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Palladium-catalyzed cyclization of benzamides with arynes: application to the synthesis of phenaglydon and *N*-methylcrinasiadine†

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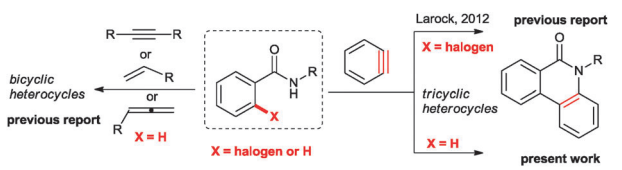
***N*-Methyl or methoxy benzamides reacted with benzynes in the presence of $Pd(OAc)_2$, organic acid and $K_2S_2O_8$ in CH_3CN yielding tricyclic phenanthridinone derivatives in good yields.**

Phenanthridinones are the key core units found in various natural products and biologically active molecules.[1] These molecules are used as potential PARP-1 inhibitors in anticancer drugs as well as neurotrophin activity enhancers for the treatment of nerve diseases.[2] Traditionally, phenanthridinones are synthesized by cyclization of nitrocarbonyl-biphenyls, Beckmann/Schmidt rearrangement of fluorenones and photoinduced rearrangement of 2-halobenzamides.[3] However, in these reactions, the preparation of key starting materials needs more steps and the overall yields observed are lower. Subsequently, phenanthridinones are prepared by a palladium-catalyzed homo coupling of *ortho*-halo benzamides and coupling of aromatic halides with *ortho*-halo benzamides.[4] Very recently, Larock's group reported the synthesis of phenanthridinones *via* a palladium-catalyzed cyclization of *ortho*-halo *N*-substituted benzamides with benzynes (eqn (1)).[5] But a preactivated carbon–halogen partner on the aromatic moiety is required for the reaction. Apart from these reactions, phenanthridinones are prepared by a metal-catalyzed *ortho* arylation of benzamides with iodobenzenes or aromatic boronic acids or electron-rich aromatics followed by intramolecular C–N bond formation.[6]



(1)

Transition metal-catalyzed cyclization of heteroatom substituted aromatics with carbon–carbon π-components *via* chelation-assisted C–H bond activation is a practical method to synthesize heterocyclic molecules in one pot.[7] By using nitrogen containing chelating groups such as amide, oxime and imine substituted aromatics or alkenes, various nitrogen-containing mono- and bicyclic heterocycles are prepared through the consecutive C–C and C–N bond formation.[7] In the cyclization reaction, alkynes, alkenes and allenes are extensively used as carbon–carbon π-components (eqn (1)). However, benzyne as a π-component has not been well explored in the literature. In fact, there are several challenges to utilize benzyne as a π-component in the reaction due to its high reactivity. It is very important to note that in the cyclization of substituted aromatics with benzynes, a tricyclic ring system can be constructed in one pot.

We focused on utilization of a highly reactive benzyne as a π-component in the cyclization reaction. Initially, we tried the cyclization of *N*-methoxy 4-methoxy benzamide (**1a**) with *o*-(trimethylsilyl)aryl triflate (**2a**) in the presence of $[\{RuCl_2(p\text{-cymene})\}_2]$, $AgSbF_6$ and $Cu(OAc)_2$ in CH_3CN at 100 °C for 12 h (Table 1, entry 1). CsF in CH_3CN was used to generate benzyne from benzyne precursor **2a**.[8] In the reaction, only *N*-arylated benzamide **3a** was observed in 30% yield and the expected cyclization product **4a** was not observed. Next, the cyclization reaction of **1a** with **2a** was examined in the presence of $Pd(OAc)_2$ (5 mol%) and acetic acid or CF_3COOH (10.0 equiv.) in CH_3CN (entries 2 and 3). In the reaction, no *N*-arylation product **3a** or cyclization product **4a** was observed. It seems AcOH or CF_3COOH might quench the CsF base. Then, acetic acid was replaced by the sterically hindered pivalic acid (entry 4). Interestingly, in the reaction, the expected cyclization product **4a** was observed in 35% yield and competitive product **3a** was also observed in 10% yield. To avoid product **3a**, the reaction was tested with a catalytic amount of 1-adamantanecarboxylic acid (Adm-1-COOH) (30 mol%) (entry 5). Surprisingly, in the reaction, product **4a** was observed in 45% yield and no *N*-arylated product **3a** was observed. To increase the yield of product **4a**, the reaction was examined with oxidants (1.0 equiv.) (entries 6–11). Interestingly, using $K_2S_2O_8$, product **4a** was observed in 74% GC yield and 66%

