Aryne Insertion

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Ligand Controlled Regiodivergent C_1 Insertion on Arynes for Construction of Phenanthridinone and Acridone Alkaloids

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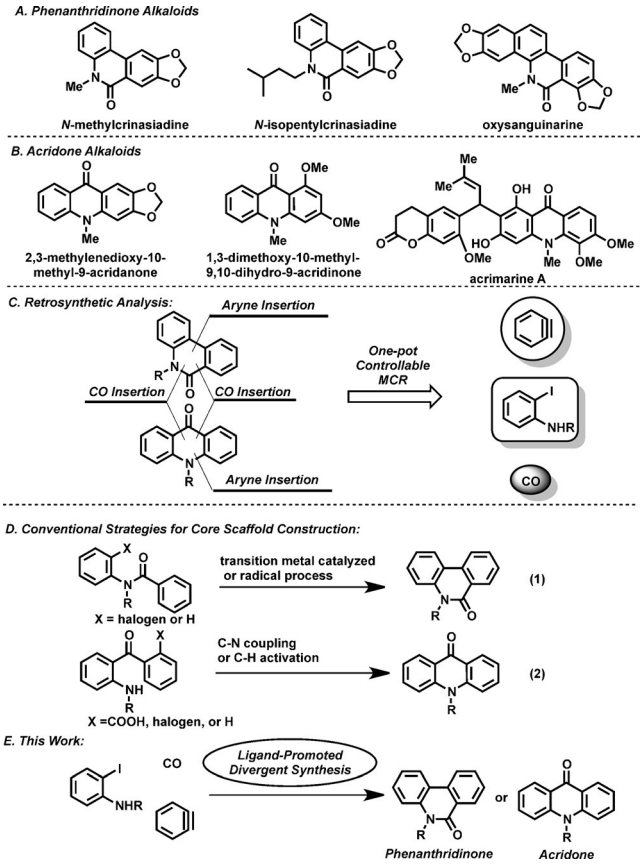
Abstract: *A palladium-catalyzed regiodivergent C_1 insertion multicomponent reaction involving aryne, CO, and 2-iodoaniline is established to construct the scaffolds of phenanthridinone and acridone alkaloids. Regioselective control is achieved under the guidance of selective ligands. The phenanthridinones are solely obtained under ligand-free condition. In comparison, application of the electron-abundant bidentate ligand dppm afforded the acridones with high efficiency. The release rate of the aryne from the precursor assists the regioselectivity of insertion as well, which was revealed through interval NMR tracking. A plausible mechanism was suggested based on the control experiments. Representative natural products and two types of natural product analogues were synthesized divergently through this tunable method.*

Nitrogen-containing heterocycles are omnipresent in natural products, drugs, and many other biologically active molecules.[1] Phenanthridinone alkaloids (Scheme 1 A) have a broad range of potent pharmaceutical activities, such as antitumor, antivirus, and DNA topoisomerase I inhibition.[2] Acridones, another type of distinguished biologically active molecules, possess close structural similarity to phenanthridinones (Scheme 1 B). Highly substituted acridones are core structures for many naturally occurring products, which have attracted much attention owing to their unique biological activities,[3] such as antileishmanial, antifungal and DNA-intercalating anticancer properties. Synthetic methods for constructing these two scaffolds have been continuously refined in recent decades (Scheme 1 D).[4,5] Transition metal catalyzed[4a,b] and radical[4c] cyclization of prefabricated aryl substituted amides was the typical method for phenanthridinones synthesis (Scheme 1, D1). In contrast, the acridone moiety was mainly constructed through the acid-promoted annulation of *N*-phenylanthranilic acids[5a–c] or intramolecular nucleophilic substitution of 2-amino-2-halobenzophenones (Scheme 1, D2).[5d,e] Recently, a carbon–hydrogen activation strategy was also utilized in phenanthridinone[4d–h] and acridone[5f–h] synthesis. It is noteworthy that arynes also serve as key building blocks in acridones synthesis, mainly through a nucleophilic addition process, which was reported by Larock and Greaney.[6] Nevertheless, an efficient, controllable strategy for constructed both phenanthridones and acridones from commercially available starting materials would be highly desireable.



Scheme 1. Strategies for constructing scaffolds of phenanthridinone and acridone alkaloids.

Retrosynthetic analysis of both phenanthridinones and acridones was orientated to the aryne, CO, and iodoaniline, (Scheme 1 C). We envisioned that a one-pot multicomponent reaction (MCR) will achieve the two natural product scaffolds by tuning the regioselectivity of aryne and CO insertion.

