracyclic product **5a**, indicating the intermediacy of **3a**. Tetracyclic product **5a** was observed after the ketone intermediate **4a** was produced, indicating Cu-

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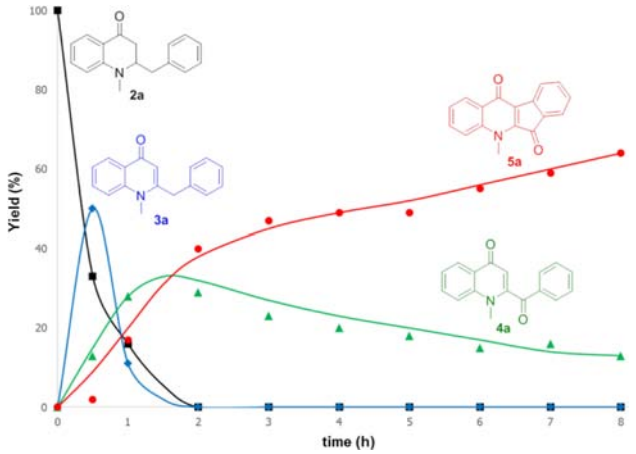
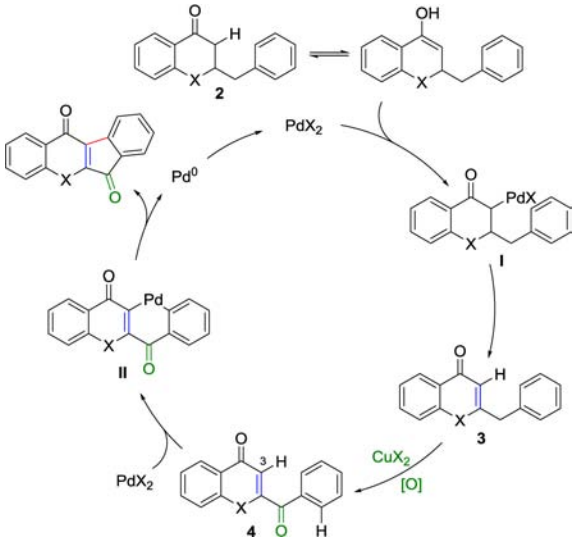


Figure 1. Reaction profile of tandem process.

catalyzed oxidation is faster than Pd-catalyzed intramolecular oxidative coupling of **3a**.

On the basis of our observations, a mechanistic proposal for the tandem process is outlined in Scheme 2. First, the enol form

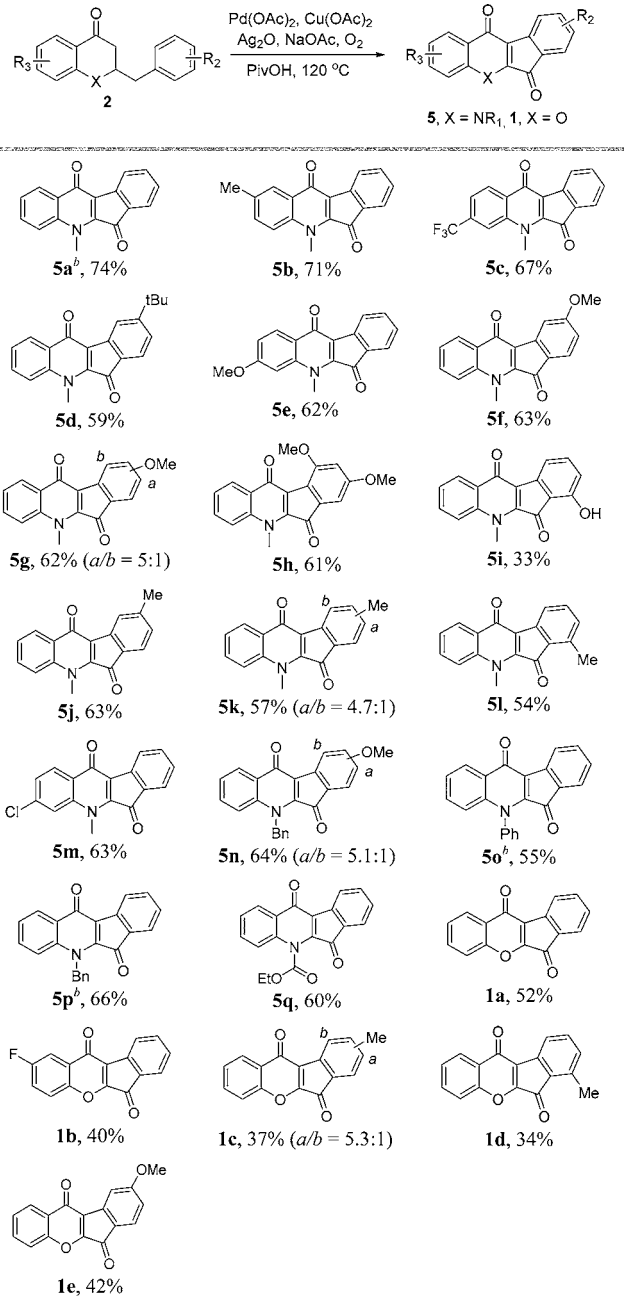
Scheme 2. Proposed Mechanistic Pathways Underlying the Present One-Pot Catalysis



