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Palladium-catalyzed annulation of benzynes with *N*-substituted-*N*-(2-halophenyl)formamides: synthesis of phenanthridinones[†]

Yuan Yang,^a Hui Huang,^a Lijun Wu^a and Yun liang*^{a,b}

A novel and efficient procedure for the synthesis of *N*-substituted phenanthridinones *via* palladium-catalyzed annulation of benzynes with *N*-substituted-*N*-(2-halophenyl)formamides has been developed. This methodology constructs two new C-C bonds *via* an arylation/annulation process, and provides the desired products in good yields.

Phenanthridinones are one of the important classes of heterocycles in a myriad of bioactive natural products and pharmaceutical molecules.¹ As a result, considerable efforts were directed toward the development of efficient methods for their synthesis.³⁻⁹ Among them, the palladium-based methodologies² have been used as an important synthetic tool for the synthesis of phenanthridinones because of their functional group tolerance, stereo- and regioselectivity and significant yields under mild reaction conditions. Recently, most of these approaches have focused on: (1) palladium-catalyzed intramolecular C-C bond formation through annulation of N-(2haloaryl)benzamides or C-H bond functionalization of N-arylbenzamides;⁷ (2) palladium-catalyzed intramolecular C-N bond formation of biarylcarboxyamides;8 (3) palladiumcatalyzed intermolecular C-C and C-N bond formation through sequential aryl-aryl and N-aryl coupling;⁹ (4) palladium-catalyzed $C(sp^2)$ -H aminocarbonylation of *o*-arylanilines.¹⁰ However, the approach of palladium-catalyzed double C-C bond formation to synthesize phenanthridinones has never been reported. To enrich synthetic methods of phenanthridinones, we envisioned that phenanthridinones could be prepared by simultaneously constructing two C-C bonds (Scheme 1).

Arynes have been attracting considerable attention since 2-(trimethylsilyl)aryl triflates, aryne precursors, were first



Scheme 1 Methods for the synthesis of phenanthridinones.

reported by Kobayashi.^{11,12} The carboannulations of arynes have become an important methodology for constructing a variety of carbocycles and heterocycles.^{12*a*} Especially, palladium-catalyzed annulations of arynes displayed particular efficiency for the construction of these cycles.^{13,14} We were also interested in this synthetic strategy, and have successfully synthesized 6*H*-benzo[*c*]chromenes,^{14*a*} 1*H*-inden-1-ones,^{14*b*} and phenanthrenes^{14*c*} through formation of multiple C–C bonds. In the persistent research, we found that benzynes and *N*-substituted-*N*-(2-halophenyl)formamide undergo a cascade

^aNational & Local Joint Engineering Laboratory for New Petro-chemical Materials and Fine Utilization of Resources, Key Laboratory of Chemical Biology and Traditional Chinese Medicine Research, Ministry of Education, Hunan Normal University, Changsha, Hunan 410081, China. E-mail: yliang@hunnu.edu.cn; Fax: +86(0731)88872533

^bBeijing National Laboratory for Molecular Sciences, Beijing, 100871, China †Electronic supplementary information (ESI) available. See DOI: 10.1039/ c4ob00997e





process to afford phenanthridinones. To the best of our knowledge, this is the first example of synthesis of phenanthridinones from benzynes and aryl halides by sequential double C–C bond formation.

Initially, the reaction of N-benzyl-N-(2-iodophenyl)formamide 1a with 2-(trimethylsilyl)phenyl triflate 2a, a benzyne precursor, was chosen as a model reaction to optimize the reaction conditions (Table 1). Our investigation started with an attempted annulation of the substrate 1a with 2a in 2 mL of 1:1 MeCN-toluene at 110 °C in the presence of $Pd(OAc)_2$ and $P(o-tolyl)_3$ (entry 1). To our delight, the desired product 3a could be isolated in 93% yield. This result encouraged us to develop an efficient method for the synthesis of phenanthridinone. A variety of palladium catalysts, such as Pd(OAc)₂, PdCl₂, $Pd(PPh_3)_4$, and Pd_2dba_3 , were investigated (entries 2-4), and the results demonstrated that $Pd(OAc)_2$ as a catalyst displayed the highest efficiency in this reaction. In order to check the effects of ligands, no ligand and a series of ligands, including P(o-tolyl), PPh₃, Xantphos, PCy₃ and dppp, were examined (entries 5–9). The ligand of $P(o-tolyl)_3$ achieved the best result. Then, the effects of the solvent were also screened (entries 10 and 11). No desired product 3a was observed when using toluene as the medium, and only 48% yield of 3a was obtained when using MeCN as the medium. Finally, the reaction temperature was evaluated (entry 12), and the reaction was less effective at 80 °C. Therefore, the optimized reaction conditions were as follows: 1a (0.3 mmol), 2a (0.36 mmol), Pd(OAc)₂ (5 mol%), P(o-tolyl)₃ (10 mol%), CsF (0.9 mmol), in MeCNtoluene (1:1, 2 mL) at 110 °C.