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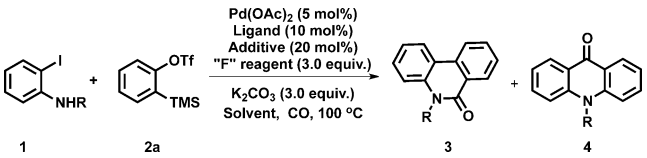
Among transition metal catalyzed carbonylations, the ligand often plays a key role in accelerating the CO insertion.[7] Very recently, the elegant work from Beller and co-workers showed that the regioselectivity of palladium-catalyzed alkoxycarbonylation can be controlled through different ligands.[8] Considering the different coordinative modes of aryne (π coordination) and CO (σ coordination) to the center metal, the regioselectivity may be predominantly tuned by the electronic and steric effects of the ligand. On the other hand, the rate of aryne release from *o*-(trimethylsilyl)aryl triflates can be controlled through selection of the fluoride source.[9] Since selectivity is the key challenge, controllable multipath MCRs often show great efficiency in divergent synthesis.[10] Herein, we report a regiodivergent aryne MCR to afford two classes of alkaloid scaffolds controlled through selection of ligand and the releasing rate of aryne (Scheme 1 E).

With this concept, we commenced our study by investigating *N*-methy-2-iodoaniline (**1a**) and benzyne precursor (**2a**). The reaction was first performed in the presence of $Pd(OAc)_2$, K_2CO_3, and KF in toluene at 100 °C, which generated the desired product **3a** in 10% yield (Table 1, entry 1). To promote the solubility of the inorganic salt in the system, MeCN was applied (entry 2) to give **3a** in 33% yield with **4a** formation in 20% yield as well. A slightly increased yield (39%) of **3a** was obtained by changing the fluoride source to CsF. To increase the generation rate of benzyne, phase transfer catalysts were tested to improve the selectivity of the reaction, and TBAI was found to produce the best yield (entries 4–6). In view of iodide anions serving as ligands in Pd-catalyzed reactions, KI was also tested as an additive, but no improvement was observed (entry 7). When 10% of water was added, **3a** could be afforded in 69% yield without formation of **4a** (entry 8). Further study showed that a diluted concentration could help to afford **3a** as the single product in 85% yield (entry 9). To our delight, the acridone product **4a** turned to be the major product when electron-abundant bidentate ligand dppm was applied for stabilizing the catalyst, which demonstrated the ligand acceleration of carbonyl insertion (entry 10). To confirm ligand effect and the influence of nitrogen coordination to the catalytic center, *N*-benzyl-2-iodoaniline was tested with and without dppm, resulting in a better yield of **4a** in the presence of dppm when reacting for 24 h (entries 11 and 12). Other bidentate phosphine ligands such as dppe, dppp, and dppb could not replace dppm for selectivity (entry 13–15), revealing the effect of the ligand bite angle on the insertion rate of CO.[11] Better yields were obtained by slowing down the rate of benzyne generation (entries 16 and 17). Three equivalents of benzyne precursor was used as the best choice for **4a** formation in 82% yield (entry 18).

The results shown in Table 2 demonstrate that this approach has a great potential in the divergent synthesis of functionalized phenanthridinones and acridones. As shown in the left part of Table 2, both electron-rich and electron-deficient iodoanilines could be efficiently transformed to the corresponding phenanthridinone products in good yields with the R group substituted both at positions 4 and 5 (**3a–l**). Notably, substrates bearing aryl bromide moieties, which were prone to oxidative addition with Pd^0, proceeded smoothly in this transformation (**3i**). In particular, **3l** was afforded without regioisomers, and the structure was confirmed by X-ray diffraction.[12] On the other hand, a set of substituted acridones were obtained in overwhelming selectivity under conditions B (**4a–n**). Electron-poor ester group was tolerated and the structure of corresponding acridones was confirmed by X-ray as well (**4n**).[12] Different acridone alkaloids analogues were obtained by utilizing *o*-silyl aryltriflates bearing naturally frequently existing methoxy (**4o**) and 3,4-methylenedioxy groups (**4p**).

