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Palladium-catalyzed cascade reactions of coumarins with alkynes: synthesis of highly substituted cyclopentadiene fused chromones†

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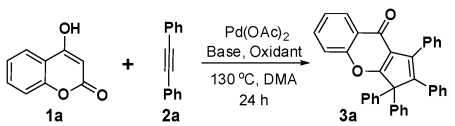
The coupling of coumarins with alkynes is described, which proceeds through a palladium-catalyzed cascade sequence. This process provides a new route to the synthesis of highly substituted cyclopentadiene fused chromones.

Polyarylated aromatic compounds are commonly found in functional materials, such as semiconductors, fluorescent and luminescent tools and materials.[1] Owing to the importance of such a framework, their synthesis has attracted considerable attention in the field of material chemistry. Alkynes, an important building block for organic transformations, have been utilized to construct polycyclic aromatic compounds *via* conventional synthetic methodologies involving a transition metal-catalyzed ring formation reaction.[2,3] These conventional synthetic methodologies involve transitional metal-catalyzed ring construction of an aromatic substrate with two alkynes. However, mono- or di-functionalized aromatic substrates, such as aryl halides and aryl boronates were required for such a reaction. Most recently, C–H activation initiated cyclization reactions of alkynes have become an impressive and powerful tool for the construction of synthetically useful building blocks, such as indoles, isoquinolines, benzothiazoles, pyridines, naphthalenes and other heteroaromatic rings.[4] Herein, we document a palladium-catalyzed cascade reaction of coumarins with alkynes involving the C–H bond activation process,[5] which could lead to a highly substituted cyclopentadiene fused chromone framework. To the best of my knowledge, this is the first report to synthesize polysubstituted cyclopenta[*b*]-chromen-9(3*H*)-one *via* this novel method.

In particular, chromones have been widely employed as important intermediates in the synthesis of many natural products and medicinal agents.[6] They have been found to potentially possess cytotoxic (anticancer),[7] neuroprotective,[8] HIV-inhibitory,[9] antimicrobial,[10] antifungal[11] and antioxidant activities.[12] Interestingly, they also can serve as a family of diet medicine because of their health-promoting effects found in the diet of humans.[13] Despite the several existing methods for the synthesis of chromone derivatives,[13c] there is still demand for diverse strategies which can efficiently provide variously substituted chromone systems. In this context, the significance of this synthetic methodology is highlighted by its correlation to the protocols for the preparation of chromone systems.

During our investigation of $Pd(OAc)_2$ (20 mol%) catalyzed cascade reaction of 4-hydroxy-2*H*-chromen-2-one (**1a**) with diphenylacetylene (**2a**) in the presence of CuI as an oxidant in dimethylacetamide (DMA) at 130 °C for 24 h, Cs_2CO_3 was discovered as the most efficient base and it could promote the yield of **3a** from 24% to 52% (Table 1, entries 1–5). Subsequently, we examined other reaction parameters by varying oxidants, temperatures and the influence of the solvents in order to improve the reaction yield. The results are summarized in Tables 1 and 2. In general, the higher reaction yields were obtained with Cu^{II} oxidants (Table 1, entries 10 and 12, 61% and 63%, respectively). The presence of

Table 1 Optimization of reaction conditions[a]



Entry	Base	Oxidant	Yield[c] (%)
1	—[b]	CuI	34
2	KOH	CuI	24
3	NaOAc	CuI	25
4	K_2CO_3	CuI	34
5	Cs_2CO_3	CuI	52
6	Cs_2CO_3	AgI	37
7	Cs_2CO_3	AgOAc	10
8	Cs_2CO_3	CuCl	28
9	Cs_2CO_3	CuBr	31
10	Cs_2CO_3	$CuCl_2$	61
11	Cs_2CO_3	$Cu(OAc)_2$	25
12	Cs_2CO_3	$CuBr_2$	63
13[d]	**Cs_2CO_3**	**$CuBr_2$**	**79**
14[d,e]	Cs_2CO_3	$CuBr_2$	69
15[d,f]	Cs_2CO_3	$CuBr_2$	77
16	Cs_2CO_3	Oxone	29
17	Cs_2CO_3	BQ	17
18	Cs_2CO_3	$K_2S_2O_8$	26

[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv.), **2a** (0.3 mmol, 1.5 equiv.), 20 mol% $Pd(OAc)_2$, base (0.4 mmol, 2.0 equiv.), oxidant (0.4 mmol, 2.0 equiv.), DMA (2 mL), 130 °C, 24 h. [b] None of the bases. [c] Isolated yield. [d] **2a** (1.0 mmol, 5.0 equiv.), 10 mol% $Pd(OAc)_2$. [e] 110 °C. [f] 150 °C.

