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Collective Synthesis of Phenanthridinone through C−H Activation Involving a Pd-Catalyzed Aryne Multicomponent Reaction

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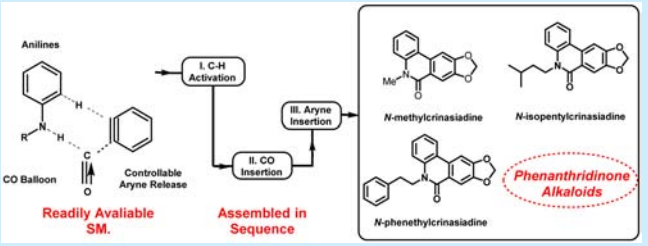
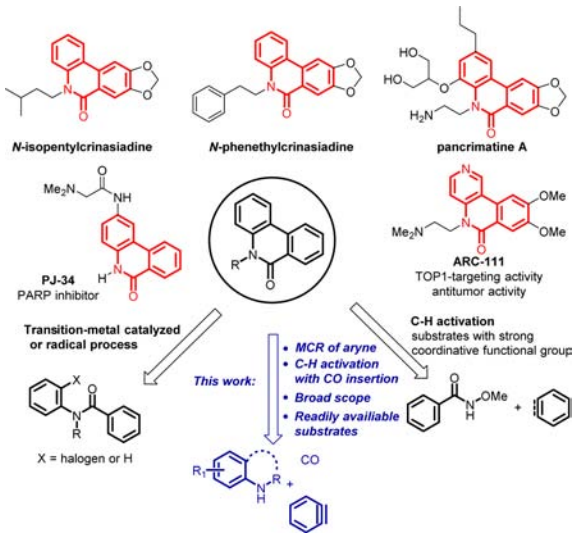
Supporting Information

ABSTRACT: A palladium-catalyzed multicomponent reaction (MCR) involving aryne, CO, and aniline is established for straightforward assembly of a phenanthridinone scaffold through C−H bond activation. Free combination with multiple kinds of readily available anilines and arynes is facilely achieved for phenanthridinone construction without prefunctionalization. Representative natural products were subsequently synthesized through this MCR strategy highly efficiently. Control experiments and interval NMR tracking revealed the mechanism, particularly the key role of CuF_2 in determining the aryne-releasing rate from the precursor in this transformation.



Phenanthridinone is key motif frequently appearing in biologically active alkaloid natural products and pharmaceuticals (Scheme 1) that presents broad range of potent activities[1] such as antivirus, antitumor, and inhibition of DNA topoisomerase. For example, PJ-34 is known as a cell-permeable PARP inhibitor.[1c,g] ARC-111 shows TOP1-targeting activity and pronounced antitumor activity.[1d] Thus, synthetic protocols for penanthridinone have been intensively pursued during the past decade.[2] An effective intramolecular direct arylation strategy on prefabricated aryl-substituted amides for phenanthridinones through palldium-catalyzed ortho carbon−hydrogen activation was achieved by the groups of Fagnou[2a] and Dong.[2c] Another novel achievement was realized by Curran[2b] group, which actualized the cyclization through a radical process. With the help of a strong coordinative directing group, *N*-methoxybenzamide[2d−g] was constantly applied to a phenanthridinone analogue synthesis reacting with several aryl partners such as aryl iodides,[2d] arenes,[2e] and arynes.[2f,g] Very recently, Jiao et al. employed aryl carbamic chlorides and aryl iodides for phenanthridinone derivatives.[2h] Our group has previously published an alternative approach using a palladium(0) catalyst to couple 2-iodoanilines, arynes, and CO whereby the ligand structure dictated the selectivity of CO 1,1-migratory insertion.[3b] Based on this work, as well as our previous interest in C−H functionalization strategies[3a,c] for natural product synthesis, the collective synthesis of phenanthridinone family molecules from readily available aniline, CO, and aryne is established.

Scheme 1. Construction Strategies for Phenanthridinone Scaffolds



Retrosynthetic analysis of penathridione was spontaneously disintegrated into three pieces with arylamine, carbonyl, and aromatic ring. We envisioned that a one-pot multicomponent reaction (MCR), involving anilines, CO, and arynes via C−H activation, would be a straightforward method for phenanthridinones. The insertion of carbon monoxide (CO), one of the most abundant C1 building blocks, is a practical protocol for carbonyl-containing molecule synthesis.[4] Diverse transition-

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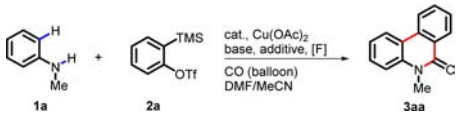
metal-catalyzed annulation via C−H functionalization[5] was tremendously established for construction of heteroaromatic molecules. Anilines are the most convenient building block for nitrogen-containing molecules synthesized via ortho C−H activation.[6] Since it is a highly reactive transient intermediate, active aryne[7] involving inert C−H functionalization synchronously with selective CO insertion is a paradox. Thus, C−H activation partners with a highly active trigger, such as aryl iodides,[8] *O*-perfluorobenzoyl oximes,[9] and strong coordinative substrates (*N*-methoxybenzamides[2f,g]), are obliged to cooperate with instantaneous aryne intermediates. Fluoride salts, which determine the releasing rate of aryne from its precursor, may keep the pace of the aryne generating rate with inert carbon−hydrogen bond activation.

