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# Construction of the flavones and aurones through regioselective carbonylative annulation of 2-bromophenols and terminal alkynes

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ABSTRACT

The easily available and efficient catalyst containing a benzimidazolium ligand and $PdCl_2(PPh_3)_2$ demonstrated excellent catalytic activity to construct the flavones and aurones, respectively. This reaction can be operated under mild conditions, affording the desired products in moderate to good yields. This protocol was used to prepare the flavones and aurones by a slight modification of amines.



Palladium-catalyzed carbonylative reactions of organic halides in the presence of various nucleophiles have undergone a great deal of development since the pioneering work of Heck and coworkers in 1974.[1] A wide range of aromatic acyl derivatives, such as aldehydes, acids, esters, amides, and ketones could be selectively synthesized by carbonylation reaction.[2] Among these compounds, both flavones and aurones are indispensable intermediate moieties in many biologically active molecules.[3–5] Therefore, developing highly efficient and selectivity methods for constructing these two classes of chromones from readily accessible substrates continues to be a hot research topic. In general, traditional synthetic methods for those compounds rely on the following strategies: (i) cyclization of l-(2-X-phenyl)-3-phenyl-1,3-propanediones (X = OH, OR, Br, Cl),[6] (ii) 2′-hydroxychalcones initiated by acid or base,[7] (iii) Pd-catalyzed oxidative arylation of chromones with phenylboronic acids,[8] (iv) Pd-catalyzed carbonylative cyclization using CO gas as carbonyl resource,[9] (v) the Wheeler aurone synthesis from chalcone dihalides,[10] (vi) oxidative cyclization of 2′-hydroxychalcones,[11] and (vii) ring closure of *o*-hydroxyaryl phenylethynyl ketones.[12] Despite the existence of many methods for the preparation of flavones and aurones, more general and easily available routes would be still highly required. Direct transformation of the simple 2-iodophenols and terminal alkynes into the corresponding chromones via the Pd-catalyzed carbonylative annulation reaction is arguably a highly efficient and easy method.[13] Until now, the difficult activation and easy availability of 2-bromophenols could not be applied successfully to construct the chromone derivatives. Therefore we present a facile route to prepare the flavones and aurones through Pd-catalyzed carbonylative annulation reaction of 2-bromophenols and terminal alkynes in secondary amines (Scheme 1). The key of the route just presents one-pot synthesis of chromones from easily available substrates. As our extending work in developing carbonylative reactions, herein we report a Pd-catalyzed cascade carbonylative cyclization approach to the flavones and aurones that proceeds in good to excellent yields. To the best of our knowledge, this is the first catalytic process to obtain the chromones from 2-bromophenols and terminal alkynes controllably by different amines.

Based on previous research on palladium-catalyzed carbonylative coupling reactions,[14] the reaction of 2-bromophenol with phenylacetylene was chosen as a model reaction to explore and optimize the cascade carbonylative reaction in the presence of 2.0 MPa CO. In our initial screens, the effects of different reaction parameters (i.e., catalytic precursor, ligand, temperature, and solvent) were investigated, respectively, and the results are summarized in Table 1. The yield decreased when the pressure of CO was below 2.0 MPa and the reaction temperature below 130 °C (Table 1, entries 1–3). To our delight, the reaction obtained a 78% yield of the desired flavones under the optimized reaction (Table 1, entry 6). Then the effect of solvent on the reaction was also investigated. A survey of solvents revealed that *n*-$Pr_2NH$ is a better solvent than the others (Table 1, entries 5–10). Subsequently, the

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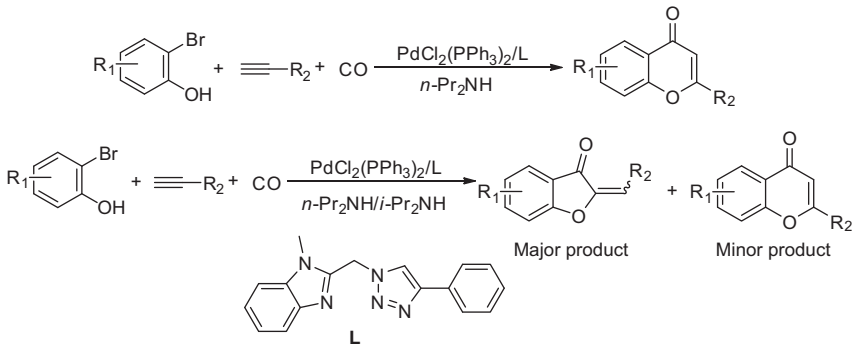
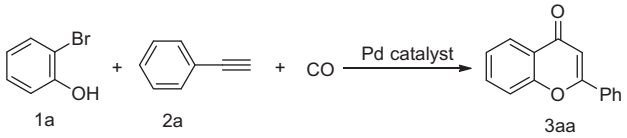