As we mentioned, penathridiones and acridones are important natural product scaffolds which show biological activities. We therefore extended the methodology to natural product synthesis (Scheme 2). The acridone alkaloid 2,3-methylenedioxy-10-methyl-9-acridanone **5** was afforded by

Table 1: Optimization of divergent conditions.[a]

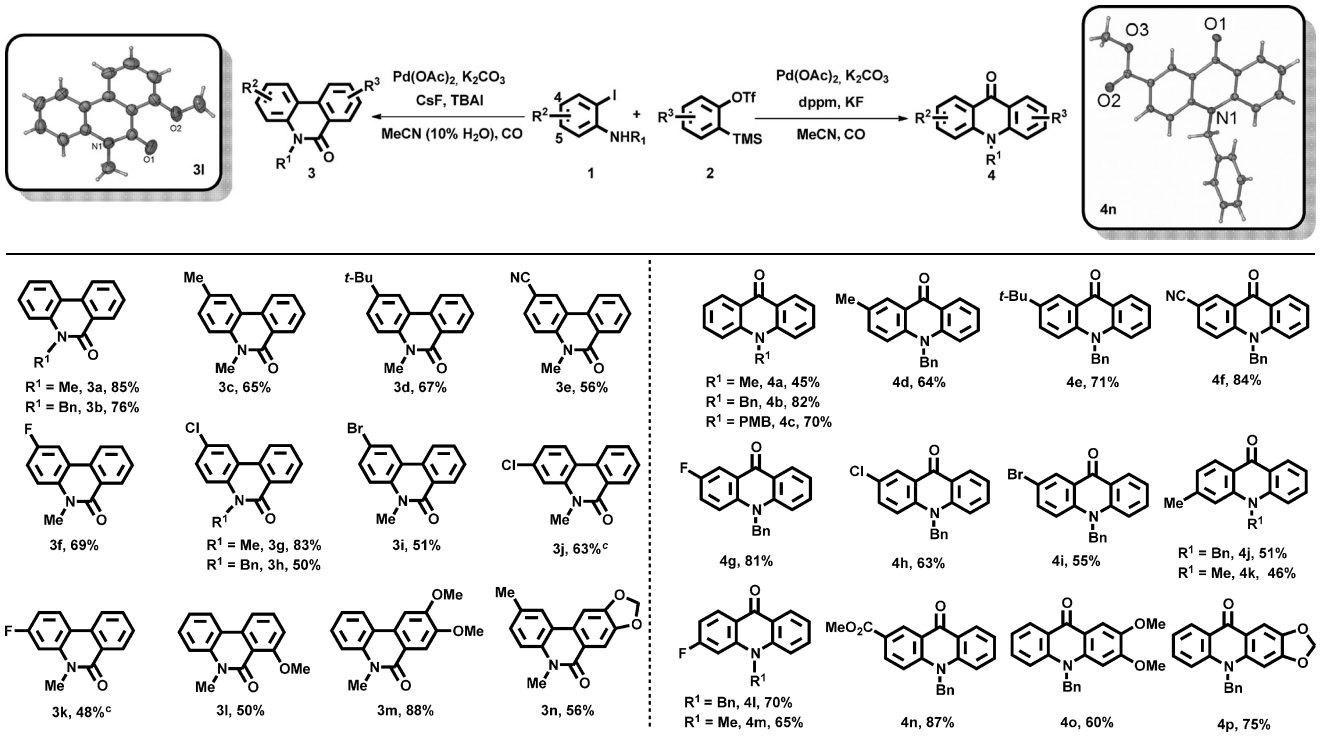


1 2a 3 4

Entry	R	Ligand	Additive	Solvent	"F" reagent	Yield of **3** [%][b]	Yield of **4** [%][b]
1	Me	–	–	toluene	KF	10	nd
2	Me	–	–	MeCN	KF	33	20
3	Me	–	–	MeCN	CsF	39	21
4	Me	–	TBAI	MeCN	CsF	49	18
5	Me	–	TBAB	MeCN	CsF	45	15
6	Me	–	TEBAc	MeCN	CsF	42	17
7	Me	–	KI	MeCN	CsF	40	25
8	Me	–	TBAI	MeCN/ 10% H_2O	CsF	69	nd
9[c]	**Me**	**–**	**TBAI**	**MeCN/ 10% H_2O**	**CsF**	**85**	**nd**
10	Me	dppm	TBAI	MeCN/ 10% H_2O	CsF	trace	30
11[d]	Bn	–	TBAI	MeCN/ 10% H_2O	CsF	76	nd
12[d]	Bn	dppm	TBAI	MeCN/ 10% H_2O	CsF	trace	35
13[d]	Bn	dppe	TBAI	MeCN/ 10% H_2O	KF	43	21
14[d]	Bn	dppp	TBAI	MeCN/ 10% H_2O	KF	35	trace
15[d]	Bn	dppb	TBAI	MeCN/ 10% H_2O	KF	trace	trace
16[d]	Bn	dppm	–	MeCN/ 10% H_2O	CsF	trace	39
17[d]	Bn	dppm	–	MeCN	KF	trace	66
18[d,e]	**Bn**	**dppm**	**–**	**MeCN**	**KF**	**trace**	**82**

