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Palladium-Catalyzed Annulation of Arynes by *ortho*-Halobenzamides: Synthesis of Phenanthridinones

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Abstract

The palladium-catalyzed annulation of arynes by substituted *o*-halobenzamides produces *N*-substituted phenanthridinones in good yields. This methodology provides this important heterocyclic ring system in a single step by simultaneous C-C and C-N bond formation, under relatively mild reaction conditions, and tolerates a variety of functional groups.

Introduction

Phenanthridinones are important subunits found in many compounds possessing interesting biological and pharmaceutical activities. They have been used as PARP inhibitor anticancer drugs,¹ and as neurotrophin activity enhancers for the treatment of nerve diseases.² One of the traditional approaches for the synthesis of phenanthridinones is through reductive cyclization of the corresponding nitro-carbonyl-biphenyls.³ However, traditional preparations of the starting nitro-carbonyl-biaryls by Ullmann coupling or the nitration of biaryls⁴ require either harsh reaction conditions or exotic functionalized arenes, significantly limiting the broad application of this approach. Other common approaches to phenanthridinones include the Schmidt/Beckmann rearrangement of fluorenone derivatives that are not all that readily available,^{4g,5} and the photochemical rearrangement of 2-halobenzamides.⁶ There are also reports of phenanthridinone synthesis involving aryne generation under harsh basic conditions and subsequent intramolecular cyclization.⁷

Transition metal-catalyzed annulation reactions are tremendously valuable in organic synthesis.⁸ Among such processes, palladium-mediated reactions are by far the most powerful in constructing carbocycles and heterocycles,⁹ due to the high efficiency with which they construct C-C and C-X (X = O, N) bonds¹⁰ and their high compatibility with functional groups. For example, some phenanthridinone derivatives have been synthesized by palladium-catalyzed intramolecular or intermolecular cyclization processes of aryl halides and amides,¹¹ or by oxidative *ortho*-arylation of benzanilides.¹²

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Supporting Information

¹H and ¹³C NMR data for compounds. This material is available free of charge via the Internet at <http://pubs.acs.org/>.

Since a convenient approach to aryne generation by the fluoride-induced 1,2-elimination of *o*-(trimethylsilyl)aryl triflates was first reported,¹³ arynes have attracted considerable attention.¹⁴ The high electrophilicity of arynes has been used extensively in the construction of many heteroaromatic structures *via* annulation reactions.¹⁵ To take further advantage of aryne chemistry, many metal-catalyzed coupling¹⁶ and annulation reactions¹⁷ of arynes have been explored. In our group, we have been especially interested in the palladium-catalyzed annulation of arynes.¹⁸

Herein, we report the palladium-catalyzed annulation of arynes by substituted *o*-halobenzamides to produce *N*-substituted phenanthridinones in good yields. In this reaction, C-C and C-N bonds are formed simultaneously to generate this important heterocyclic ring system.

Results and Discussion

Optimization Studies

We attempted to optimize the reaction of *N*-ethyl-2-bromobenzamide (**1a**) and the benzyne precursor *o*-(trimethylsilyl)phenyl trifluoromethanesulfonate (**2a**) in 4:1 toluene/acetonitrile with CsF as the fluoride source (Table 1). In all cases, the cyclotrimerization side product **4a**¹⁹ and the desired benzyne annulation product **3a** were observed.

Optimization work was conducted with respect to different palladium catalysts, ligands, solvent ratios and temperatures (Table 1). Without any ligand, palladium black precipitated out very quickly with only a trace amount of the desired product being formed and the aryl halide **1a** was left in large amounts (entry 1). Simple triphenylphosphine ligand did not improve the yield (entry 2). Both tri(*o*-tolyl)phosphine and *o*-(dicyclohexylphosphino)biphenyl ligands increased the yield to ~50% (entries 3 and 7). Several bidentate ligands have also been examined (entries 4–6). Among them, dppm proved the most efficient, producing lactam **3a** in a 66% yield, although 10 mol % of ligand seemed necessary to obtain a decent yield (entry 8). Besides examining the effect of the ligand on the yield, several bases have also been tested in this reaction (entries 9–12). The results indicate that with 1.0 equiv of Na₂CO₃, a 73% yield of the desired product can be achieved (entry 9). Other bases gave lower yields (entries 10–11). Based on our previous experience, the solvent can often prove critical for palladium-catalyzed aryne reactions, mostly because the aryne is generated at substantially different rates in different solvents.¹⁷ With a toluene/acetonitrile mixed solvent and CsF as the fluoride source, benzyne is generated more slowly in mixtures with less acetonitrile, because CsF has a lower solubility in toluene. Thus, the solvent ratio was examined and 4:1 toluene/acetonitrile afforded the best result (compare entries 9, 13 and 14). With a 3:1 ratio, more of the trimer **4a** is formed; with a 6:1 ratio, the benzyne is generated too slowly, giving a lower yield of the desired product.

An effort was made to lower the temperature and the benzyne precursor loading (entries 15 and 16), but it appears that 110 °C and 2 equiv of the benzyne precursor, plus 5 equiv of CsF, are necessary in order to obtain a high yield. Several other palladium catalysts, including PdCl₂(MeCN)₂ (63%), Pd(dba)₂ (65%) and Pd(PPh₃)₄ (61%), have also been examined in this process, but none proved better than Pd(OAc)₂. We have chosen the reaction conditions reported in entry 9 of Table 1 as our optimal conditions.

