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# Access to Flavones via a Microwave-Assisted, One-Pot Sonogashira−Carbonylation−Annulation Reaction

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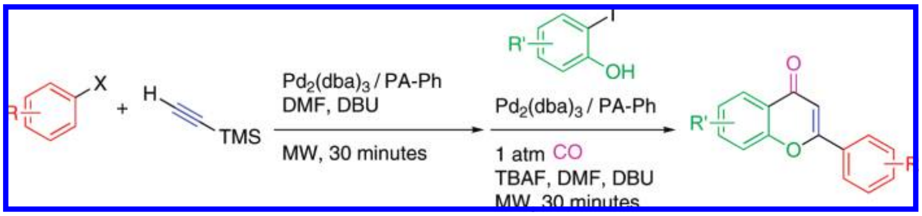
## ABSTRACT



**Palladium complexes of 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane are shown to be effective catalytic systems facilitating the sequential application of a microwave-assisted Sonogashira and carbonylative annulation reaction for the preparation of substituted flavones.**

Flavones[1] are a major group of secondary metabolites found throughout the plant kingdom and have been shown to possess a wide variety of biological activity.[2] A number of classical synthetic approaches to this family of compounds exist. The Baker−Venkataraman[3] method involves the conversion of 2-hydroxyacetophenones into benzoyl esters, rearrangement in base to 1,3-diphenylpropane 1,3-diones, followed by cyclization in acid to yield the flavone ring system.[4] Alternatively, treatment of a 2-hydroxyacetophenone and benzaldehyde under Claisen−Schmidt conditions yields a 2-hydroxychalcone that can be oxidatively cyclized to yield the flavone system.[5] Both approaches utilize harsh conditions such as strong bases, acid, and elevated temperatures. A particularly attractive alternate approach involves the Pd-catalyzed carbonylation[6]/cyclization reaction between 2-iodophenols and terminal alkynes.[7] Given our work with palladium complexes of 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane (PA-Ph)[8] and their ability to

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(8) Available from Cytec Canada Inc., PO Box 240, Niagara Falls, Ontario, L2E 6T4, Canada.

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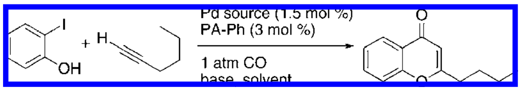
catalyze the coupling of aryl halides with terminal acetylenes,[9] we envisioned a reaction sequence wherein the product of a Sonogashira reaction could then undergo Pd-catalyzed carbonylative annulation with a 2-iodophenol to yield a flavone scaffold. The present paper describes a microwave-assisted, one-pot method that allows the efficient and mild preparation of flavones from aryl halides and 2-iodophenol derivatives.

Our initial effort focused on the Pd-catalyzed carbonylation annulation reaction between 2-iodophenol and 1-hexyne using the PA-Ph ligand. The screening of various Pd sources, solvents, temperatures, and bases is presented in Table 1.