With this concept, we commenced our study with carbonylative assembly of *N*-methylaniline (**1a**) and a benzyne precursor (**2a**). The reaction was first conducted with $Rh(PPh_3)_3Cl$ (Table 1, entry 1), $Pd(PPh_3)_2Cl_2$ (Table 1, entry 2), and $Pd(dppm)Cl_2$ (Table 1, entry 3) as catalysts, which afforded trace amounts of **3aa**. $Pd(OAc)_2$ without phosphine ligands afforded the desired product **3aa** in 11% yield (Table 1, entry 4). Because of the accelerating effect from iodide ion in the reductive elimination step of Pd-catalyzed carbonylations,[6e] 40% yield of **3aa** was achieved when 20 mol % of potassium iodide was added (Table 1, entry 5). KOAc was the best and indispensable base for this transformation, giving **3aa** in 40% yield (Table 1, entries 5−10), which also served as the proton transfer assisting C−H activation.[10] Fluoride salts, the key factor for aryne releasing, were intensively tested. Tetrabutylammonium fluoride (Table 1, entry 11) and cesium fluoride (Table 1, entry 12), which were supposed to release arynes in faster rate,[5b] afford **3aa** in lower yields. In contrast, a significant promotion (70%) was obtained when copper(II) fluoride was utilized (Table 1, entry 13) compared to nickel fluoride (45%, Table 1, entry 14) and iron(III) fluoride (55%, Table 1, entry 15). Further study showed that copper(II) fluoride could be replaced by its dihydrate $CuF_2{\cdot}2H_2O$, which is easier to handle and store (Table 1, entry 15). A better yield (84%) was achieved when the temperature was raised to 120 °C (Table 1, entry 16).

Table 1. Conditions Optimization[a,b]



entry	cat.	base	additive	[F]	yield[b] (%)
1	$Rh(PPh_3)_3Cl$	KOAc		KF	trace
2	$Pd(PPh_3)_2Cl_2$	KOAc		KF	trace
3	$Pd(dppm)Cl_2$	KOAc		KF	trace
4	$Pd(OAc)_2$	KOAc		KF	11
5	$Pd(OAc)_2$	KOAc	KI	KF	40
6	$Pd(OAc)_2$		KI	KF	trace
7	$Pd(OAc)_2$	CsOAc	KI	KF	21
8	$Pd(OAc)_2$	CsOPiv	KI	KF	20
9	$Pd(OAc)_2$	K_2CO_3	KI	KF	39
10	$Pd(OAc)_2$	Cs_2CO_3	KI	KF	15
11	$Pd(OAc)_2$	KOAc	KI	TBAF	trace
12	$Pd(OAc)_2$	KOAc	KI	CsF	38
13	$Pd(OAc)_2$	KOAc	KI	CuF_2	70
14	$Pd(OAc)_2$	KOAc	KI	NiF_2	45
15	$Pd(OAc)_2$	KOAc	KI	FeF_3	55
16	$Pd(OAc)_2$	KOAc	KI	$CuF_2{\cdot}\ 2H_2O$	72
17[c]	**$Pd(OAc)_2$**	**KOAc**	**KI**	**$CuF_2{\cdot}2H_2O$**	**84**

[a]Reaction conditions: *N*-methylaniline (0.10 mmol), aryne precursor (0.15 mmol), catalyst (0.01 mmol), additive (0.02 mmol), $Cu(OAc)_2$ (0.11 mmol), base (0.3 mmol), fluoride salt (0.3 mmol), and DMF/MeCN (0.5/0.5 mL) under CO (balloon) at 100 °C for 12 h. [b]Isolated yields. [c]120 °C.

With the optimized conditions in hand, the substrate scope of aniline was systematically probed (Figure 1). Not only electron-neutral (**3ca−da,ja**) but also electron-donating (**3ea,ka**) and electron-withdrawing (**3fa−ha,la**) substituents at the C4 and C2 positions were well tolerated to give the corresponding penanthridinones. Substrates with substituents at the C3 position afforded the desired product smoothly without any isomer at the C2 position (**3ma**). Notably, strongly electron-donating aniline with triple methoxy groups at the C2, C3, and C4 positions still exhibited moderate reactivity and afforded multiply substituted penanthridinone **3na**. It is noteworthy that 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazinetetrahydroquinoline, tetrahydro-1*H*-benzo[*b*]azepine, and hexahydrobenzo[*b*]azocine performed well to afford the corresponding complex polycyclic heteroaromatics (**3oa−ra**),[11] which offers novel types of penanthridinone libraries for drug discovery.