Based on our experimental results and previous experience with related processes,¹⁸ we propose that this phenanthridinone synthesis proceeds through either of the possible pathways shown in Scheme 1.

One possible pathway proceeds by the oxidative cyclization of Pd(0) with the aryne generated from the silyl triflate to form the palladacycle **I** (path a).²⁰ Oxidative addition of **1a** to this palladacycle forms the Pd(IV) intermediate **II**. Reductive elimination gives rise to the arylpalladium(II) intermediate **III**. However, we cannot rule out the possibility that Pd(0) inserts directly into the C-Br bond of **1a** to form the intermediate **IV**, which then undergoes carbopalladation of the aryne to give rise to intermediate **III**²¹ (path b). Regardless of how the intermediate **III** is formed, under the basic conditions, it is expected to cyclize to the intermediate **V**. Finally, through reductive elimination the desired product **3a** can be generated, alongside Pd(0), which can reenter the catalytic cycle. There does not appear to be any particular evidence favoring either of these pathways.

Reaction Scope and Limitations

To test the scope and limitations of this reaction, we have examined a variety of substituted 2-halobenzamides and the results are summarized in Table 2. Different amide nitrogen substituents, including alkyl (entries 1–4), allyl (entry 5), phenyl (entry 6) and benzyl groups (entries 7–10), have been examined. Among them, excellent yields were achieved for *N*-primary and secondary alkyl (entries 1–3) substituted amides, as well as *N*-benzyl substituted amides (entries 7–10). The analogous amide with an *N*-*t*Bu (entry 4) afforded a lower yield presumably due to the steric hindrance of the *t*Bu group. The presence of an *N*-allyl group (entry 5) also caused complications - the reaction looked messier on the TLC plate than the parent system (**1a**) with a resulting lower yield. Aryl-substituted amide **1f** produced some uncharacterized products, which overlapped with the starting amide left on the TLC plate (entry 6). The reaction was also performed using the 2-iodobenzamide **1k** (entry 11), where a much lower yield was obtained than the corresponding bromobenzamide **1g**. Although for most palladium-catalyzed reactions of aryl halides, aryl iodides provide better results than the corresponding aryl bromides, because the oxidative addition of Pd(0) to the aryl halide is easier and faster (see the later mechanistic discussion), there are several publications where the same halide effect as seen here has been reported and mechanistic studies on such reactions have been conducted.²² The reason for this halogen effect is not clear. However, we have observed that palladium precipitates out more quickly with a lower conversion and more side products in the reaction of **1k** than in the reaction of **1g**.

To further test the scope and limitations of the reaction, we examined a variety of 2-bromobenzamides with various functional groups (entries 12–22). Amides with slightly electron-donating methyl groups at the 3 (entry 14), 4 (entry 12), and 5 (entry 13) positions generally afforded excellent yields of above 70%, although **1n** provided a slightly lower yield than the others presumably due mainly to the steric hindrance of the methyl group during oxidative addition of the carbon-halogen bond to the palladium catalyst. Strong electron-donating methoxy groups also did not lower the yield significantly and yields above 70% were generated from **1o** and **1p**, which suggested that the oxidative addition of the aryl bromide to Pd(0) is not very difficult under these reaction conditions. Halogens, such as F (entries 19 and 20) and Cl (entry 17), were well tolerated in these reactions, providing good yields of the corresponding amides.

α -Bromobenzamides with electron-withdrawing groups, including CF₃ (entry 18), NO₂ (entry 21) and an amide group (entry 22), were also tested and lower yields were obtained when compared to **1g**. The reason for this decrease can be explained as follows. Although the electron-withdrawing nature of these functional groups facilitates oxidative addition of the carbon-bromine bond in the amide to Pd(0), it at the same time decreases the nucleophilic nature of the nitrogen in the amide, which is critical for the cyclization step (see the later mechanistic discussion).

In addition to these *N*-benzyl-2-bromobenzamide derivatives, the pyridine-derived amide **1w** has also been examined, but only a 36% yield of the desired product was isolated, which may be caused by deactivation of the Pd catalyst through strong coordination of the nitrogen in the pyridine to Pd.

This reaction was also applied to 2-bromobenzamide (**1x**, entry 24) and *N,N*-dimethyl-2-bromobenzamide (**1y**, entry 25). Both amides **1x** and **1y** remained in the reaction system in very large amounts after the reaction and neither of the desired products was observed. The reason for the failure of these two reactions may not, however, be the same. In the reaction of amide **1x**, strong coordination of the NH₂ group with the Pd in either complex **III** or **IV** (see Scheme 1) may inhibit the cyclization; while, in amide **1y**, two methyl groups on the nitrogen prohibit nucleophilic attack of the nitrogen on the Pd in complex **III** (see the step from **III** to **V** in Scheme 1).

In addition to the silylphenyl triflate **2a**, other aryne precursors have also been examined as an annulation partner in our methodology (Table 3). The 4,5-dimethylbenzyne precursor **2b**, the 4,5-dimethoxybenzyne precursor **2c** and the 4,5-difluorobenzyne precursor **2d** have all been examined under our annulation conditions. They formed the expected annulation products **3gb**, **3gc** and **3gd** respectively, not surprisingly, with lower yields compared to benzyne precursor **2a** (Table 2, entries 1–3). This may be due to either the slower rate of generation of the arynes or the lack of stability of these arynes, as has been suggested by earlier work in our group.^{18d,e}

Conclusions

In summary, we have developed a novel synthesis of phenanthridinones, which involves the palladium-catalyzed annulation of arynes by 2-halobenzamides. This method provides an efficient synthesis of substituted phenanthridinones from readily available starting materials. Our process has been shown to be tolerant of a wide variety of functional groups, which makes further elaboration possible.