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Table 1 Cyclization of benzamide **1a** with benzyne precursor **2a**[a]

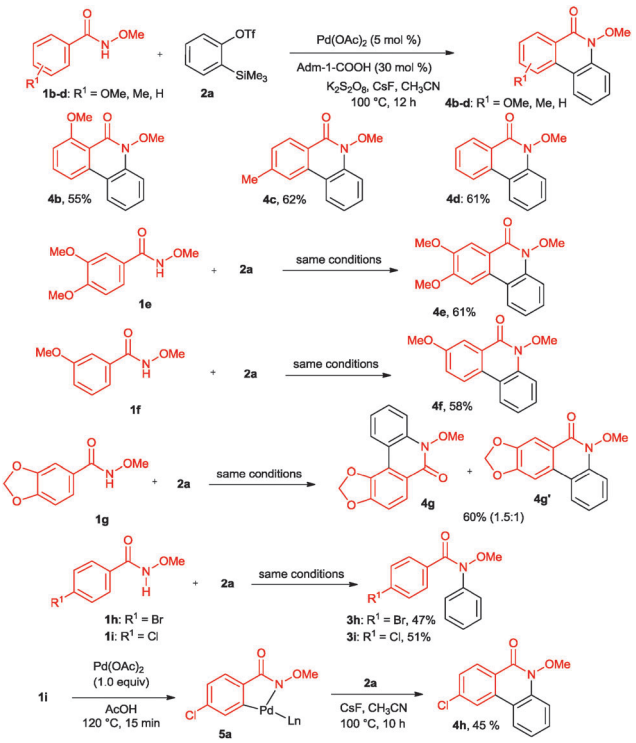
Entry	Catalyst/additive	Oxidant	**3a**/**4a** yield[b] (%)
1	$[RuCl_2(p\text{-cymene})]_2/AgSbF_6$[c]	$Cu(OAc)_2$	30/0
2	$Pd(OAc)_2$/AcOH	—	—
3	$Pd(OAc)_2$/TFA	—	—
4	$Pd(OAc)_2$/pivalic acid	—	10/35
5	$Pd(OAc)_2$/Adm-1-COOH[d]	—	0/45
6	$Pd(OAc)_2$/Adm-1-COOH[d]	Ag_2O	0/33
7	$Pd(OAc)_2$/Adm-1-COOH[d]	Ag_2CO_3	0/27
8	$Pd(OAc)_2$/Adm-1-COOH[d]	AgOAc	0/45
9	$Pd(OAc)_2$/Adm-1-COOH[d]	$K_2S_2O_8$	0/74
10	$Pd(OAc)_2$/Adm-1-COOH[d]	$PhI(OAc)_2$	—
11	$Pd(OAc)_2$/Adm-1-COOH[d]	$(NH_4)_2S_2O_8$	—

[a] Reactions conditions: **1a** with **2a** (1.5 equiv.) in the presence of cat (5.0 mol%), additive (10.0 equiv.) and oxidant (2.0 equiv.) in CH_3CN at 100 °C for 12 h. [b] GC yield. [c] $AgSbF_6$ (20 mol%) was used. [d] Adm-1-COOH (30 mol%) was used.

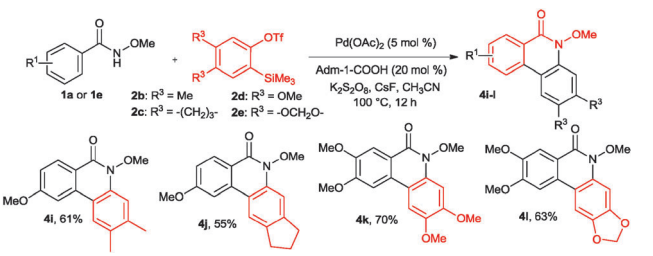
isolated yield (entry 9). Remaining oxidants were partially effective or totally ineffective, yielding **4a** in 0–45% yields (entries 6–11).