**Table 1.** Optimization of Pd-Catalyzed Carbonylation−Annulation Conditions[a]



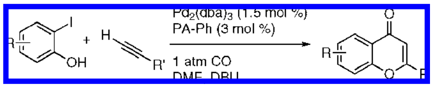
| entry | Pd source | solvent | base | temp (°C)/ time (h) | % yield |
|---|---|---|---|---|---|
| 1 | $PdCl_2$ | $H_2O$ | $Et_3N$ | 25/2 | 0 |
| 2 | $Pd_2(dba)_3$ | MeCN | $(i\mathrm{Pr})_2NEt$ | 25/2 | 42 |
| 3 | $Pd_2(dba)_3$ | MeCN | $Et_3N$ | 25/2 | 0 |
| 4 | $Pd_2(dba)_3$ | MeCN | $Cs_2CO_3$ | 25/2 | 54 |
| 5 | $Pd_2(dba)_3$ | dioxane | $(i\mathrm{Pr})_2NEt$ | 25/2 | 0 |
| 6 | $Pd_2(dba)_3$ | toluene | $(i\mathrm{Pr})_2NEt$ | 25/2 | 0 |
| 7 | $Pd_2(dba)_3$ | THF | $(i\mathrm{Pr})_2NEt$ | 25/2 | 20 |
| 8 | $Pd_2(dba)_3$ | THF | $Cs_2CO_3$ | 25/14 | 40 |
| 9 | $Pd_2(dba)_3$ | toluene/THF | $(i\mathrm{Pr})_2NEt$ | 25/2 | 0 |
| 10 | $Pd_2(dba)_3$ | toluene/MeCN | $(i\mathrm{Pr})_2NEt$ | 25/2 | 0 |
| 11 | $Pd_2(dba)_3$ | DMSO | $Cs_2CO_3$ | 25/14 | 20 |
| 12 | $Pd_2(dba)_3$ | DMF | $Cs_2CO_3$ | 25/14 | 76 |
| 13 | $Pd_2(dba)_3$ | DMF | $Cs_2CO_3$ | 50/4 | 91 |
| 14 | $Pd_2(dba)_3$ | DMF | DBU | 50/4 | 93 |

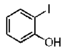
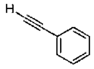
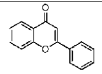
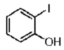
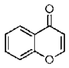
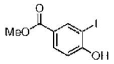
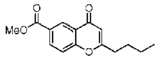
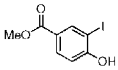
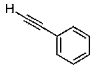
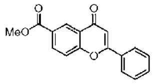
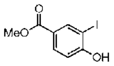
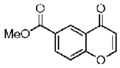
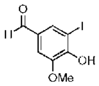
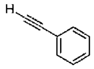
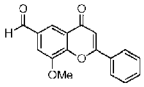
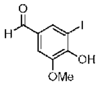
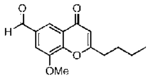
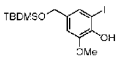
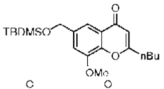
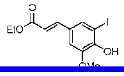
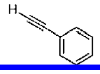
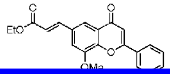
[a] Reactions were carried out using 0.50 mmol of 2-iodophenol and 0.75 mmol of 1-hexyne.

Reagents were combined in a reaction vessel, and the reaction was carried out under 1 atm of CO gas. These experiments quickly revealed that using DMF as the solvent with $Cs_2CO_3$ or DBU as the base at 50 °C resulted in 91% and 93% isolated yield, respectively, of the desired flavone (Table 1, entries 13 and 14). Under these conditions we produced the flavone products exclusively and did not observe any of the aurone byproduct. The relatively low catalyst loading (1.5 mol % equivalent of $Pd_2(dba)_3$ and 3 mol % equivalent of PA-Ph), short reaction time, high conversion, and mild temperatures render our catalytic system more efficient than previously reported protocols.[7]

With the optimal set of conditions in hand, we proceeded to generate a small library of flavones (Table 2). Overall, the method works well and tolerates a variety of functional groups. With entries 2 and 5, desilylation during the annulation step proceeds without the need for any additional reagents. Entries 8 and 9 required longer reaction times (12 h). The lower yield observed for entry 8 was not due to desilylation as might be expected; rather, under the conditions employed, significant amounts of starting material remain unreacted. It is likely that the electron-donating substituents on the aryl iodide slow the rate of oxidative addition with the Pd-catalyst system.

