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**COMMUNICATION**

# Synthesis of isochromenones and oxepines *via* Pd-catalyzed cascade cyclization of alkynes and benzynes involving C–H activation†

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**A new method for the synthesis of various isochromen-6-ones and phenanthro[1,10-*bc*]oxepines *via* a palladium-catalyzed cascade carbocyclization of 2-iodobenzyl-3-phenylpropiolates and 1-iodo-2-(2-(phenylethynyl)benzyloxy)benzenes with arynes is described. The reactions involve interesting biscarbocyclization of alkynes and benzynes and C–H bond activation.**

Aryne is one of the most interesting substrates in metal-catalyzed reactions since it can be transformed into a wide range of synthetically important intermediates in organic synthesis.[1,2] In particular, palladium-catalyzed carbocyclization of arynes has great potential for the synthesis of polycyclic compounds from simple starting materials.[3]

The palladium-catalyzed carbocyclization of alkynes or alkenes is a useful method for multiple carbon–carbon bond formation reaction in organic synthesis. In 1982, Catellani and Chiusoli reported carbocyclization of aryl iodides with two norbornenes to give methanotriphenylene derivatives.[4] Heck *et al.* and Nomura *et al.* independently reported that the cocyclotrimerization of aryl halide with two alkynes leads to tetrasubstituted naphthalene derivatives.[5a,b] Apart from alkynes, arynes are also interesting substrates in carbocyclization reaction. In this context, the metal-catalyzed cyclotrimerization of arynes[6a,b] and the cocyclizations of arynes with a variety of alkynes,[6c,d] diynes,[6e] allyl derivatives,[2h,i,6f,g] allenes,[6h] and CO[6i,j] have been extensively investigated. Larock *et al.* reported a partial intermolecular carbocyclization of 2-halobiaryl with arynes affording triphenylene.[7] Previously, we have reported a palladium-catalyzed intermolecular carbocyclization of aromatic halide with two benzynes leading to the formation of triphenylene[8a] and aryliodides/bicyclic alkene/benzyne to give annulated 9,10-dihydrophenanthrenes.[8b] In 2007, Larock and Liu reported the synthesis of substituted phenanthrene derivatives *via* palladium-catalyzed sequential intermolecular coupling of aryl halides, alkynes, and arynes.[9] Recently, Zhang *et al.* demonstrated a palladium-catalyzed reaction of arynes and 1-(2-bromophenyl)-1*H*-indoles, which allows an efficient synthesis of indolo[1,2-*f*]-phenanthridine.[10] All of the above carbocyclization reactions involve C–H bond functionalization and form two,[11] three,[12] or four carbon–carbon bonds[13] in a one-pot manner, but lead only to monocyclized products. The carbocyclization reaction involving a biscyclization process has been less explored. Grigg *et al.* reported a palladium-catalyzed intramolecular bis- or triscyclization of aryl or alkenyl halides bearing carbon–carbon multiple bonds for the synthesis of highly fused heterocyclic compounds.[14] In 2005, Tanaka *et al.* reported a tandem biscyclization of bromoenynes through intramolecular carbopalladation and functionalization of an aromatic C–H bond.[15] We have been interested in C–H bond activation,[16a–c,20d,e] carbocyclization[16c–f] and benzyne reaction.[2f–h,k–m] In this communication, we wish to report a new palladium-catalyzed reaction, which combines these three reactions in one pot, the biscarbocyclization of 2-iodobenzyl-3-phenylpropiolates and 1-iodo-2-(2-(phenylethynyl)benzyloxy)benzenes with benzynes to give isochromenone and oxepine derivatives, respectively. It is noteworthy that the isochromenone and oxepine cores are present in various natural products and biologically active compounds.[17]

Treatment of 2-iodobenzyl-3-phenylpropiolate **1a** and benzyne precursor **2a** in the presence of Pd(dba)$_2$ (5 mol%), CsF (4 equiv.) and Tl(OAc) (1.2 equiv.) in a 1 : 1 mixture of CH$_3$CN and toluene at 85 °C for 8 h gave the expected isochromenone product **3a** in 76% isolated yield (Table 1, entry 1). Product **3a** was thoroughly characterized by $^1$H and $^{13}$C NMR and mass spectral analysis.

Under the same reaction conditions, various substituted benzyne precursors **2b–d** were tested for the reaction with **1a** affording the corresponding phenanthroisochromen-6-ones, **3b–d**, in 56–82% yield, respectively (entries 2–4). The effect of substituents on the benzylic group was also investigated. Thus, alkyne **1b** reacted well with **2a** and **2b** to give **3e** and **3f** in 79% and 87% yields, respectively (entries 5 and 6). It is noteworthy that the structure of compound **3f** was further confirmed by single crystal X-ray diffraction. In a similar manner, alkyne **1c** also reacted with **2a** and **2b** to provide **3g** and **3h** in 75% and 80% yields, respectively (entries 7 and 8).