**Scheme 1.** Synthesis of flavones and aurones.

**Table 1**
Screening the conditions for the Pd-catalyzed carbonylative annulation of 2-bromophenol and phenylacetylene[a]




| Entry | Catalyst | *N*-Ligand | T (°C) | Solvent | Yield[b] (%) |
|---|---|---|---|---|---|
| 1[c] | $PdCl_2(PPh_3)_2$ | **L** | 130 | *n*-$Pr_2NH$ | 46 |
| 2 | $PdCl_2(PPh_3)_2$ | **L** | 110 | *n*-$Pr_2NH$ | 21 |
| 3 | $PdCl_2(PPh_3)_2$ | **L** | 90 | *n*-$Pr_2NH$ | 10 |
| 4 | $PdCl_2$ | **L** | 130 | *n*-$Pr_2NH$ | Trace |
| 5 | $PdCl_2(PPh_3)_2$ | **L** | 130 | $Et_2NH$ | 68 |
| 6 | $PdCl_2(PPh_3)_2$ | **L** | 130 | *n*-$Pr_2NH$ | 78 |
| 7 | $PdCl_2(PPh_3)_2$ | **L** | 130 | *i*-$Pr_2NH$ | NR |
| 8 | $PdCl_2(PPh_3)_2$ | **L** | 130 | *n*-$Bu_2NH$ | 72 |
| 9 | $PdCl_2(PPh_3)_2$ | **L** | 130 | Morpholine | 19 |
| 10 | $PdCl_2(PPh_3)_2$ | **L** | 130 | $Et_3N$ | 5.0 |
| 11 | $PdCl_2(PPh_3)_2$ | Phen | 130 | *n*-$Pr_2NH$ | 36 |
| 12 | $PdCl_2(PPh_3)_2$ | — | 130 | *n*-$Pr_2NH$ | 37 |

[a] Reactions were carried out in 4.0 mL of solvent under 2.0 MPa pressure of CO at 130 °C for 24 h with 2-bromophenol (1.0 mmol), phenylacetylene (2.0 mmol), Pd catalyst (0.05 mmol), and benzimidazolium ligands (0.05 mmol).
[b] Isolated yield.
[c] 1.0 MPa CO.

desired product was observed in a 36% yield in the presence of 1,10-phenanthroline (Table 1, entry 11).

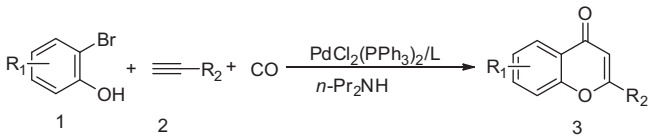
Having established the effective catalytic system for the one-pot synthesis of flavones, then we focus our attention on exploring the generality of this methodology with respect to various acetylenes and substitute of 2-bromophenols. Under the optimal reaction,[15] it was found that alkyne reagents with an alkyl group in the *para* positions of phenyl group with 2-bromophenol were able to undergo the cascade reaction to afford the desired products in 72–86% yields (Table 2, entries 2–4). Furthermore, the reaction of 1-hexyyne with 2-bromophenols occurs in a highly regioselective fashion to give the corresponding flavones in 65% and 43% yields, respectively (Table 2, entries 5 and 6). To probe the scope and limitation of this process, we also examined other 2-bromophenols under the standard reaction conditions. All of the substrates bearing either an electron-rich group or an electron-poor group at the *para*-positions of the phenyl groups were well tolerated in this transformation (Table 2, entries 7–13). From the results, it is evident that 2-bromophenols bearing an electron-withdrawing group lead to an increase obviously in the yields. Overall, no adjustments on the reaction conditions are necessary to afford good yields of flavones, and no formation of aurones was observed in this transformation.

