# A New Palladium-Catalyzed Addition: A Mild Method for the Synthesis of Coumarins

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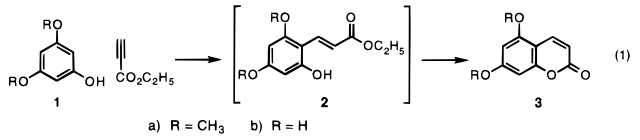
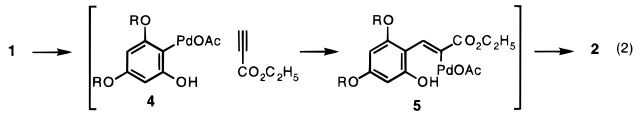
Palladium(0) complexes in the presence of carboxylic acids have proven to be an interesting catalyst system. In spite of the absence of any discernable reaction between Pd(0) and the carboxylic acid, this catalyst system effects cycloisomerizations of enynes,[1] reductive cyclizations of enynes and diynes,[2] and semihydrogenation of alkynes.[3] All of these reactions are best interpreted as initiated by a hydropalladation with a hydridopalladium carboxylate formed in equilibrium albeit at very low concentration. In conjunction with a projected synthesis of aflatoxins,[4a] our desire to find a mild route to coumarins led to a new reaction involving this catalyst system which follows a completely different course.

Although coumarins retain a high degree of importance because of their biological relevancy,[5] improved methods of synthesis have not evolved.[4] One of the most attractive methods is the Pechmann condensation[6] and a variation wherein an alkynoate replaces the more typical $\beta$-ketoester.[7] The major drawbacks of this protocol stem from the requirement of stoichiometric amounts of strong Bronsted or Lewis acids at high temperature that also frequently limit its scope.

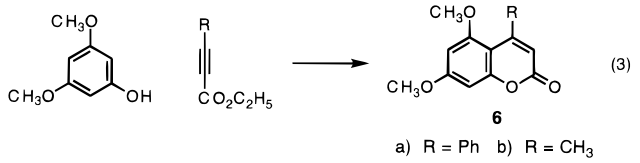
We chose the reaction depicted in eq 1 as our test reaction,




consistent with our goal directed toward the aflatoxins. The initial concept was based upon an electrophilic palladation[8,9] of the phenol **1a** to give **4a** (eq 2). Standard carbametalation of the alkynoate to give **5a** followed by protonolysis would give the cinnamate **2a** which, in turn, should readily cyclize to the coumarin **3a**. In the event, treatment of ethyl propynoate with phenol **1a** in acetic acid buffered with sodium acetate at room temperature (rt) to 70° gave either starting material or decom-

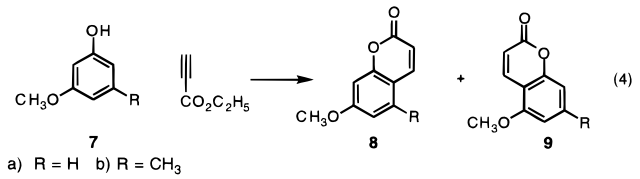



position, but none of the desired coumarin. A dramatic change occurred by switching to formic acid. Using 30% palladium acetate and 50% sodium acetate at 50 °C, a 40% yield of the coumarin **3a**, mp 143−5 °C,[10] was obtained. Reducing the palladium acetate to 10% and the sodium acetate to 20% at 35 °C increased the yield to 82% (method A). To ascertain the source of this effect, consideration of the reducing properties of formic acid toward Pd(+2) salts[11] led to the notion that perhaps a Pd(0) species was the actual catalyst. Indeed, using 2.5 mol % $(dba)_3Pd_2{\cdot}CHCl_3$ and 10 mol % sodium acetate in formic acid at 25 °C gave **3a** in yields up to 88% (method B). Although sodium acetate is not required, the reactions proceeded faster and at lower temperature in its presence. The methyl ethers are not required. Phloroglucinol (**1b**) reacts equally well to give 5,7-dihydroxycoumarin, (**3b**) mp 270−272 °C,[7] by method B in 79% yield. Extension of the reaction to substituted alkynoates was also examined. Running the reaction according to method A with ethyl phenylpropynoate and ethyl 2-butynoate led to the corresponding 4-substituted coumarins **6a**, mp 164−5 °C,[12] and **6b**, mp 168−170 °C,[13] (eq 3) in 69% and 51% yields,




respectively. In the latter case, switching to method B increased the yield to 63%.

The regioselectivity was examined in the case of phenols **7a** and **7b** (eq 4). In both cases, good selectivity for formation of




the new bond occurred para to the methoxy group. Using method A, phenol **7a** gave isolated yields of herniarin (**8a**), mp 119−120 °C,[14] and **9a**, mp 80−82 °C,[15] of 52% and 7%, respectively. Using method B, phenol **7b** gave isolated yields of **8b**, mp 139−142 °C,[16] and **9b** of 72% and 10%, respectively. The fact that the absence or presence of the methyl group had essentially no effect on the regioselectivity suggests that electronic more than steric effects account for the regioselectivity.