The present palladium-catalyzed carbocyclization reaction was also successfully extended to the synthesis of oxepine derivatives. The results of these studies are listed in Table 2. Thus, **1d** reacted with benzyne precursor **2a** to give phenanthro-[1,10-*bc*]oxepine derivative **4a** in 78% yield (Table 2, entry 1). Under similar reaction conditions, treatment of alkyne **1d** with

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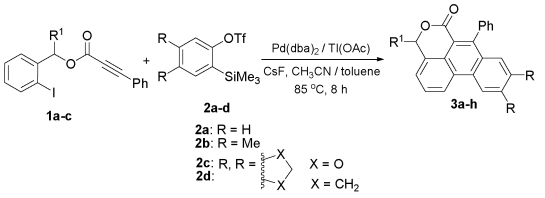
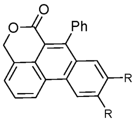
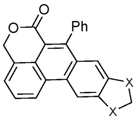
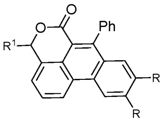
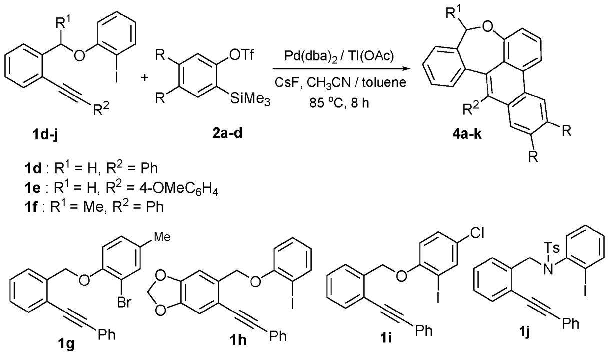
**Table 1** Results of the reaction of alkynes **1a–c** with arynes **2**[a]



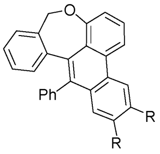
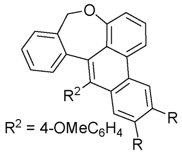
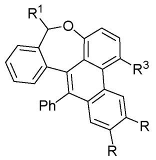
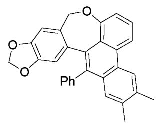
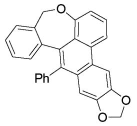
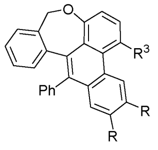
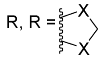
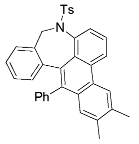
| Entry | 1 | 2 | Product | | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | **1a** | **2a** |  | **3a**: R = H | 76 |
| 2 | **1a** | **2b** | | **3b**: R = Me | 82 |
| 3 | **1a** | **2c** |  | **3c**: X = O | 56 |
| 4 | **1a** | **2d** | | **3d**: X = $CH_2$ | 74 |
| 5 | **1b** | **2a** |  | **3e**: R = H, $R^1$ = Me | 79 |
| 6 | **1b** | **2b** | | **3f**: R = Me, $R^1$ = Me | 87 |
| 7 | **1c** | **2a** | | **3g**: R = H, $R^1$ = Ph | 75 |
| 8 | **1c** | **2b** | | **3h**: R = Me, $R^1$ = Ph | 80 |

[a] Unless otherwise mentioned, all reactions were carried out using alkyne **1** (1.0 mmol), benzyne precursors **2** (1.2 mmol), $Pd(dba)_2$ (5 mol%), CsF (4 equiv.) and 1.2 equiv. Tl(OAc) in $CH_3CN$–toluene (3.0 mL, 1 : 1 mixture) at 85 °C for 8 h. [b] Isolated yields.