Experimental Section

General

The ¹H and ¹³C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. All melting points are uncorrected. High resolution mass spectra (HRMS) were obtained using EI at 70 eV (TOF) or using an Agilent QTOF 6540 mass spectrometer (APCI at 70 eV). All reagents were used directly as obtained commercially unless otherwise noted. All reactions were carried out in oven-dried glassware and monitored by thin layer chromatography (SiO₂, hexanes or hexanes/EtOAc). THF was distilled over Na. The silylaryl triflate **2a**, CsF, TBAF solution (1M in THF) and acetonitrile were purchased from Sigma-Aldrich Co. The 4,5-dimethyl-substituted silylaryl triflate **2b**, the 4,5-dimethoxy-substituted silylaryl triflate **2c** and the 4,5-difluoro-substituted silylaryl triflate **2d** were prepared according to a previous literature procedure.^{18e,23}

Non-commercially available compounds

Non-commercially available starting materials were prepared according to literature procedures.²⁴

***N*-Benzyl-2-bromo-5-methylbenzamide (1m).** White solid: mp 133–135 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.41–7.21 (m, 7H), 7.04 (dd, $J = 9.0, 3.0$ Hz, 1H), 6.47 (s, 1H), 4.59 (d, $J = 3.0$ Hz, 2H), 2.28 (s, 3H); ^{13}C NMR (300 MHz, CDCl_3) δ 167.8, 137.8, 137.7, 137.4, 133.2, 132.2, 130.3, 128.8, 128.1, 127.7, 115.9, 44.2, 20.9; HRMS (EI) calcd for $\text{C}_{15}\text{H}_{14}\text{NOBr}$: 303.0259, found 303.0265.

***N*-Benzyl-2-bromo-5-(trifluoromethyl)benzamide (1r).** White solid: mp 148–150 °C; ^1H NMR (300 MHz, d_6 -DMSO) δ 9.17 (t, $J = 6.0$ Hz, 1H), 7.93 (d, $J = 9.0$ Hz, 1H), 7.80 (s, 1H), 7.74 (dd, $J = 9.0, 3.0$ Hz, 1H), 7.42–7.25 (m, 5H), 4.50 (d, $J = 6.0$ Hz, 2H); ^{13}C NMR (300 MHz, d_6 -DMSO) δ 166.0, 139.9, 138.7, 134.1, 128.4, 127.4, 127.4, 127.0, 125.5, 125.4, 123.9, 121.9, 42.7; HRMS (EI) calcd for $\text{C}_{15}\text{H}_{11}\text{NOBrF}_3$: 356.9976, found 356.9973.

***N*-Benzyl-2-bromo-4-nitrobenzamide (1u).** White solid: mp 148–150 °C; ^1H NMR (300 MHz, CDCl_3) δ 8.42 (s, 1H), 8.17 (dd, $J = 9.0, 3.0$ Hz, 1H), 7.65 (d, $J = 9.0$ Hz, 1H), 7.37–7.26 (m, 5H), 6.39 (br s, 1H), 4.63 (d, $J = 6.0$ Hz, 2H); ^{13}C NMR (300 MHz, CDCl_3) δ 165.9, 148.7, 143.5, 137.1, 130.3, 129.1, 128.6, 128.2, 128.2, 122.7, 120.2, 44.6; HRMS (EI) calcd for $\text{C}_{14}\text{H}_{11}\text{N}_2\text{O}_3\text{Br}$: 333.9953, found 334.9960.

***N,N'*-Dibenzyl-2-bromo-1,4-benzenedicarboxamide (1v).** White solid: mp 219–221 °C; ^1H NMR (300 MHz, d_6 -DMSO) δ 9.28 (t, $J = 6.0$ Hz, 1H), 9.09 (t, $J = 6.0$ Hz, 1H), 8.18 (s, 1H), 7.95 (d, $J = 9.0$ Hz, 1H), 7.55 (d, $J = 9.0$ Hz, 1H), 7.41–7.25 (m, 10H), 4.49 (d, $J = 6.0$ Hz, 2H); ^{13}C NMR (300 MHz, d_6 -DMSO) δ 168.9, 164.2, 141.4, 139.3, 139.0, 136.3, 131.4, 128.8, 128.4, 128.4, 127.3, 126.9, 126.9, 126.6, 119.0, 42.8, 42.5; HRMS (EI) calcd for $\text{C}_{22}\text{H}_{19}\text{N}_2\text{O}_2\text{Br}$: 422.0630, found 422.0625.

General Procedure for the Palladium-Catalyzed Synthesis of Phenanthridinones The 2-bromobenzamide (**1a**) (0.25 mmol), the 2-(trimethylsilyl)aryl triflate (2.0 equiv), CsF (5.0 equiv), Na_2CO_3 (1.0 equiv), $\text{Pd}(\text{OAc})_2$ (5 mol %), dppm (10 mol %), 4 ml of toluene, and 1 ml of MeCN were placed in a 4 dram vial, and the vial was sealed. The reaction mixture was stirred first at room temperature for 1 min and then heated to 110 °C for 16–24 h. The mixture was allowed to cool to room temperature, diluted with ethyl acetate, washed with brine, dried over anhydrous MgSO_4 , and concentrated under reduced pressure. The product was isolated by flash chromatography on silica gel using hexanes/EtOAc as the eluent.