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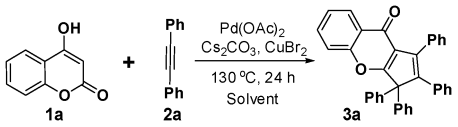
Table 2 Solvent effect[a]

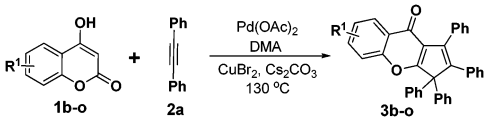


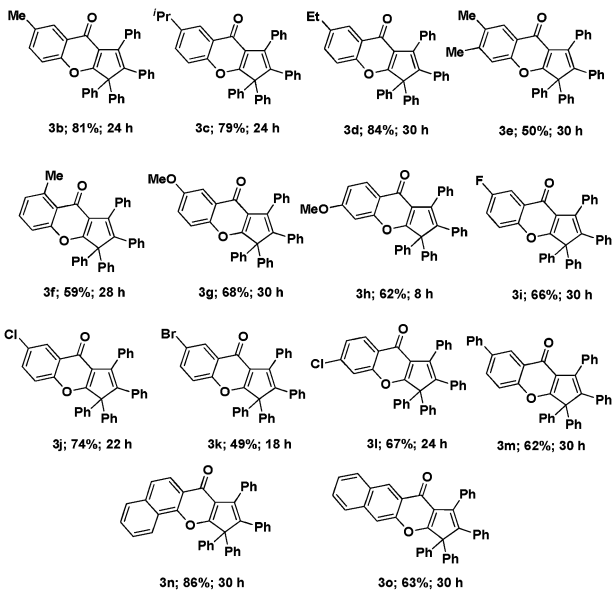
Entry	Solvent	Yield[c] (%)
1[b]	Toluene	15
2[b]	DCE	17
3[b]	CH_3CN	12
4	DMF	30
5	DMSO	56
6	NMP	67

[a] Reaction conditions: **1a** (1.0 equiv.), **2a** (5.0 equiv.), 10 mol% $Pd(OAc)_2$, Cs_2CO_3 (2.0 equiv.), $CuBr_2$ (2.0 equiv.), solvent (2 mL), 130 °C, 24 h. [b] Reflux. [c] Isolated yield.

other common oxidants, such as oxone, benzoquinone (BQ), and $K_2S_2O_8$, did not favour this process (Table 1, entries 16–18, 17–29%). Gratifyingly, the best result with regard to the reaction yield and time was obtained through the condition of 10 mol% $Pd(OAc)_2$ and 5.0 equivalent diphenylacetylene **2a** (Table 1, entry 13, 79% yield). Changing of the organic solvents from non-polar to polar did not show any improvement in the reaction yield and reaction rate (Table 2, entries 1–6, 12–67%). When the reaction was conducted in lower temperature, it proceeded smoothly with a lower reaction yield (Table 1, entry 14, 110 °C, 69%). Surprisingly, a higher reaction temperature did not increase the yield (Table 1, entry 14, 150 °C, 77%).

Table 3 Palladium catalyzed cascade reactions of coumarins **1b–o** with diphenylacetylene **2a**[a]

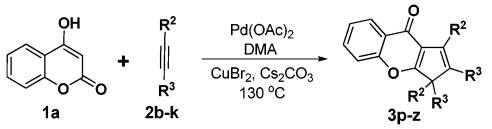


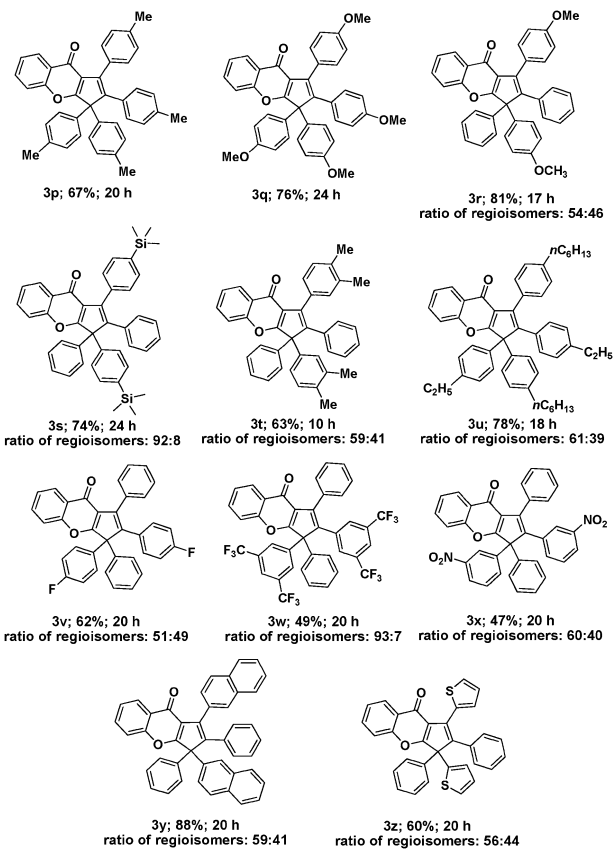


[a] Reaction conditions: **1b–o** (1.0 equiv.), **2a** (5.0 equiv.), 10 mol% $Pd(OAc)_2$, Cs_2CO_3 (2.0 equiv.), $CuBr_2$ (2.0 equiv.), DMA (2 mL), 130 °C.