This reaction succeeds where the Pechmann condensation is claimed to perform poorly. For example, the synthesis of umckalin methyl ether (**10**) required a four-step protocol from

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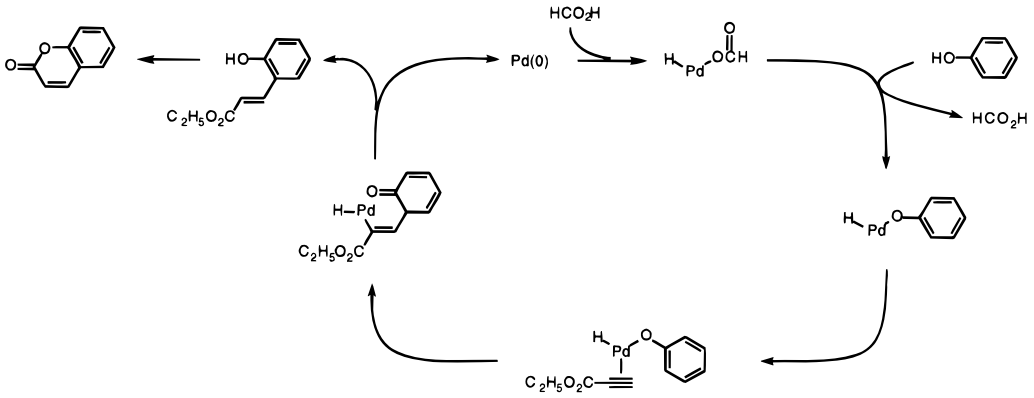
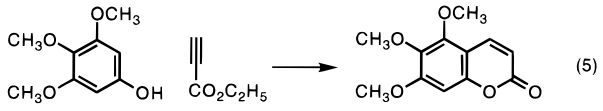
**Scheme 1.** A Mechanistic Proposal



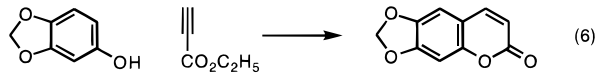

3,4,5-trimethoxyphenol.[17] The one-step palladium-catalyzed reaction (method B) provided coumarin **10**, mp 72−74 °C,[18] in 46% yield unoptimized (eq 5).




(5)

**10**

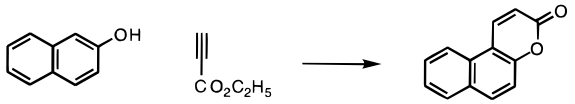
Ayapin (**11**) represents another difficult example[19] and required a four-step synthesis.[20] As shown in eq 6, this




(6)

**11**

coumarin, mp 225−227 °C,[19] is available in 67% yield using method B. The regioselectivity follows that observed in eq 4. $\beta$-Naphthol is also reported as an unsuitable substrate for the Pechmann condensation.[6] In contrast to that observation, it participates satisfactorily in this palladium-catalyzed version whereby a single product **12**, mp 139−142 °C,[16] as shown in eq 7 forms. Because of the partial solubility of $\beta$-naphthol in

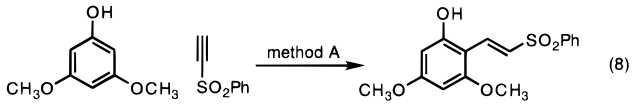



(7)

**12**

formic acid, use of sonication improved the isolated yield from 46% to 61%.

The mechanism of this new palladium-catalyzed reaction is quite interesting since it appears to involve Pd(0) rather than Pd(+2). Use of palladium acetate in acetic acid does not effect reaction, whereas replacing acetic acid by formic acid, which can reduce Pd(+2) to Pd(0), leads to reaction. Indeed, in the case of palladium acetate as a palladium source, Pd black formed under the reaction conditions in the absence of substrate. In addition, when using a Pd(0) complex as the precatalyst, both acetic and formic acids led to catalytic cycles although the latter gave more satisfactory results. Further, starting from a Pd(0) complex gave faster reactions at lower temperatures. Control experiments verify the absence of any reaction in the absence of palladium. A ligand like 2-diphenylphosphinobenzoic acid shuts down reaction. A reasonable rationale builds from our observations of the effectiveness of $(dba)_3Pd_2$ in formic acid to cycloisomerize enynes.[21] Since this reaction is initiated by a hydropalladation, the formation of HPdX appears likely. Scheme 1 outlines the proposed mechanism. Although this mechanistic proposal supports the concept of a *cis* addition to produce *E*-cinnamic esters, their known ease of ***E*−*Z*** isomerization accounts for the isolation of the coumarin rather than the *E*-cinnamates.[5] Employing phenylsulfonylethyne which cannot cyclize did produce the expected E-alkene (eq 8). The low




(8)

reactivity of the palladium phenoxide requires the alkyne to bear an electron-withdrawing group. Further, the aryl ring must be at least as electron rich as $\beta$-naphthol; for example, *m*-cresol did not react. This proposal suggests a new way to effect direct electrophilic aromatic substitution using catalytic "catalysts" in contrast to the normal Lewis acid "catalyzed" reactions which, almost invariably, require more than stoichiometric amounts of "catalyst". Defining the types of substitutions that this more atom economical approach allows will be the subject of future work in these laboratories.

A sample experimental procedure follows. Ethyl propynoate (2.6 mL, 26.0 mmol) was added to a solution of 3,5-dimethoxyphenol (2.00 g, 13.0 mmol), $(dba)_3Pd_2{\cdot}CHCl_3$ (0.34 g, 0.325 mmol), and sodium acetate (0.11 g, 0.725 mmol) in 13 mL of formic acid. The resulting brown/purple reaction mixture was stirred at rt for 16 h, diluted with methylene chloride (25 mL), washed with water (25 mL), 5% aqueous sodium bicarbonate (25 mL), and brine (25 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give a brown solid. Flash chromatography ($CH_2Cl_2$) followed by recrystallization from methylene chloride−hexanes afforded 2.51 g (77% yield) of 2,5-dimethoxycoumarin as a yellow solid, mp 143−5 °C (lit[10] mp 143−4 °C).

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