According to the results obtained by the synthesis of flavones between 2-iodophenols and terminal alkynes previously,[13] a plausible mechanism for the present process can be proposed as shown in Figure 1. Benzimidazole–triazole ligand maybe stabilized the generated Pd(0), this can make for the oxidative insertion of the aryl halide to generate the arylpalladium complex. The Pd(0) catalyst first underwent oxidative addition of the aryl halide to generate the arylpalladium complex. Insertion of carbon monoxide into the aryl carbon–palladium bond could afford the aroylpalladium bromide complex (**I**), and then the α,β-alkynyl ketone intermediate **II** could be obtained by alkynes' attack of the enolate carbon on the palladium atom and reductive elimination. In this catalytic cycle, **II** would be a critical intermediate in the formation of **VII** and **VIII**. The intermediate **II** then underwent Michael addition of the *n*-$Pr_2NH$ to proceed through IV and V stages or a direct 6-endo-dig cyclization to generate flavones (**VII**). On the other hand,[13f] the compound **II** may subsequently form a complex **III** with palladium (0), followed by undergoing rearrangement and reductive elimination to afford aurones (**VIII**).

Encouraged by the good results mentioned above, we then tested the catalytic activity of benzimidazole–triazole ligand and $PdCl_2(PPh_3)_2$ for the formation of aurones. We observed that decreasing the amount of *n*-$Pr_2NH$ proceeded uneventfully to obtain the product of aurone. While *i*-$Pr_2NH$ was used as solvent, no flavone and aurone were obtained. A probable reason why the compound **II** was not formed was that the cabonylative reaction of acetylene with 2-bromophenol was not carried out. Such results suggest that the intermediate **II** did not undergo Michael addition of *i*-$Pr_2NH$ to obtain **IV**. Then it may form a complex **III** with Pd(0), followed by the rearrangement and reductive elimination to afford aurones. On the basis of the above studies, the reaction conditions using benzimidazole–triazole ligand and $PdCl_2(PPh_3)_2$ in *n*-$Pr_2NH$ (8.0 μL) and *i*-$Pr_2NH$ (4.0 mL) were employed as the standard reaction conditions for other substrates. The results are presented in Scheme 2. It indicated that benzimidazole–triazole ligand and $PdCl_2(PPh_3)_2$ catalyst system could be successfully employed for the one-pot synthesis of a range of aurones. All processes were highly regioselective, and gave the *E*-isomer as the main product. When different alkynes were employed, the 2-bromophenol efficiently provided the aurones in 62–75% yields (**4aa**–**4ad**) and the flavones in 3–8% yields (**3aa**–**3ad**). Gratifyingly, the reaction of alkynes with 2-bromophenols with electron-rich and electron-poor phenyl moieties gave the desired products in good to high yields (**4ba**–**4cd**).

In summary, we have developed a simple and efficient Pd-catalyzed cascade carbonylative cyclization of various 2-bromophenols

**Table 2**
Carbonylative annulation of various 2-bromophenol and acetylenes[a]



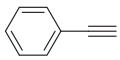
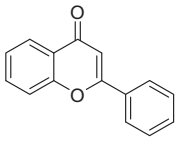
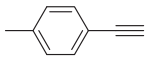
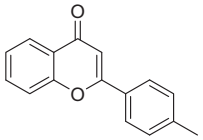
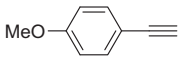
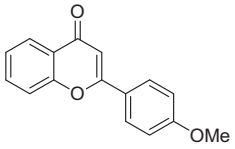
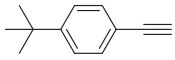
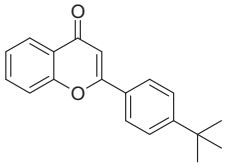
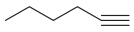
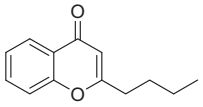
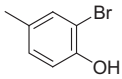
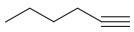
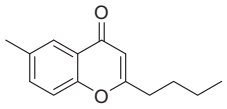
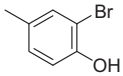
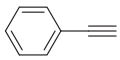
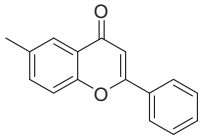
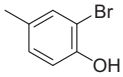
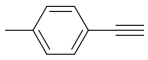
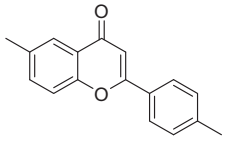
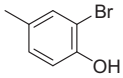
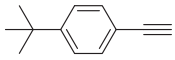
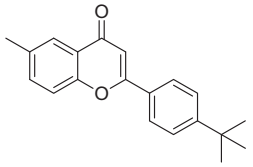
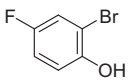
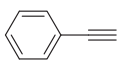
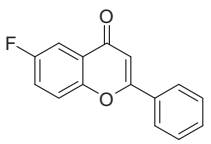
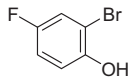
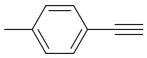
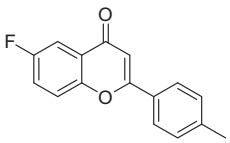
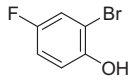
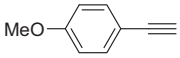
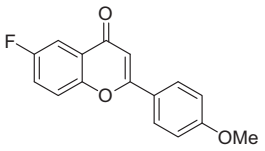
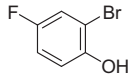
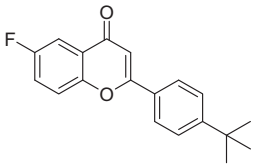