5-Ethylphenanthridin-6(5H)-one (3a). White solid (41.0 mg, 73%): mp 98–99 °C (lit.²⁵ mp 87–90 °C); ¹H NMR (300 MHz, d₆-acetone) δ 8.48–8.44 (m, 3H), 7.82 (td, *J* = 9.0, 3.0 Hz, 1H), 7.65–7.59 (m, 3H), 7.35–7.30 (m, 1H), 4.46 (q, *J* = 6.0 Hz, 2H), 1.35 (t, *J* = 6.0 Hz, 3H); ¹³C NMR (300 MHz, d₆-acetone) δ 160.4, 137.3, 133.8, 132.6, 130.0, 128.5, 128.0, 125.9, 123.9, 122.4, 122.2, 119.3, 115.7, 37.3, 12.4; HRMS (EI) calcd for C₁₅H₁₃NO: 223.0997, found 223.0995. The ¹H and ¹³C NMR spectral data are in good agreement with the literature data.²⁶

5-Isopropylphenanthridin-6(5H)-one (3b). White solid (41.4 mg, 70%): mp 99–101 °C; ¹H NMR (300 MHz, d₆-acetone) δ 8.44 (dd, *J* = 9.0, 3.0 Hz, 3H), 7.84–7.76 (m, 2H), 7.64–7.54 (m, 2H), 7.32 (t, *J* = 9.0 Hz, 1H), 5.42 (m, 1H), 1.68 (d, *J* = 9.0 Hz, 6H); ¹³C NMR (300 MHz, d₆-acetone) δ 162.5, 135.1, 133.8, 130.8, 129.6, 129.2, 128.0, 125.3, 123.5, 123.3, 121.1, 117.2, 49.1, 20.5; HRMS (EI) calcd for C₁₆H₁₅NO: 237.1154, found 237.1152.

5-Cyclohexylphenanthridin-6(5H)-one (3c). White solid (60.1 mg, 87%): mp 117–120 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.50 (d, *J* = 7.8 Hz, 1H), 8.23 (dd, *J* = 10.0, 7.5 Hz, 2H), 7.74–7.45 (m, 4H), 7.26 (t, *J* = 7.2 Hz, 1H), 2.72 (m, 2H), 2.00–1.76 (m, 6H), 1.56–1.36 (m, 3H); ¹³C NMR (300 MHz, CDCl₃) δ 162.2, 138.1, 133.7, 132.3, 129.1, 128.7, 128.0, 126.8, 123.7, 122.2, 121.5, 120.3, 115.9, 57.9, 29.3, 26.9, 25.7; HRMS (EI) calcd for C₁₉H₁₉NO: 277.1467, found 277.1465.

5-tert-Butylphenanthridin-6(5H)-one (3d). White solid (40.3 mg, 64%): mp 128–130 °C; ¹H NMR (300 MHz, d₆-acetone) δ 8.30–8.21 (m, 3H), 7.76–7.72 (m, 2H), 7.56 (t, *J* = 9.0 Hz, 1H), 7.42 (t, *J* = 9.0 Hz, 1H), 7.25 (td, *J* = 9.0, 3.0 Hz, 1H), 1.79 (s, 9H); ¹³C NMR (300 MHz, CDCl₃) δ 165.6, 138.1, 133.9, 132.1, 129.6, 127.9, 127.7, 126.8, 123.8, 122.7, 122.2, 121.5, 120.8, 60.7, 30.7; HRMS (EI) calcd for C₁₇H₁₇NO: 251.1310, found 251.1311.

5-Allylphenanthridin-6(5H)-one (3e). White solid (38.4 mg, 65%): mp 97–98 °C (lit.²⁷ mp 99 °C); ¹H NMR (600 MHz, CDCl₃) δ 8.60 (d, *J* = 8.0 Hz, 1H), 8.33 (dd, *J* = 8.3, 3.7 Hz, 2H), 7.81 (t, *J* = 7.6 Hz, 1H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 6.12–5.98 (m, 1H), 5.27 (d, *J* = 10.5 Hz, 1H), 5.20 (d, *J* = 17.3 Hz, 1H), 5.10 (d, *J* = 4.7 Hz, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 161.4, 137.3, 133.7, 132.6, 132.0, 129.5, 129.0, 128.0, 125.5, 123.3, 122.5, 121.7, 119.5, 117.0, 115.8, 45.1; HRMS (APCI) calcd for C₁₆H₁₄NO [M+H]⁺: 236.1070, found 236.1073.

5-Benzylphenanthridin-6(5H)-one (3g). Pale yellow solid (from **1g**: 58.5 mg, 82%; from **1k**: 27.4 mg, 38%): mp 126–129 °C (lit.²⁸ mp 112–113 °C); ¹H NMR (600 MHz, CDCl₃) δ 8.66 (d, *J* = 8.7 Hz, 1H), 8.35–8.27 (m, 2H), 7.82 (t, *J* = 7.6 Hz, 1H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 8.4 Hz, 1H), 7.36–7.23 (m, 7H), 5.70 (s, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 162.0, 137.3, 136.6, 133.9, 132.8, 129.6, 129.2, 128.8, 128.1, 127.2, 126.6, 125.4, 123.3, 122.6, 121.7, 119.6, 116.1, 46.5; HRMS (APCI) calcd for C₂₀H₁₆NO [M+H]⁺: 286.1226, found 286.1232. The ¹H and ¹³C NMR spectral data are in good agreement with the literature data.²⁹