The scope of the catalytic reaction was tested with substituted *N*-methoxy benzamides **1b–i** (Scheme 1). 2-Methoxy (**1b**), 4-methyl (**1c**) and *N*-methoxy benzamides (**1d**) underwent cyclization with **2a**, yielding phenanthridinones **4b–d** in 55%, 62% and 61% yields, respectively. Next, the cyclization reaction was tested with unsymmetrical benzamides. *N*-Methoxy 3,4-dimethoxy benzamide (**1e**) and *meta* methoxy benzamide **1f** afforded phenanthridinones **4e** and **4f** in 61% and 58% yields, respectively, in which the *ortho* C–H bond activation takes place selectively at a sterically less hindered side. Whereas, benzamide **1g** provided mixtures of regioselective cyclization products **4g** and **4g′** in 60% combined yield in a 1.5 : 1 ratio. Furthermore, the cyclization reaction was tested with 4-bromo and 4-chloro benzamides **1h** and **1i**. However, only *N*-arylated benzamides **3h** and **3i** were observed in 47% and 51% yields, respectively, and the expected cyclization products **4** were not observed. Similarly, 4-trifluoromethyl, 4-cyano and 4-nitrobenzamides were also not favorable for the reaction. These results clearly reveal that electron-donating substituents on the aromatic moiety of benzamides favor the *ortho* C–H bond activation–cyclization reaction. But, halogen and electron deficient aromatic benzamides favor only competitive nucleophilic addition of the free N–H moiety of benzamide with benzyne. Surprisingly, the palladacycle of 4-chloro benzamide **5a** reacted with benzyne precursor **2a**, yielding cyclization product **4h** in 45% yield. This result clearly says that the *ortho* C–H bond activation process is very slow in the electron deficient benzamides, and the competitive nucleophilic addition is very fast. Although, at present, the catalytic reaction was compatible with only electron-rich benzamides, it has been shown that a highly reactive benzyne can be used as a π-component for the cyclization reaction.

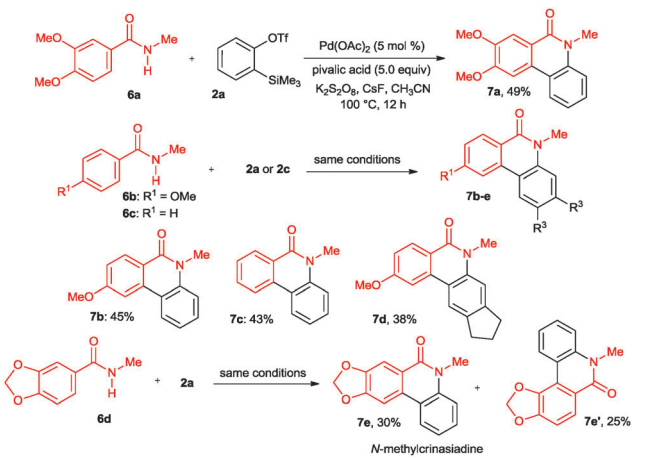
The cyclization reaction was also examined with benzyne precursors **2b–e** (Scheme 2). Treatment of benzamide **1a** with benzyne precursors **2b** and **2c** gave phenanthridinones **4i** and **4j** in 61% and 55% yields, respectively. Interestingly, synthetically



Scheme 1 Scope of the *N*-methoxy benzamides **1**.



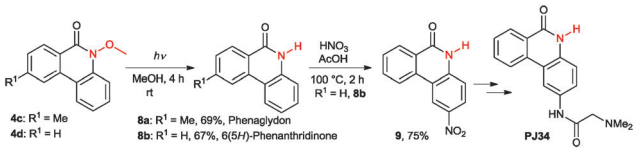
Scheme 2 Scope of the benzyne precursors **2b–e**.



Scheme 3 Scope of the *N*-methyl benzamides **6a–d**.

useful benzyne precursors **2d** and **2e** reacted with **1e**, giving products **4k** and **4l** in 70% and 63% yields, respectively.

The catalytic reaction was further tested with other *N*-methyl benzamides (Scheme 3). *N*-Methyl benzamide (**6a**) underwent cyclization with **2a**, providing *N*-methyl phenanthridinone **7a** in 49% yield, in which *ortho* C–H bond activation takes place selectively at the sterically less hindered side. Further, *N*-methyl 4-methoxy benzamide (**6b**) and *N*-methyl benzamide (**6c**) reacted with **2a** or **2c** affording cyclization products **7b–d** in 45%, 43% and 38% yields, respectively. Treatment of *N*-methyl benzamide **6d** with **1a** gave natural product *N*-methylcrinasiadine[9b] (**7e**) in 30% yield and other regioisomer **7e′** in 25% yield. It is important to point out that natural product *N*-methylcrinasiadine (**7e**) shows several biological activities.[1]