With the optimal reaction conditions in hand, various *N*-(2-iodophenyl)formamides were employed to react with 2-(trimethylsilyl)phenyl triflate **2a** under the standard reaction

Table 2 Palladium-catalyzed annulation of *N*-substituted-*N*-(2-halo-phenyl)formamides (1) with o-silyl phenyltriflate $(2a)^{a,b}$



^{*a*} Reaction conditions: **1** (0.3 mmol), **2** (0.36 mmol), $Pd(OAc)_2$ (5 mol %), $P(o-tol)_3$ (10 mol%), CsF (0.9 mmol), MeCN-toluene (1:1, 2 mL), 110 °C, under a N₂ atmosphere. ^{*b*} Isolated yields. ^{*c*} *N*-Benzyl-*N*-(2-iodophenyl)formamide was replaced by *N*-benzyl-*N*-(2-bromophenyl)-formamide.

conditions, and the results are summarized in Table 2. Various phenanthridinones (Type I–V) were obtained in good to perfect yields. For Type I (\mathbb{R}^1 = benzyl), the phenyl ring could be substituted with either an electron-donating group such as methyl (**1b**) or electron-withdrawing groups such as COOMe and NO₂ (**1c** and **1d**). *N*-(2-Iodophenyl)-*N*-(4-methylbenzyl)formamide and *N*-(2-iodophenyl)-*N*-(4-nitrobenzyl)formamide, for example, were treated with 2-(trimethylsilyl)phenyl triflate **2a**, furnishing the corresponding products **3b** and **3d** in 88% and 85% yield respectively. Furthermore, 5-(naphthalen-2-ylmethyl)phenanthridin-6(*5H*)-one was obtained in 89% yield. For Type II (\mathbb{R}^1 = alkyl), similarly, *N*-alkyl phenanthridinones **3f–3h** could be obtained in good to high isolated yields. However, for Type III, the yields of the corresponding products **3i** and **3j** from *N*-aryl-*N*-(2-iodophenyl)formamide were decreased.

For instance, 5-phenylphenanthridin-6(5H)-one 3i was only obtained in 60% yield. Subsequently, we also examined a series of substituted N-benzyl-N-(2-iodophenyl)formamides (Type IV). Substituted N-benzyl-N-(2-iodophenyl)formamide with either electron-withdrawing groups such as fluoro, chloro, cvano, and trifluoromethyl groups (3k-3n and 3p) or an electron-donating group such as the methyl group (30) on the benzene rings were all well-tolerated under the reaction conditions and proceeded with almost equal efficiency. These results indicated that the electronic effect on the benzene ring did not play a significant role in regulating the reaction, and revealed the inherent high reactivity of N-benzyl-N-(substituted-2-iodophenyl)formamides. Finally, we investigated the reactivity of N-benzyl-N-(2-bromophenyl)formamide, affording the corresponding product 3a in 88% yield (Type V). Compared with N-benzyl-N-(2-iodophenyl)formamide, the yield of 3a was decreased slightly. The possible reason was that the reactivity of oxidative addition of $Pd(0)L_n$ with the C–Br bond was lower than that with the C-I bond.

To expand the scope of this methodology, a set of substituted *o*-silyl aryltriflates **2b–2e** reacted with *N*-benzyl-*N*-(2iodophenyl)formamide **1a**, CsF, Pd(OAc)₂ and P(*o*-tolyl)₃ was examined (Table 3). The *o*-silyl aryltriflates **2b** and **2c**, bearing alkyl groups on the aryl moiety, afforded the target products in 83% and 91% yields. However, the reaction of *o*-silyl aryltriflates **2d** and **2e** bearing two fluoro groups or a chloro group with *N*-benzyl-*N*-(2-iodophenyl)formamide **1a** was conducted in 24% and 32% yields. Among these substituted *o*-silyl aryltriflates, substrates **2c** and **2d** provided two regioisomers, respectively, in a **1.1**: 1 ratio and a **1.6**: 1 ratio. The lack of regioselectivity of the reaction is consistent with insertion of unsymmetrical benzyne into a palladium–carbon bond. These results clearly support that the reaction takes place through a benzyne mechanism.

On the basis of the present results and the reported mechanism,^{13–15} a possible mechanism is proposed as outlined in Scheme 2. First, oxidative addition of $Pd(0)L_n$ with *N*-substituted-*N*-(2-iodophenyl)formamide **1** affords intermediate **A**. Insertion of a benzyne into intermediate **A** forms intermediate **B**. Subsequently, the phenanthridinone synthesis proceeds from intermediate B through either of possible pathways: one pathway involves addition of intermediate **B** itself to the carbonyl group¹⁶ and a following β -hydride elimination to give the desired product **3** (path a), and the other pathway is oxidative addition of intermediate **C** provides the desired product and regenerates the Pd(0) catalyst (path b).

In summary, we have developed a high-efficiency method for the synthesis of *N*-substituted phenanthridinones by palladium-catalyzed annulation of benzynes with *N*-substituted-*N*-(2-halophenyl)formamide. In the reaction, double C–C bonds are formed *via* an arylation/annulation process, and the corresponding products are obtained in good yields. In addition, the reaction has been proved to be tolerant of a wide variety of functional groups. Work to probe the detailed mechanism and apply the reaction in organic synthesis is currently ongoing. Table 3Palladium-catalyzed annulation of N-benzyl-N-(2-iodophenyl)-formamide (1a) with the o-silyl aryltriflates $(2)^a$





^{*a*} Reaction conditions: **1a** (0.3 mmol), **2** (0.36 mmol), Pd(OAc)₂ (5 mol %), P(*o*-tol)₃ (10 mol%), CsF (0.9 mmol), MeCN-toluene (1:1, 2 mL), 110 °C, 18 h, under a N₂ atmosphere. ^{*b*} Isolated yields.



Scheme 2 Possible mechanism for the reaction.

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