[a] Reaction conditions: iodoaniline (0.1 mmol), benzyne precursor (0.15 mmol), $Pd(OAc)_2$ (0.01 mmol), ligand (0.01 mmol), additive (0.02 mmol), "F" reagent (0.3 mmol), K_2CO_3 (0.3 mmol), CO balloon, solvent (1 mL), 100 °C, 12 h. [b] Yields of the isolated products. [c] 2 mL of solvents was used. [d] Reacted for 24 h. [e] Benzyne precursor (0.30 mmol) was used. TBAI = tetrabutylammonium iodide, TBAB = tetrabutylammonium bromide, TEBAC = benzyl triethylammonium chloride, dppm = bis(diphenylphosphino)methane, dppe = bis(diphenylphosphino)ethane, dppp = bis(diphenylphosphino)propane, dppb = bis(diphenylphosphino)butane.

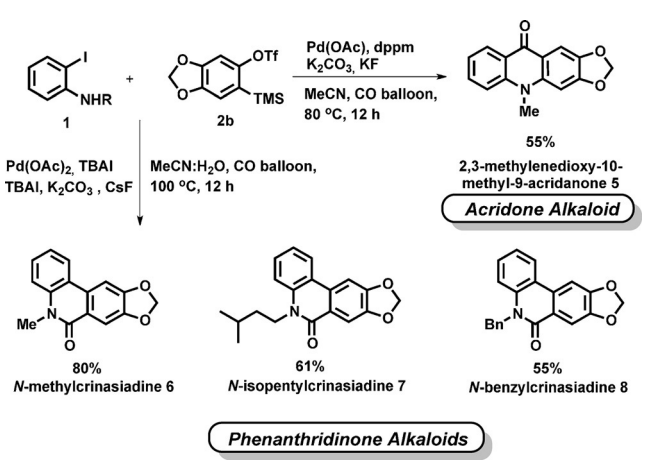
Table 2: Divergent synthesis of functionalized phenanthridinones and acridones.[a,b]



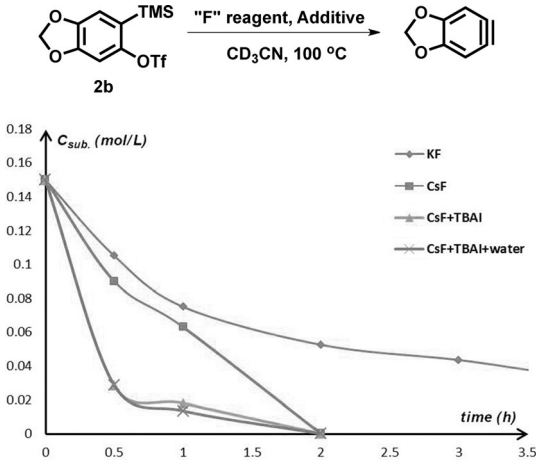
[a] Conditions A: iodoaniline (0.1 mmol), aryne precursor (0.15 mmol), $Pd(OAc)_2$ (0.01 mmol), TBAI (0.02 mmol), CsF (0.3 mmol), K_2CO_3 (0.3 mmol), CO balloon, MeCN (10% H_2O, 2 mL), 100 °C, 12 h; conditions B: iodoaniline (0.1 mmol), aryne precursor (0.3 mmol), $Pd(OAc)_2$ (0.005 mmol), dppm (0.01 mmol), KF (0.3 mmol), K_2CO_3 (0.3 mmol), CO balloon, MeCN (1 mL), 100 °C, 24 h. [b] Yields of the isolated products. [c] Iodoaniline (0.1 mmol), aryne precursor (0.3 mmol), $Pd(OAc)_2$ (0.005 mmol), dppe (0.02 mmol), CsF (0.3 mmol), K_2CO_3 (0.3 mmol), CO balloon, MeCN (1 mL), 100 °C, 12 h. dppm = bis(diphenylphosphino)methane, dppe = bis(diphenylphosphino)ethane.

using *N*-methyl-2-iodoaniline **1a** and 6-(trimethylsilyl)benzo[*d*][1,3]dioxol-5-yl trifluoromethanesulfonate **2b** as the starting materials at lower temperature (80 °C). Moreover, using different *N*-substituted iodoanilines as the partners, **2b** can be transformed into phenanthridinone alkaloids and the synthetic precursors (**6**–**8**) using this one-step strategy.