5-(4-Methylbenzyl)phenanthridin-6(5H)-one (3h). White solid (57.7 mg, 77%): mp 106–108 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.62 (d, *J* = 8.1 Hz, 1H), 8.27 (t, *J* = 6.3 Hz, 1H), 7.77 (t, *J* = 7.2 Hz, 1H), 7.60 (t, *J* = 7.2 Hz, 1H), 7.36–7.07 (m, 8H), 5.61 (s, 2H), 2.28 (s, 3H); ¹³C NMR (300 MHz, CDCl₃) δ 162.1, 137.6, 137.0, 134.0, 133.7, 132.8, 129.7, 129.6, 129.3, 128.2, 126.7, 125.6, 123.4, 122.7, 121.9, 119.7, 116.2, 46.4, 21.3; HRMS (EI) calcd for C₂₁H₁₇NO: 299.1310, found 299.1307.

5-(4-Methoxybenzyl)phenanthridin-6(5H)-one (3i). Pale brown glassy solid (59.4 mg, 75%): mp 136–137 °C; ¹H NMR (600 MHz, CDCl₃) δ 8.66 (d, *J* = 8.0 Hz, 1H), 8.31 (t, *J* = 9.1 Hz, 2H), 7.81 (t, *J* = 8.3 Hz, 1H), 7.65 (t, *J* = 7.9 Hz, 1H), 7.43 (t, *J* = 8.4 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.29 (t, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.63 (s, 2H), 3.78 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 161.9, 158.8, 137.4, 133.8, 132.7, 129.6, 129.2, 128.7, 128.1, 127.9, 125.5, 123.3, 122.6, 121.7, 119.5, 116.1, 114.2, 55.3, 46.0; HRMS (APCI) calcd for C₂₁H₁₈NO₂ [M+H]⁺: 316.1332, found 316.1322. The ¹H and ¹³C NMR spectral data are in good agreement with the literature data.²⁹

5-(4-Nitrobenzyl)phenanthridin-6(5H)-one (3j). White solid (68.5 mg, 83%): mp 235–237 °C; ^1H NMR (300 MHz, CDCl_3) δ 8.60 (d, J = 9.0 Hz, 1H), 8.36 (d, J = 9.0 Hz, 2H), 8.25 (dd, J = 6.0, 3.0 Hz, 1H), 7.85 (t, J = 9.0 Hz, 1H), 7.65 (t, J = 9.0 Hz, 1H), 7.42–7.27 (m, 4H), 7.09 (d, J = 9.0 Hz, 1H), 6.99 (dd, J = 6.0, 3.0 Hz, 1H), 6.05 (s, 2H); ^{13}C NMR (300 MHz, CDCl_3) δ 166.6, 137.3, 134.4, 133.3, 132.6, 130.1, 129.4, 128.5, 128.4, 127.7, 125.9, 125.4, 123.8, 123.3, 122.1, 119.9, 115.7, 45.1; HRMS (EI) calcd for $\text{C}_{20}\text{H}_{14}\text{N}_2\text{O}_3$: 330.1004, found 330.1011.

5-Benzyl-9-methylphenanthridin-6(5H)-one (3l). White solid (62.6 mg, 84%): mp 173–175 °C; ^1H NMR (300 MHz, d_6 -acetone) δ 8.47 (d, J = 6.0 Hz, 1H), 8.42 (d, J = 6.0 Hz, 1H), 8.35 (s, 1H), 7.51 (d, J = 9.0 Hz, 1H), 7.43 (dd, J = 6.0, 3.0 Hz, 2H), 7.31–7.23 (m, 6H), 5.70 (s, 2H), 2.59 (s, 3H); ^{13}C NMR (300 MHz, CDCl_3) δ 162.1, 143.4, 137.7, 136.9, 134.0, 129.7, 129.6, 129.4, 129.0, 127.3, 126.7, 123.4, 122.6, 121.9, 119.7, 116.2, 46.6, 22.4; HRMS (EI) calcd for $\text{C}_{21}\text{H}_{17}\text{NO}$: 299.1310, found 299.1304.

5-Benzyl-8-methylphenanthridin-6(5H)-one (3m). White solid (59.0 mg, 79%): mp 173–175 °C; ^1H NMR (300 MHz, CDCl_3) δ 8.43 (s, 1H), 8.25 (d, J = 7.8 Hz, 1H), 8.19 (d, J = 8.4 Hz, 1H), 7.61 (dd, J = 8.1, 1.8 Hz, 1H), 7.38–7.21 (m, 8H), 5.67 (s, 2H), 2.54 (s, 3H); ^{13}C NMR (300 MHz, CDCl_3) δ 162.2, 138.4, 137.2, 136.9, 134.2, 131.6, 129.2, 129.1, 129.0, 127.3, 126.7, 125.5, 123.2, 122.7, 121.9, 119.8, 116.1, 46.6, 21.6; HRMS (EI) calcd for $\text{C}_{21}\text{H}_{17}\text{NO}$: 299.1310, found 299.1306.