**Table 2.** Flavones and Chromones via a Pd-Catalyzed Carbonylation−Cyclization Reaction[a]



| entry | iodophenol | alkyne | product | yield[b] |
|---|---|---|---|---|
| 1[c] |  |  |  | 81 |
| 2[c] |  |  |  | 86 |
| 3[c] |  |  |  | 83 |
| 4[c] |  |  |  | 82 |
| 5[c] |  |  |  | 79 |
| 6[c] |  |  |  | 92 |
| 7[c] |  |  |  | 76 |
| 8[d] |  |  |  | 31 |
| 9[d] |  |  |  | 86 |

[a] Reactions were carried out using 0.50 mmol of the substituted 2-iodophenol and 0.75 mmol of the alkyne. [b] Isolated yield. [c] 50 °C, 4 h. [d] 50 °C, 12 h.

Microwave-assisted organic synthesis has demonstrated itself to be superior in many instances when compared to reactions carried out using conventional heating.[10] The use of microwave irradiation often helps to reduce reaction times, minimize side products, increase yields, and improve reproducibility. A number of examples of microwave-assisted carbonylation reactions have been described in the literature.[11] These previous approaches have generally utilized $Mo(CO)_6$ and, as a result, require elevated temperatures to induce the decomposition of the molybdenum reagent and

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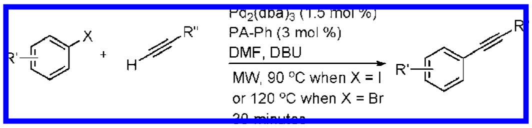
**Table 3.** Microwave-Assisted Sonogashira Reactions[a]



| entry | aryl halide | alkyne | product | yield[b] |
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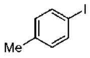
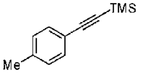
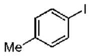
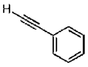
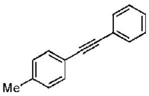
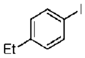
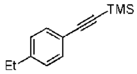
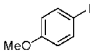
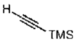
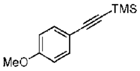
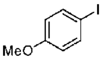
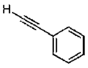
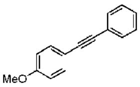
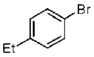
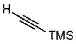
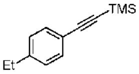
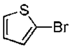
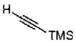
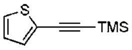
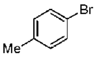
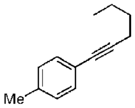
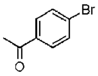
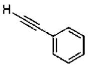
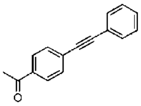
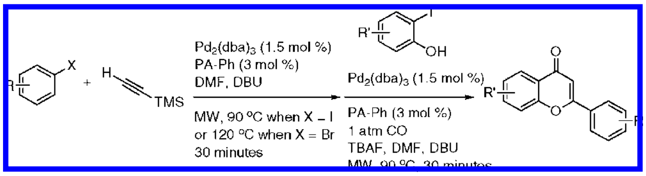
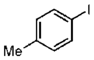
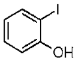
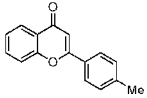
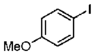
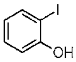
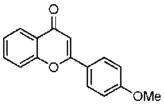
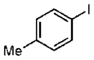
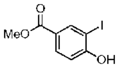
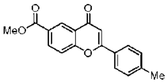
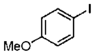
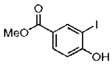
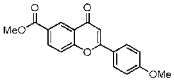
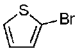
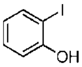
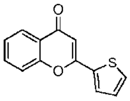
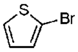
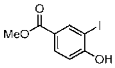
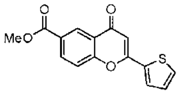
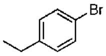
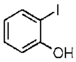
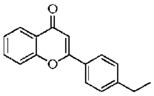
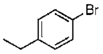
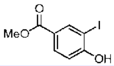
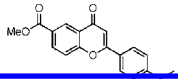
| 1 |  |  |  | 94 |
| 2 |  |  |  | 96 |
| 3 |  |  |  | 92 |
| 4 |  |  |  | 89 |
| 5 |  |  |  | 93 |
| 6 |  |  |  | 85 |
| 7 |  |  |  | 96 |
| 8 |  |  |  | 94 |
| 9 |  |  |  | 96 |

[a] Reactions were carried out using 1.0 mmol of aryl halide and 1.5 mmol of alkyne. [b] Isolated yield.