From the optimization stage, different fluoride reagents and additives showed great influence on regioselectivity and efficiency of the MCR. An interval NMR experiment was carried out to find the relationship among fluoride reagents, additives, and aryne generation rates through monitoring aryne precursor consumption (Scheme 3). When subjected to potassium fluoride in CD_3CN at 100 °C, aryne precursor **2b** was completely consumed in ten hours at a relatively slow rate. In contrast, when exposed to CsF, **2b** was consumed in less than two hours. The addition of TBAI further increased



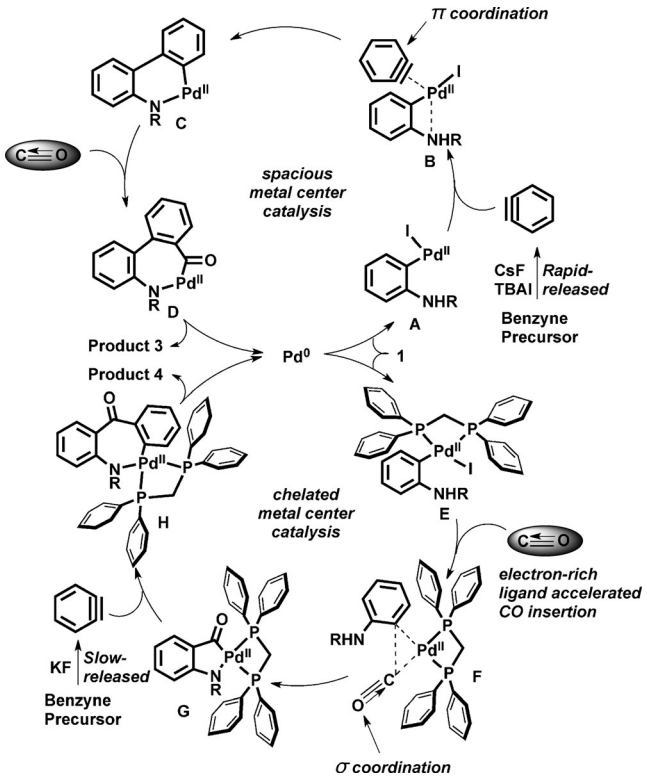
Scheme 2. Natural product synthesis. Yields are given for the isolated products.



Scheme 3. Rate control of aryne generation by different fluoride reagents and additives.

the consumption rate of aryne precursor. The addition of water made no difference on the consumption rate of aryne precursor, which was thought to promote the dissolution of fluoride reagents. Based on these results, it was illustrated that the aryne assembled in high concentration by the rapid-releasing process under the guidance of CsF, TBAI, and water, which tended to preferentially coordinate the catalytic center. Comparably, the slow-releasing of aryne, assisted by single KF, trended to the generation of acridone product **4**.

Based on these results, a mechanistic proposal is drawn in Scheme 4. When no extra ligand was involved, the spacious catalytic center of **A** was formed by the oxidative addition of iodoaniline **1**. Highly concentrated benzyne coordinated to



Scheme 4. Proposed mechanism.

the catalytic center of **A** to generate intermediate **B** by π coordination, which then underwent insertion of aryne giving **C**. Subsequently, CO insertion took place to afford acyl Pd species **D**. Reductive elimination of **D** gave the corresponding phenanthridinone product **3** and regenerate Pd^0. In contrast, a chelated catalytic center of **E** was formed in the presence of bidentate phosphine ligand bis(diphenylphosphino) methane. Owing to the steric hindrance of the four-membered ring from bis(diphenylphosphino) methane coordinating the palladium center and low concentration of aryne in the system, the relatively electron-deficient ligand CO was inclined to coordinate to the electron-abundant chelated catalytic palladium of **E**. After the subsequent CO and aryne insertion, the aryl Pd species **H** was formed. Reductive elimination of Pd from **H** gave the acridone product **4**.

In conclusion, we have developed a palladium-catalyzed regiodivergent C_1 insertion multicomponent reaction to construct a variety of phenanthridinones and acridones. Depending on the ligand and the releasing rate of aryne, two classes of biologically active alkaloids scaffolds can be synthesized in high yields divergently. Representative natural products and a series of their analogues were achieved by this tunable manner, which offers essential compound libraries for drug discovery. Further synthetic applications in complex natural products total synthesis will be reported in due course.

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[12] CCDC 1415210 (**3l**), CCDC 1415209 (**4n**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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