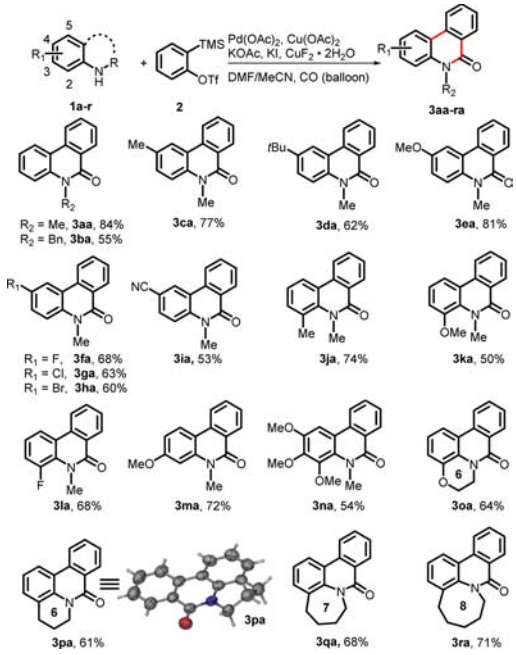


Figure 1. Substrate scope of anlines. (a) Standard conditions. (b) Isolated yields.

Diverse types of aryne precursors, *o*-(trimethylsily)aryl triflates, were further found to demonstrate excellent generality of the protocol (Figure 2). To our delight, aryne precursors bearing both electron-donating groups (**3db−gc,ae−af**) and electron-withdrawing groups (**3cd**) were tolerated in the transformation. In the case of monosubstituted arynes, 2-methoxy-6-(trimethylsilyl)phenyl trifluoromethanesulfonate afforded **3ae** as the sole product., while 4-methoxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate gave two regioisomers **3af**:**3af′** in a 1.2:1 ratio. Natural product phenathridinone alkaloids (Figure 2, compound **4−6**) were

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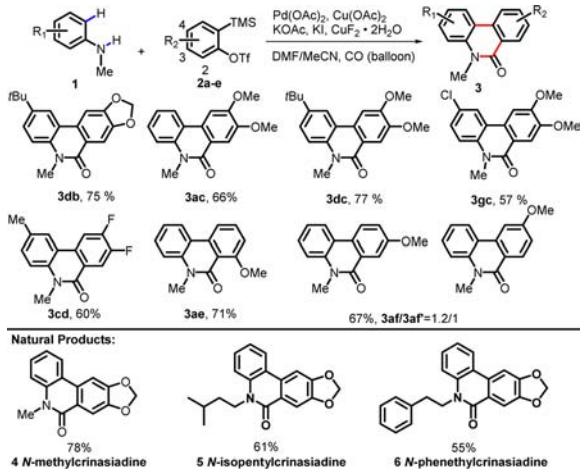


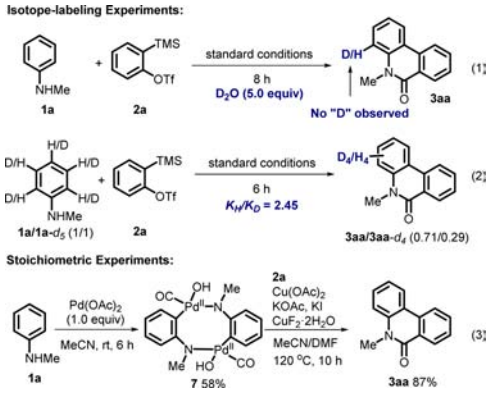
Figure 2. Substrates scope of arynes. (a) Standard conditions. (b) Isolated yields.

highly efficiently achieved through 6-(trimethylsilyl)benzo[*d*]-[1,3]dioxol-5-yltrifluoromethanesulfonate **2b** assembly with different *N*-substituted anilines.