**Table 4.** Flavones via a Microwave-Assisted Sonogashira−Carbonylation−Cyclization Reaction[a]



| entry | aryl halide | iodophenol | product | yield[b] |
|---|---|---|---|---|
| 1 |  |  |  | 67 |
| 2 |  |  |  | 56 |
| 3 |  |  |  | 63 |
| 4 |  |  |  | 46 |
| 5 |  |  |  | 65 |
| 6 |  |  |  | 71 |
| 7 |  |  |  | 62 |
| 8 |  |  |  | 58 |

[a] Reactions were carried out using 1.0 mmol of aryl halide, 1.5 mmol of alkyne, and 0.5 mmol of substituted 2-iodophenol. [b] Isolated yield over two steps based on starting amount of substituted 2-iodophenol used.

liberation in situ of CO gas. Given the relatively mild temperatures used above and the efficacy of the PA-Ph ligand, we examined the effect of microwave heating on our reaction conditions. We determined, ultimately, that comparable yields for the carbonylation−annulation reaction could be obtained when the reaction mixture was irradiated in a microwave at 90 °C using a shortened reaction time of only 30 min. However, a much improved yield of 68% was obtained when the microwave-assisted conditions were applied to preparation of the TBDMS-protected flavone (Table 2, entry 8). While the use of a CEM gas addition unit[12] greatly facilitated the introduction of CO into the reaction vessel, we also found that simply bubbling CO gas into the reaction prior to microwave irradiation allowed an equally efficient reaction and avoided the need for Mo(CO)$_6$.

The alkyne required for the Pd-catalyzed carbonylative annulation developed above could be generated via a Sonogashira reaction. Using our previously developed protocol as a starting point,[9] we modified the reaction conditions so as to integrate with those developed for the carbonylation−annulation reaction. In this way, we found that the optimal conditions (1.5% Pd$_2$(dba)$_3$; 3% PA-Ph, DMF, DBU) using microwave irradiation allowed a reduction in reaction times and the elimination of the CuI co-catalyst generally required by the Sonogashira reaction (see Table 3). For example, the coupling of *p*-iodotoluene with phenylacetylene (entry 2) could be achieved at 90 °C in 30 min in 96% yield. When aryl bromides were used (entries 6−9) as coupling partners, an increase in temperature (to 120 °C) allowed excellent yields with comparable reaction times.

Having established the conditions and scope of both the microwave-assisted, Pd-catalyzed carbonylative−annulation and the Sonogashira reaction, a natural extension of the work involves a sequential combination of the two reactions effectively allowing a one-pot flavone synthesis.

In all cases, the initial microwave-mediated Sonogashira reaction involved an aryl halide and TMS acetylene. The products from this reaction were then introduced into a reaction vessel containing the iodophenol, fresh Pd/PA-Ph

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(12) Available from CEM Corporation, P. O. Box 200, 3100 Smith Farm Road, Matthews, NC 28106, USA.

catalyst system, solvent, and base. Introduction of CO followed by microwave irradiation allowed the preparation of the flavones listed in Table 4. It should be noted that addition of TBAF in the second step allowed deprotection of the TMS group and permitted a smoother, more reproducible annulation reaction. The yields of the isolated flavone range from moderate to very good with the entire sequence completed in approximately 1 h.

Overall, the synthetic method developed above for the preparation of substituted flavones involves mild reaction conditions and relatively short reaction times and provides good yields of the desired products. Given the range of commercially available components for this protocol (aryl iodides and bromides as well as substituted *o*-iodophenols), the method should prove valuable in the preparation of combinatorial libraries of flavones.

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

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