of **2** is coordinated to Pd(II), followed by H-abstraction to provide Pd(II) enolate **I**. Intermediate **3**, generated by β-hydride elimination, is oxidized with a copper catalyst and molecular oxygen to afford the ketone intermediate **4**. Next, the six-membered palladacycle **II** is expected to be formed by initial *ortho*-C−H bond activation of intermediate **4** via a concerted metalation−deprotonation (CMD) process and subsequent intramolecular C−H bond cleavage at the C3-position.[13] In the process, other mechanistic possibility involving initial electrophilic palladation at the C3-position can also be conceived.[15] Subsequent reductive elimination produces the desired product, and oxidation of Pd(0) species to Pd(II) species completes the catalytic cycle.

The optimal conditions were then applied to a variety of substrates to test the utility of the new method (Scheme 3). The tetracyclic scaffold could be easily equipped with an additional substituent, such as an alkyl, methoxy, hydroxyl, trifluoromethyl, or chloro group, by this tandem catalytic process. A variety of *N*-

Scheme 3. Substrate Scope of Tandem Dehydrogenation/Oxidation/Oxidative Cyclization Reactions[a]



[a]Reaction conditions: **2** (0.1−0.2 mmol), $Pd(OAc)_2$ (20 mol %), $Cu(OAc)_2$ (3 equiv), Ag_2O (1.5 equiv), NaOAc (0.5 equiv), PivOH (1 mL), O_2, 120 °C, 8−24 h, Schlenk flask; isolated yields. [b]*t*-BuOAc/PivOH = 1:10 (v/v).

substituents including phenyl, benzyl, and ethyl formate groups were all tolerable under the reaction conditions to afford the desired products in modest to good yields (**5n−q**). In addition, expanding the scope from dihydroquinolinones to a chromanone system was also possible, giving rise to wrightiadione (**1a**) and its derivatives (**1b−e**). The use of a ^{t}BuOAc/PivOH (1:9) cosolvent system did not influence the efficiency of the reaction in most of substrates, except **2a**, **2o**, and **2p**. A mixture of isomers was observed for substrates bearing a *meta*-substituent, and intramolecular oxidative coupling occurred at the more sterically accessible C−H bond of the aryl group, thereby leading to the

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major isomers (**5g**, **5k**, **5n**, and **1c**) The present strategy allows the rapid generation of corresponding tetracyclic isoflavones and their nitrogen-containing derivatives, which constitute the core of naturally occurring compounds and privileged medicinal scaffolds.

In summary, we have developed an efficient method for constructing the tetracyclic isoflavone motif through three-step tandem dehydrogenation/oxidation/oxidative cyclization reactions with a Pd/Cu catalytic system. This unprecedented one-pot route illustrates the efficiency of generating the molecular complexity of wrightiadione derivatives. Further studies to broaden the synthetic application toward other heterocycles and bioevaluation of the newly synthesized compounds are in progress.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure and characterization of new compounds (^{1}H and ^{13}C NMR spectra). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01618.

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Notes

The authors declare no competing financial interest.

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