Several competition experiments were performed to provide insight into the mechanism (see the Supporting Information for details). Substituted anilines with different electron effects were first explored. 4-OMe-substituted aniline afforded dramatically higher conversion compared to 4-CN-substituted aniline for the corresponding penanthridinone, demonstrating that electron-rich aromatic aniline possesses a faster rate (1.01) than the electron-poor aromatic aniline (0.17) of carbon−hydrogen bond activation on concerted metalation−deprotonation. However, electronic property of arynes, [*d*][1,3]dioxole-substituted aryne (0.94) and 1,2-difluoro substituted aryne (0.87), were not a key factor for the rate-limiting step.[12]

To gain further evidence of a rate-limiting step in this transformation, isotope-labeling experiments were conducted. Deuterated water (5 equiv) was added in the model reaction, and no H/D exchange was observed in the product **3aa** (Scheme 2, eq 1). An intermolecular kinetic isotope effect

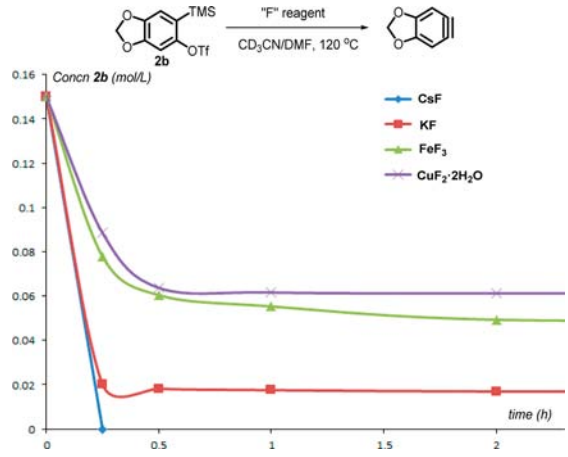
Scheme 2. Mechanistic Study



(KIE) of k_H/k_D = 2.45 was determined for the annulation reaction (Scheme 2, eq 2), indicating that C−H bond cleavage might be involved in the rate-determining step (an alternative possibility is that a previous step not involving the substrate molecule could be rate determining). A stoichiometric reaction of $Pd(OAc)_2$ with **1a** was conducted under CO atmosphere to give palladium dimer **7**[6e] in 58% yield. When subjected to the standard conditions in the absence of $Pd(OAc)_2$, the palladium dimer **7** provided the desired **3aa** in 87% yield (Scheme 2, eq 3), which indicated that palladium complex **7** should be the key intermediate in the transformation.

During optimization, different fluoride reagents revealed great influence on efficiency. An interval NMR experiment was carried out to monitor aryne precursor consumption (Scheme 3). When subjected to CsF in CD_3CN/DMF at 120 °C, aryne

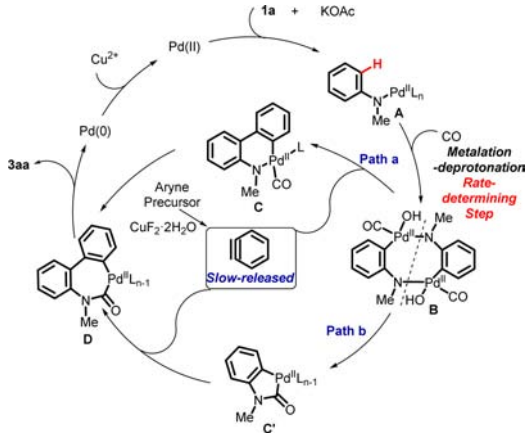
Scheme 3. Rate Control of Aryne Generation via Fluoride Reagents



precursor **2b** was completely consumed in 30 min. Exposed to KF and FeF_3, **2b** was consumed at a relatively slow rate. Slower releasing rates were obtained when $CuF_2{\cdot}2H_2O$ was utilized as the fluoride salt. On the basis of these results, it is illustrated that slow-release of aryne well matches the C−H activation and CO insertion, which once again indicates C−H activation is the rate-determining step. The excess active arynes trend to decompose if not coupled with reactive intermediate.

Finally, a tentative mechanism for this MCR is proposed in Scheme 4. Intermediate **A** was formed through coordination from palladium to substrate **1a**, followed by a metalation−deprotonation process under CO atmosphere to give a dimeric palladium intermediate **B**, which is the rate-determining step of catalytic cycle. Then, two possible pathways could be considered: (1) insertion of slow-released aryne into dimeric palladium intermediate **B** to generate the Pd(II) intermediate

Scheme 4. Proposed Mechanism



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C, which may evolve into acyl Pd specie D after CO migration, and (2) carbon monoxide insertion launched first with cyclopalladated intermediate C′. Aryne insertion into complex C′ led to intermediate D, followed by reductive elimination affording annulated product **3aa**. Meanwhile Pd(0) is reoxidized to Pd(II) in the presence of Cu(II).

In summary, we have developed a palladium-catalyzed multicomponent reaction (MCR) involving aryne, CO, and aniline for straightforward synthesis of a phenanthridinone scaffold through carbon−hydrogen bond activation. Readily available anilines without preactivation, broad substrate scope including polycyclic rings, and high-value scaffolds make this protocol efficient and practical. Representative natural products and a series of novel penanthridinones were successfully achieved through this method. Further synthetic applications in complex natural product total synthesis will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02109.

Experimental procedures, NMR spectra, and X-ray and analytical data for all new compounds (PDF)

X-ray data for **3pa** (CIF)

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Notes

The authors declare no competing financial interest.

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