| Entry | 2-Bromophenol | RC≡CH | Product | Yield[b] (%) |
|---|---|---|---|---|
| 1 |  |  |  | 78 |
| 2 |  |  |  | 82 |
| 3 |  |  |  | 72 |
| 4 |  |  |  | 86 |
| 5 |  |  |  | 65 |
| 6 |  |  |  | 43 |
| 7 |  |  |  | 83 |
| 8 |  |  |  | 73 |
| 9 |  |  |  | 84 |
| 10 |  |  |  | 90 |

**Table 2** (*continued*)

| Entry | 2-Bromophenol | RC≡CH | Product | Yield[b] (%) |
|---|---|---|---|---|
| 11 |  |  |  | 88 |
| 12 |  |  |  | 81 |
| 13 |  |  |  | 89 |

[a] Reactions were carried out in 4.0 mL of *n*-$Pr_2NH$ under 2.0 MPa pressure of CO at 130 °C for 24 h with 2-bromophenols (1.0 mmol), phenylacetylene (2.0 mmol), $PdCl_2(PPh_3)_2$ (0.05 mmol), and benzimidazolium ligands (0.05 mmol).
[b] Isolated yield.

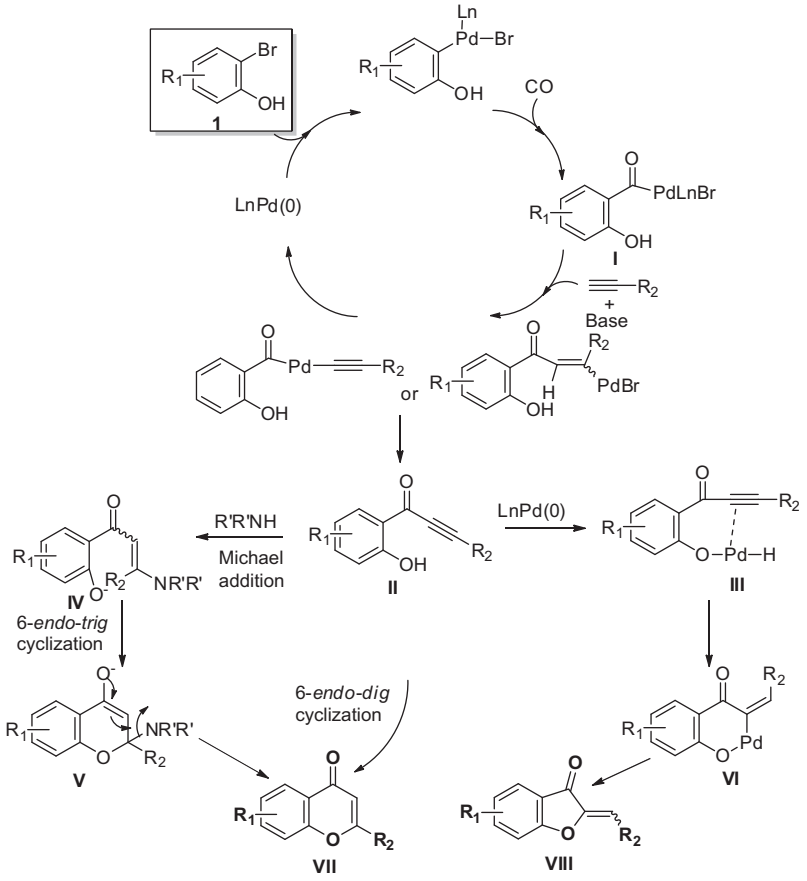
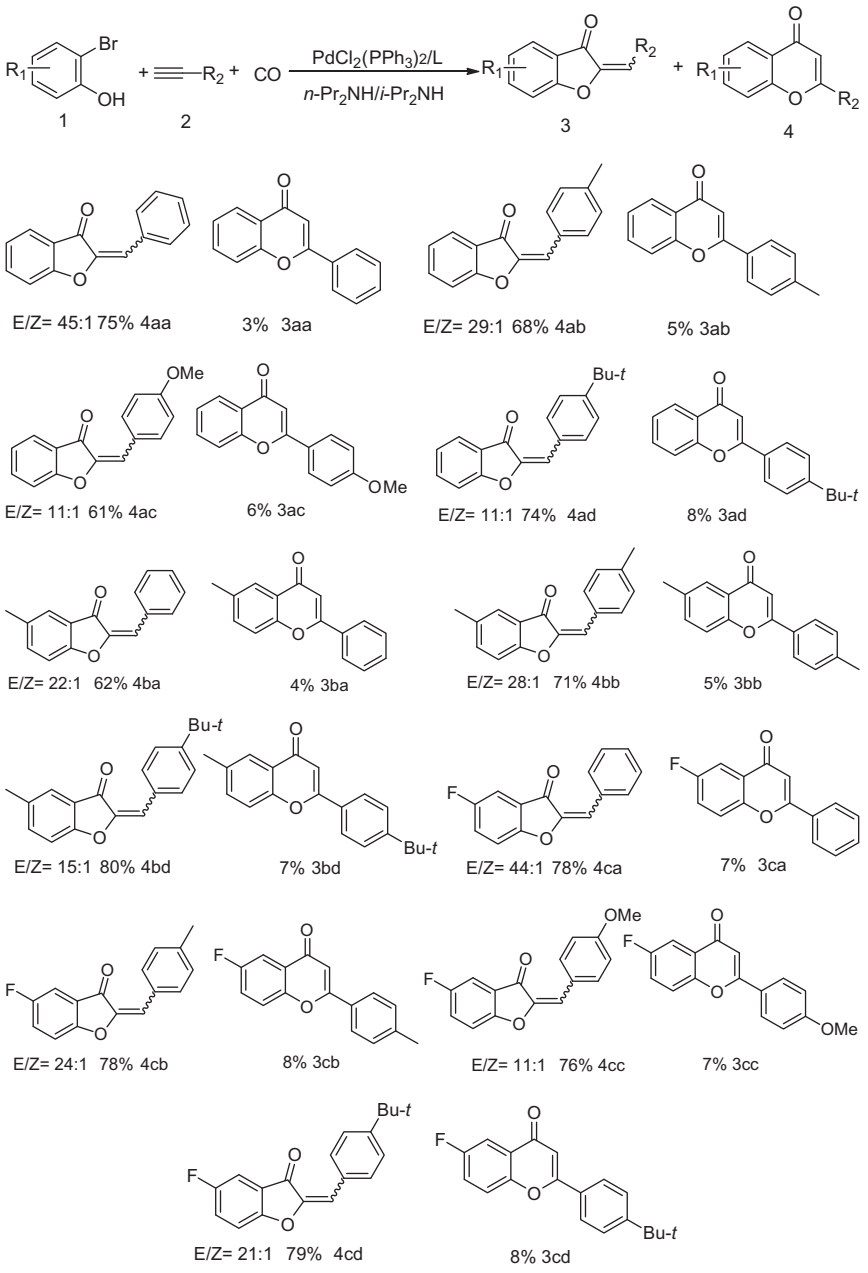



**Figure 1.** Proposed mechanistic interpretation for the formation of flavone and aurone.

and phenylacetylenes for the synthesis of flavone and aurone derivatives. A range of 2-bromophenols and various phenylacetylenes could undergo the cascade reaction smoothly to give the responding chromones in satisfactory yields. The reaction tolerates various functionalities, such as methyl, methoxy, tert-buty, and fluoro groups.




**Scheme 2.** Carbonylative annulation of various 2-bromophenols and phenylacetylenes.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.01.043.

## Reference and notes

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15. General procedure for the carbonylative annulation reaction: A 50 mL autoclave equipped with a magnetic stirring bar was charged with 2-bromophenols (1.0 mmol), alkynes (2.0 mmol), Pd catalyst (0.05 mmol), benzimidazolium ligands (0.05 mmol), and solvent (*n*-$Pr_2NH$, 4.0 mL). Then the autoclave was pressurized with carbon monoxide to 2.0 MPa (CO purity, 99.9%). The autoclave was placed in an oil bath pre-heated at 130 °C, and the reaction mixture was stirred for 24 h. After the reaction, the autoclave was cooled, and excess gas was purged slowly. After removal of the solvent in vacuo, the residual mixture was chromatographed by TLC using hexane/ethyl acetate to give the desired product.