**Table 2** Results of the reaction of alkynes **1d–j** with arynes **2**[a]



**1d** : $R^1$ = H, $R^2$ = Ph
**1e** : $R^1$ = H, $R^2$ = 4-OMe$C_6H_4$
**1f** : $R^1$ = Me, $R^2$ = Ph

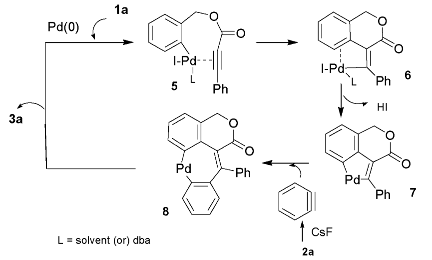
| Entry | 1 | 2 | Product | | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | **1d** | **2a** |  | **4a**: R, R = H | 78 |
| 2 | **1d** | **2b** | | **4b**: R, R = Me | 86 |
| 3 | **1e** | **2a** |  $R^2$ = 4-OMe$C_6H_4$ | **4c**: R, R = H | 80 |
| 4 | **1e** | **2b** | | **4d**: R, R = Me | 82 |
| 5 | **1f** | **2b** |  | **4e**: R, R, $R^1$ = Me, $R^3$ = H | 75 |
| 6 | **1g** | **2b** | | **4f**: R, R, $R^3$ = Me, $R^1$ = H | 77[c] |
| 7 | **1h** | **2b** |  | **4g** | 80 |
| 8 | **1d** | **2c** |  | **4h** | 79 |
| 9 | **1i** | **2b** |  | **4i**: R = Me, $R^3$ = Cl | 76 |
| 10 | **1i** | **2d** | | **4j** R, R =  X = $CH_2$ <br> $R^3$ = Cl | 85 |
| 11 | **1j** | **2b** |  | **4k** | 80 |

[a] Unless otherwise mentioned, all reactions were carried out using alkyne **1** (1.0 mmol), benzyne precursors **2** (1.2 mmol), $Pd(dba)_2$ (5 mol%), CsF (4 equiv.) and 1.2 equiv. Tl(OAc) in $CH_3CN$–toluene (3.0 mL, 1 : 1 mixture) at 85 °C for 8 h. [b] Isolated yields. [c] 5 mol% of P-(*o*-tolyl)$_3$ was added.

aryne precursors **2b** having two methyl groups on the phenyl ring afforded **4b** in 86% yield (entry 2). Similarly **1e** reacted with arynes **2a** and **2b** to give **4c** and **4d** in 80 and 82% yield, respectively (entries 3 and 4). It is noteworthy that the structure of compound **4c** was further confirmed by single crystal X-ray diffraction. The reaction of **1f** with **2b** also proceeded smoothly to give **4e** in 75% yield (entry 5). In addition to iodoalkynes, bromoalkyne **1g** also reacted successfully with **2b** affording **4f** in 77% yield (entry 6). In this reaction, additional 5 mol% of P(*o*-tolyl)$_3$ was required to achieve a good yield of **4f**. Interestingly, alkyne **1h** also reacted efficiently with **2b** to provide oxepine derivative **4g** in 80% yield (entry 7).

The present catalytic reaction was also successfully extended to different aryne precursors **2c–d**. As a result, electron-donating substituent aryne **2c** reacted with **1d** and **1i** to give the corresponding oxepine derivatives **4h** and **4i** in 79 and 76% yield, respectively (entries 8 and 9). Similarly, aryne **2d** reacted efficiently with **1i** to give **4j** in 85% yield (entry 10). Further, **1j** was treated with **2b** under similar reaction conditions to afford the expected azepine derivative **4k** in 80% yield (entry 11).

On the basis of known palladium-catalyzed carbocyclization reactions,[2–8] a mechanism is proposed to account for the present catalytic reaction (Scheme 1). The first step involves oxidative addition of **1a** to the Pd(0) species to form aryl palladium π-complex **5**, followed by insertion of the Pd–C bond into the triple bond in **5** to form vinylarylpalladium species **6**, in which the aryl group is $\eta^2$-bonded to the palladium center. It is well-known that $\eta^2$-arene complexes are intermediates in the C–H bond activation of arene systems.[18] Cyclopalladation through intramolecular C–H bond activation affords a five membered palladacycle **7**. Further reaction of this intermediate with benzyne and the subsequent cyclopalladation



Scheme 1

form a seven-membered palladacycle **8**. A second cyclization occurred *via* reductive elimination of **8** to give product **3a** and the Pd(0) catalyst.

The role of the TlOAc is unclear at this moment, but it may be involved in removing the iodide from the palladium center.[19] In addition, it would not oxidize Pd(0) generated during the catalytic reaction. Although silver salts are also well known halide scavengers, the use of silver(I) salts such as $AgBF_4$, $AgNO_3$ or AgOAc to replace TlOAc did not lead to the expected product. This is likely due to the ability of $Ag^+$ to oxidize Pd(0) to Pd(II)[20] terminating the oxidative addition step in the catalytic reaction (Scheme 1).[20]

In conclusion, we have developed a new palladium-catalyzed carbocyclization reaction involving biscyclization of alkynes and benzynes to afford isochromen-6-one and phenanthro[1,10-*bc*]-oxepine derivatives in good to excellent yields. Further studies on the mechanistic details as well as potential synthetic applications of the present methodology are underway.

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