5-Benzyl-10-methylphenanthridin-6(5H)-one (3n). White solid (55.1 mg, 74%): mp 122–123 °C; ^1H NMR (300 MHz, CDCl_3) δ 8.62 (d, J = 9.0 Hz, 1H), 8.46 (d, J = 6.0 Hz, 1H), 7.65 (d, J = 9.0 Hz, 1H), 7.52 (t, J = 9.0 Hz, 1H), 7.38–7.23 (m, 8H), 5.67 (s, 2H), 2.97 (s, 3H); ^{13}C NMR (300 MHz, CDCl_3) δ 162.4, 137.7, 137.4, 136.8, 134.7, 133.5, 129.0, 128.8, 128.1, 127.8, 127.5, 127.3, 126.7, 121.9, 121.3, 116.0, 47.0, 26.3; HRMS (EI) calcd for $\text{C}_{21}\text{H}_{17}\text{NO}$: 299.1310, found 299.1303.

5-Benzyl-8-methoxyphenanthridin-6(5H)-one (3o). White solid (58.3 mg, 74%): mp 133–135 °C; ^1H NMR (300 MHz, d_6 -acetone) δ 8.42 (d, J = 9.0 Hz, 1H), 8.36 (d, J = 6.0 Hz, 1H), 7.96 (d, J = 3.0 Hz, 1H), 7.46–7.24 (m, 9H), 5.71 (s, 2H), 3.98 (s, 3H); ^{13}C NMR (300 MHz, d_6 -acetone) δ 162.3, 161.2, 138.8, 137.8, 130.1, 129.9, 128.7, 128.4, 128.3, 128.0, 125.5, 124.3, 123.9, 123.3, 120.8, 117.4, 110.9, 56.5, 47.1; HRMS (EI) calcd for $\text{C}_{21}\text{H}_{17}\text{NO}_2$: 315.1259, found 315.1259.

5-Benzyl-8,9-dimethoxyphenanthridin-6(5H)-one (3p). White solid (60.2 mg, 70%): mp 210–212 °C; ^1H NMR (300 MHz, CDCl_3) δ 8.13 (d, J = 7.8 Hz, 1H), 7.98 (s, 1H), 7.59 (s, 1H), 7.38–7.21 (m, 8H), 5.65 (s, 2H), 4.09 (s, 3H), 4.04 (s, 3H); ^{13}C NMR (300 MHz, CDCl_3) δ 161.5, 153.6, 150.0, 137.0, 137.0, 128.9, 128.8, 128.8, 127.3, 126.7, 122.8, 122.5, 119.5, 119.5, 116.2, 109.4, 102.7, 56.4, 56.3, 46.6; HRMS (EI) calcd for $\text{C}_{22}\text{H}_{19}\text{NO}_3$: 345.1365, found 345.1370.

5-Benzyl-8-chlorophenanthridin-6(5H)-one (3q). White solid (53.5 mg, 67%): mp 155–157 °C; ^1H NMR (300 MHz, CDCl_3) δ 8.59 (d, J = 2.1 Hz, 1H), 8.23 (d, J = 9.0 Hz, 1H), 8.22 (d, J = 8.1 Hz, 1H), 7.73 (dd, J = 8.1, 2.4 Hz, 1H), 7.41 (m, 1H), 7.32–7.24 (m, 7H), 5.65 (s, 2H); ^{13}C NMR (300 MHz, CDCl_3) δ 161.1, 137.4, 136.5, 134.5, 133.2, 132.5, 130.1, 129.1, 128.9, 127.5, 126.9, 126.7, 123.7, 123.5, 123.0, 119.0, 116.4, 46.8; HRMS (EI) calcd for $\text{C}_{20}\text{H}_{14}\text{NOCl}$: 319.0764, found 319.0756.

5-Benzyl-8-(trifluoromethyl)phenanthridin-6(5H)-one (3r). White solid (45.7 mg, 52%): mp 186–188 °C; ^1H NMR (300 MHz, CDCl_3) δ 8.92 (s, 1H), 8.41 (d, J = 8.4 Hz, 1H), 8.30 (dd, J = 8.1, 1.5 Hz, 1H), 7.99 (dd, J = 8.7, 1.8 Hz, 1H), 7.47 (m, 1H), 7.36–7.24 (m, 7H), 5.67 (m, 2H); ^{13}C NMR (300 MHz, CDCl_3) δ 161.3, 138.1, 136.3, 131.1, 129.1, 129.0, 129.0, 127.6, 127.1, 127.0, 126.7, 125.7, 124.1, 123.2, 122.9, 118.6, 116.5, 46.9; HRMS (EI) calcd for $\text{C}_{21}\text{H}_{14}\text{NOF}_3$: 353.1027, found 353.1035.

5-Benzyl-8-fluorophenanthridin-6(5H)-one (3s). Pale solid (49.3 mg, 65%): mp 164–166 °C; ^1H NMR (600 MHz, CDCl_3) δ 8.33–8.29 (m, 2H), 8.24 (d, J = 7.9 Hz, 1H), 7.54 (td, J = 8.4, 2.9 Hz, 1H), 7.43 (t, J = 8.4 Hz, 1H), 7.38–7.24 (m, 7H), 5.68 (s, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 162.0, 137.3, 136.6, 133.9, 132.8, 129.6, 129.2, 128.8, 128.1, 127.2, 126.6, 125.4, 123.3, 122.6, 121.7, 119.6, 116.1, 46.5 (extra peaks due to C-F coupling); ^{19}F NMR (600 MHz, CDCl_3) δ -112.0; HRMS (APCI) calcd for $\text{C}_{20}\text{H}_{15}\text{FNO}$ $[\text{M}+\text{H}]^+$: 304.1132, found 304.1136.