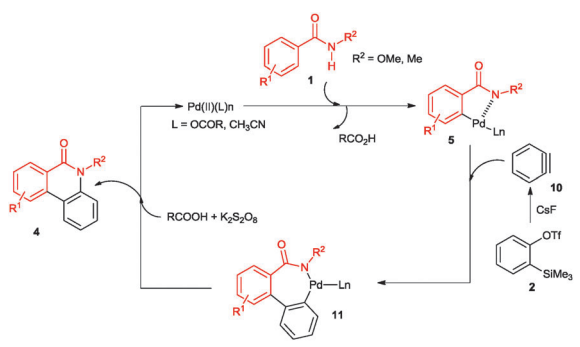


(2)

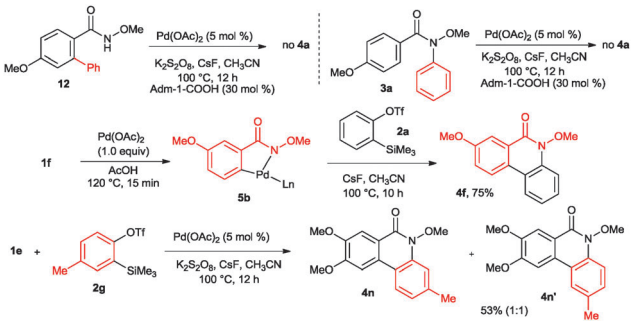
Later, OMe groups on the cyclic amides of **4c** and **4d** were cleaved into the natural product phenaglydon[9a,b] **8a** in 69% yield and 6(5*H*)-phenanthridinone **8b** in 67% yield under the photochemical irradiation conditions[7a,b] (eqn (2)). Later, compound **8b** underwent nitration at the C-5 position of phenanthridinone in the presence of HNO_3/H_2SO_4, providing 5-nitro phenanthridinone **9** in 75% yield. It is important to note that compound **9** is a key precursor for the preparation of anticancer drug PJ34.[9c]

A possible reaction mechanism is proposed in Scheme 4 to account for the present cyclization reaction. Coordination of the amide nitrogen of benzamide **1** to the palladium species followed by *ortho*-metalation provides a five-membered palladacycle intermediate **5**. Coordinative insertion of benzyne **10** into intermediate **5** yields a seven-membered palladacycle intermediate **11**. Subsequent C–N bond formation and reductive elimination afford product **4** and regenerate the active palladium species in the presence of RCOOH and $K_2S_2O_8$.

Apart from the above proposed mechanism, other possible pathways such as *ortho*-arylation of benzamide with benzyne yielding product **12** followed by intramolecular C–N bond formation or



Scheme 4 Proposed mechanism.



Scheme 5 Mechanistic investigation.

N–H arylation of benzamide with benzyne providing compound **3** followed by intramolecular dehydrogenative aryl–aryl coupling are also possible.[7] To support the proposed mechanism in Scheme 4, the following reactions were done (Scheme 5). *ortho*-Arylated benzamide **12** was prepared separately and treated with $Pd(OAc)_2$, CsF and $K_2S_2O_8$ in CH_3CN at 100 °C for 12 h. In the reaction, no cyclization product **4a** was observed. Subsequently, *N*-arylated benzamide **3a** was treated with $Pd(OAc)_2$ and $K_2S_2O_8$ under similar reaction conditions. However, no cyclization product **4a** was observed. Further, a five-membered palladacycle intermediate **5b** was prepared separately and treated with benzyne precursor **2a** in the presence of CsF in CH_3CN at 100 °C for 12 h. As expected, the cyclization product **4f** was observed in 75% yield. These results clearly revealed that the present reaction proceeds *via* a coordinative insertion pathway. To support the hypothesis that benzyne is involved in the cyclization reaction, the reaction of benzamide **1e** with unsymmetrical benzyne precursor **2g** was performed. In the reaction, a mixture of regioisomeric compounds **4n** and **4n′** was observed in 53% combined yield in a 2:1 ratio. The lack of regioselectivity of the reaction is consistent with insertion of unsymmetrical benzyne into a Pd–carbon bond in intermediate **5**.

In conclusion, we have demonstrated a palladium-catalyzed oxidative cyclization of *N*-substituted benzamides with benzynes providing phenanthridinones with diverse substituents.

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