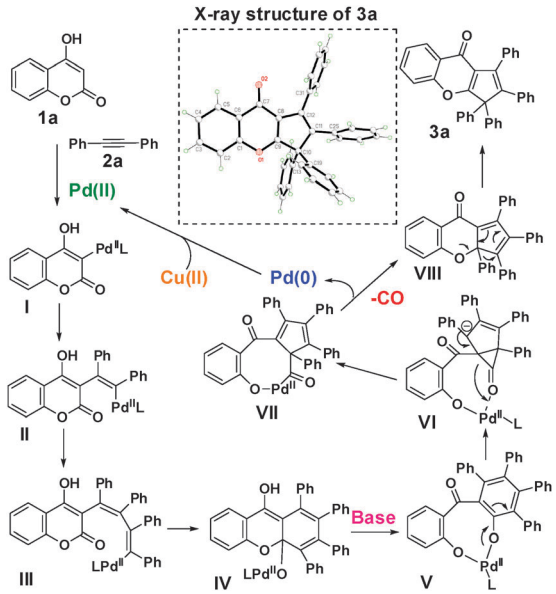
With the optimized conditions in hand, we decided to explore the scope of this unprecedented cascade reaction. The substrate scope of a $Pd(OAc)_2$ catalyzed cascade process of coumarins **1b–o** with diphenylacetylene **2a** is shown in Table 3 and it was found that a wide range of coumarines bearing an electron-donating group or electron-withdrawing group, as well as a naphthalene ring, afforded the desired highly substituted cyclopentadiene fused chromones **3b–o** in moderate to good yields (Table 3, 49–86%). Extension of the substrate scope was examined using a wide range of symmetric and asymmetric diarylacetylenes, as well as the heterocyclic ring involved asymmetric alkynes (Table 4). Moderate to high yields were observed within 24 h (Table 4, 47–88%). Notably, the electron-donating group involved diarylacetylenes gave higher yields (Table 4, **3p–u** and **3y**, 63–88%). On the other hand, the electron-withdrawing group involved diarylacetylenes led to lower yields (Table 4, **3v–x**, 47–62%). Moreover, the heterocyclic ring tolerated alkyne **2z** was also proved to be a good substrate to afford the desired product **3z** (Table 4, 60%, 20 h). Regarding the substrates of

Table 4 Cascade reactions of coumarins **1a** with alkynes **2b–k**[a]





[a] Reaction conditions: **1a** (1.0 equiv.), **2b–k** (5.0 equiv.), 10 mol% $Pd(OAc)_2$, Cs_2CO_3 (2.0 equiv.), $CuBr_2$ (2.0 equiv.), DMA (2 mL), 130 °C.



Scheme 1 Postulated catalytic pathway for a Pd-catalyzed cascade process.

asymmetric diarylacetylene (Table 4), two regioisomers were obtained with *ca.* 1 : 1 ratio (Table 4, **3r**, **3s–v**, and **3x–z**). Interestingly, if the phenyl ring bearing two CF_3 groups on the *meta* position or the TMS group on the *para* position, an excellent ratio of regioisomers could be achieved (Table 4, **3s** and **3w**, ratio of regioisomers: 92 : 8 and 93 : 7, respectively).

Our postulated reaction pathway is summarized in Scheme 1. In the initial step, a regioselective direct electrophilic aromatic palladation at the 3-position of the coumarin forms a palladium complex **I**. The subsequent insertion of two diphenylacetylene molecules forms a dienylpalladium intermediate **III**, which will then undergo intramolecular 6-*exo*-dig insertion into coumarin leads to a polycyclic palladium intermediate **IV**. Subsequent trapping by the OH group from coumarin generated intermediate **V**. Intermediate **V** undergoes a set of rearrangements to offer a cyclopentadiene fused intermediate **VII**. The intermediate **VII** is transferred to intermediate **VIII** *via* reductive elimination and Pd^0 is reoxidized by $CuBr_2$ to regenerate the Pd^{II} catalyst for the next catalytic cycle. Finally, the desired product **3a** is obtained *via* a phenyl ring migration. The configuration of the compound was determined by X-ray crystal structure analysis of a suitable single crystal (Scheme 1, product **3a**) (see ESI†).

In summary, we have disclosed an unprecedented palladium-catalyzed cascade reaction between coumarins and alkynes. The coupling of coumarins with alkynes in the presence of $Pd(OAc)_2$ enabled us to trigger a cascade process to furnish the highly substituted cyclopentadiene fused chromone framework in moderate to high chemical yields (47–88%).

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