5-Benzyl-9-fluorophenanthridin-6(5H)-one (3t). Pale white solid (60.1 mg, 79%): mp 155–158 °C (lit.²⁸ mp 157–158 °C); ^1H NMR (600 MHz, CDCl_3) δ 8.67 (dd, J = 8.9, 5.9 Hz, 1H), 8.19 (d, J = 7.3 Hz, 1H), 7.94 (dd, J = 10.3, 2.4 Hz, 1H), 7.46 (t, J = 8.5 Hz, 1H), 7.37–7.25 (m, 8H), 5.68 (s, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 166.7, 165.0, 161.3, 137.8, 136.5, 136.5, 136.4, 132.5, 132.4, 130.3, 129.6, 128.9, 127.3, 126.5, 123.6, 122.7, 122.0, 122.0, 118.8, 118.8, 116.4, 116.3, 116.2, 115.4, 107.8, 107.6, 46.5 (extra peaks due to C-F coupling); ^{19}F NMR (600 MHz, CDCl_3) δ -105.4; HRMS (APCI) calcd for $\text{C}_{20}\text{H}_{15}\text{FNO}$ $[\text{M}+\text{H}]^+$: 304.1132, found 304.1136. The ^1H and ^{13}C NMR spectral data are in good agreement with the literature data.²⁸

5-Benzyl-9-nitrophenanthridin-6(5H)-one (3u). Yellow solid (58.0 mg, 70%): decomposes above 300 °C; ^1H NMR (300 MHz, CDCl_3) δ 9.18 (d, J = 2.1 Hz, 1H), 8.80 (d, J = 8.7 Hz, 1H), 8.41–8.36 (m, 2H), 7.56–7.50 (m, 2H), 7.40–7.27 (m, 6H), 5.69 (s, 2H); ^{13}C NMR (300 MHz, CDCl_3) δ 160.4, 147.2, 139.1, 138.4, 136.8, 132.3, 129.0, 127.5, 127.0, 126.9, 125.8, 125.5, 125.1, 124.2, 123.7, 118.0, 116.9, 46.2; HRMS (EI) calcd for $\text{C}_{20}\text{H}_{14}\text{N}_2\text{O}_3$: 330.1004, found 330.1001.

5-Benzyl-9-[(benzylamino)carbonyl]phenanthridin-6(5H)-one (3v). White solid (57.9 mg, 55%): mp 197–200 °C; ^1H NMR (300 MHz, CDCl_3) δ 8.80 (s, 1H), 8.58 (d, J = 8.1 Hz, 1H), 8.30 (d, J = 7.8 Hz, 1H), 7.85 (dd, J = 8.4, 1.5 Hz, 1H), 7.33–7.22 (m, 13H), 6.88 (s, 1H), 5.61 (s, 2H), 4.72 (d, J = 5.7 Hz, 2H); ^{13}C NMR (300 MHz, CDCl_3) δ 166.8, 161.4, 138.1, 138.0, 136.4, 134.3, 130.3, 129.8, 129.0, 129.0, 128.2, 127.9, 127.4, 126.6, 125.3,

123.8, 123.0, 121.9, 119.2, 116.2, 46.7, 44.6; HRMS (EI) calcd for $C_{28}H_{22}N_2O_2$: 418.1681, found 418.1689.

6-Benzylbenzo-1,6-naphthyridin-5-one (3w). White solid (25.7 mg, 36%): mp 129–131 °C; 1H NMR (300 MHz, $CDCl_3$) δ 9.04 (dd, J = 6.0, 3.0 Hz, 1H), 8.90 (d, J = 9.0 Hz, 1H), 8.83 (dd, J = 9.0, 3.0 Hz, 1H), 7.57–7.47 (m, 2H), 7.37–7.24 (m, 7H), 5.66 (s, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 162.1, 154.2, 138.8, 137.2, 136.4, 131.5, 129.1, 127.6, 126.7, 125.5, 123.3, 123.2, 121.1, 115.7, 46.7; HRMS (EI) calcd for $C_{19}H_{14}N_2O$: 286.1106, found 286.1098.

5-Benzyl-2,3-dimethylphenanthridin-6(5H)-one (3gb). White solid (39.0 mg, 50%): mp 155–157 °C; 1H NMR (300 MHz, $CDCl_3$) δ 8.64–8.58 (m, 1H), 8.32–8.25 (m, 1H), 8.01 (s, 1H), 7.78–7.73 (m, 1H), 7.65–7.54 (m, 1H), 7.32–7.25 (m, 3H), 7.09 (s, 1H), 6.87 (d, J = 12.0 Hz, 2H), 5.64 (s, 2H), 3.90 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 162.1, 138.9, 137.1, 132.9, 132.7, 129.8, 129.4, 129.0, 129.0, 128.2, 127.3, 126.7, 123.5, 121.9, 116.2, 46.6, 20.7, 19.6; HRMS (EI) calcd for $C_{22}H_{19}NO$: 313.1467, found 313.1470.

5-Benzyl-2,3-dimethoxyphenanthridin-6(5H)-one (3gc). White solid (39.6 mg, 46%): mp 153–155 °C; 1H NMR (300 MHz, $CDCl_3$) δ 8.61 (dd, J = 8.1, 1.5 Hz, 1H), 8.14 (d, J = 8.1, 1H), 7.76 (td, J = 8.1, 1.5 Hz, 1H), 7.64 (s, 1H), 7.56 (t, J = 8.1 Hz, 1H), 7.30–7.23 (m, 5H), 6.79 (s, 1H), 5.66 (s, 2H), 3.99 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 162.2, 150.8, 145.3, 137.1, 134.0, 132.8, 132.4, 129.5, 129.1, 127.5, 127.2, 126.8, 124.7, 121.3, 112.4, 105.4, 100.1, 56.5, 56.1, 47.1; HRMS (EI) calcd for $C_{22}H_{19}NO_3$: 345.1365, found 345.1370.

5-Benzyl-2,3-difluorophenanthridin-6(5H)-one (3gd). White solid (34.7 mg, 43%): mp 187–189 °C; 1H NMR (300 MHz, $CDCl_3$) δ 8.61 (d, J = 9.0 Hz, 1H), 8.05 (m, 1H), 7.82 (t, J

= 9.0 Hz, 1H), 7.65 (d, J = 9.0 Hz, 1H), 7.35–7.08 (m, 7H), 5.60 (s, 2H); ^{13}C NMR (300 MHz, CDCl_3) δ 161.9, 152.7, 148.1, 136.8, 135.9, 133.3, 129.6, 129.2, 129.0, 128.7, 128.3, 127.8, 127.4, 126.7, 116.3, 111.8, 105.6, 47.2; HRMS (EI) calcd for $\text{C}_{20}\text{H}_{13}\text{NOF}_2$: 321.0965, found 321.0973.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1. Tentative Mechanisms

Table 1Optimization of the Pd-Catalyzed Annulation of Benzyne^a

entry	ligand (mol %)	additive (equiv)	solvent ratio (toluene/MeCN)	% yield of 3a ^b
1	-----	-----	4:1	10
2	PPh ₃ (10)	-----	4:1	13
3	P(<i>o</i> -tolyls) ₃ (10)	-----	4:1	50
4	dppm (10)	-----	4:1	66
5	dppe (10)	-----	4:1	30
6	dppf (10)	-----	4:1	25
7	L (10) ^c	-----	4:1	56
8	dppm (5)	-----	4:1	53
9	dppm (10)	Na₂CO₃ (1)	4:1	73
10	dppm (10)	K ₂ CO ₃ (1)	4:1	70
11	dppm (10)	Cs ₂ CO ₃ (1)	4:1	67
12	dppm (10)	Na ₂ CO ₃ (2)	4:1	57
13	dppm (10)	Na ₂ CO ₃ (1)	3:1	52
14	dppm (10)	Na ₂ CO ₃ (1)	6:1	49
15	dppm (10)	Na ₂ CO ₃ (1)	4:1	50 ^d
16	dppm (10)	Na ₂ CO ₃ (1)	4:1	60 ^e

^a All reactions were run using substrate **1a** (0.25 mmol), 5 mol % of Pd(OAc)₂, 2.0 equiv of **2a**, 5.0 equiv of CsF, 5 ml of solvent at 110 °C for 16–24 h, unless otherwise specified.

^b Isolated yield.

^c *o*-(Dicyclohexyl-phosphino)biphenyl.

^d The reaction was conducted at 90 °C for 12 h, at which time the Pd had precipitated out.

^e 1.6 Equiv of **2a** and 4.0 equiv of CsF were employed.

Table 2

Pd-Catalyzed Annulation of Benzynes **2a**^a

entry	1		2a		entry	3b		substrate	3
	substrate	1	substrate	2a		% yield of 3b	% yield of 3b		
1					14	(3a) 73	(3n) 74
2					15	(3b) 70	(3o) 74
3					16	(3c) 87	(3p) 70
4					17	(3d) 64	(3q) 67
5					18	(3e) 65	(3r) 52
6					19	(3f)-c	(3s) 65

entry	substrate	1	2a	5% Pd(OAc) ₂ , 10% dppm 5 CsF, 1 Na ₂ CO ₃ , 110 °C 4:1 toluene/MeCN, 16-24 h	substrate	3	% yield of 3b	entry	% yield of 3b	substrate	3b	% yield of 3b
7							(3g) 82	20	(3t) 79		(3t) 79	
8							(3h) 77	21	(3u) 70		(3u) 70	
9							(3i) 75	22	(3v) 55		(3v) 55	
10							(3j) 83	23	(3w) 36		(3w) 36	
11							(3k) 38	24	(3x) 0		(3x) 0	
12							(3l) 84	25	(3y) 0		(3y) 0	

entry	substrate			entry	substrate	% yield of 3 ^b	% yield of 3 ^b
		1	2a				
13	1m					(3m) 79	

^aRepresentative procedure: **1** (0.25 mmol), 2.0 equiv of **2**, 5.0 equiv of CsF, 5 mol % Pd(OAc)₂, 10 mol % dppm, 1.0 equiv of Na₂CO₃ in 5 ml of 4:1 toluene/MeCN at 110 °C for 16–24 h.

^bIsolated yield.

^cAn unknown mixture was generated with products overlapping with the starting material **1d** on the TLC plate.

Table 3Investigation of Different Arynes in the Pd-Catalyzed Annulation of *o*-Halobenzamide **1g**^a

entry	aryne	% yield of 3 ^b
1	 2b	(3gb) 50
2	 2c	(3gc) 46
3	 2d	(3gd) 43

^aRepresentative procedure: **1g** (0.25 mmol), 2.0 equiv of **2**, 5.0 equiv of CsF, 5 mol % Pd(OAc)₂, 10 mol % dppm, 1.0 equiv of Na₂CO₃ in 5 ml of 4:1 toluene/MeCN at 110 °C for 16–24 h.

^bIsolated yield.