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Pd(II)-Catalyzed One-Pot, Three-Step Route for the Synthesis of Unsymmetrical Acridines

Hai-Ming Guo,*,† Run-Ze Mao,† Qiao-Tian Wang,† Hong-Ying Niu,†,‡ Ming-Sheng Xie,† and Gui-Rong Qu*,†

School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang 453007, Henan, China, and School of Chemistry and Chemical Engineering, Henan Institute of Science and Technology, Xinxiang 453003, China

guohm518@hotmail.com; guguir@sina.com

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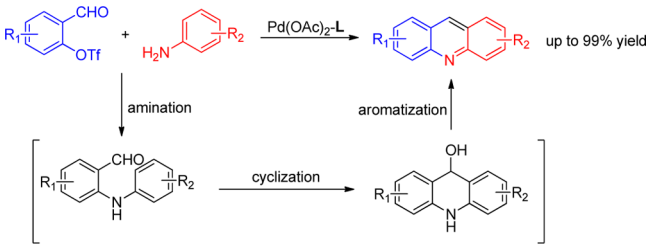
ABSTRACT



Unsymmetric acridines are synthesized via a one-pot amination/cyclization/aromatization reaction for the first time. With $Pd(OAc)_2$-X-Phos as the catalyst, a series of unsymmetric acridines are obtained in moderate to excellent yields (up to 99% yield). Meanwhile, the diphenylamine intermediate could be isolated, which is evidence of the domino process.

Acridines have attracted considerable attention due to their important biological and medicinal activities.[1] As shown in Figure 1, Porflavine, a disinfectant bacteriostatic against many gram-positive bacteria, has been approved by the FDA as a drug.[2] Acrisorcin, a new agent for the control of tinea versicolor, has also been approved by the FDA to serve as a drug.[3] Mepacrine, an intrapleural sclerosing agent, is known to act as a histamine *N*-methyltransferase inhibitor.[4] Since acridines have been proven to be important in many areas, searching for a useful and efficient approach for the synthesis of acridines is therefore highly desirable.

The Bernthsen acridine synthesis, a name reaction, consists of heating diphenylamine and carboxylic acids with zinc chloride as the catalyst (Scheme 1a).[5] Later, Larock's group developed a [4 + 2] annulation of 2-aminoaryl ketones with arynes generated in situ from *o*-(trimethylsilyl)aryl triflate with CsF (Scheme 1b).[6] In 2010, Buchwald et al.

† Henan Normal University.
‡ Henan Institute of Science and Technology.

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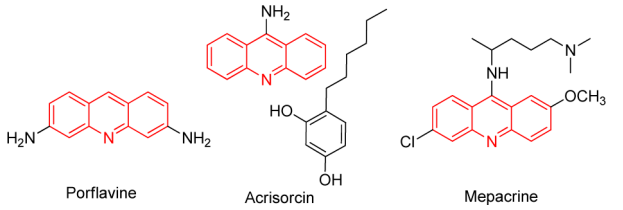


Figure 1. Selected examples of acridines that exhibit important biological and medicinal activities.

reported the *N*-arylation/Heck type transformation of 2-bromostyrene and 2-chloroaniline to construct an acridine derivative (Scheme 1c).[7] Very recently, when we were preparing the present manuscript, Ellman et al. reported Ru(III)-catalyzed [3 + 3] annulations of aromatic azides and aromatic imines to give acridines, in which the imine part functioned as the directing group (Scheme 1d).[8] Although great endeavors have been devoted to the synthesis of acridines,[9] a new and efficient method for the synthesis of acridines is still in great demand. Herein, we report our findings on the domino amination/cyclization/aromatization reaction of 2-formylphenyl triflate and anilines to construct unsymmetrical acridines (Scheme 1e).

Scheme 1. Strategies for the Synthesis of Acridines

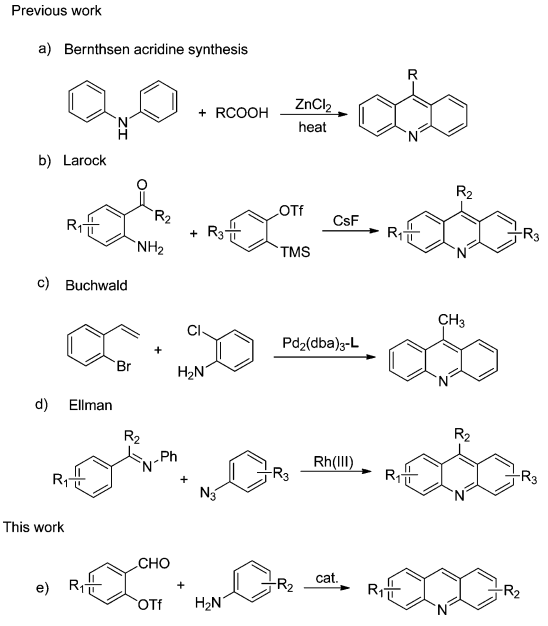
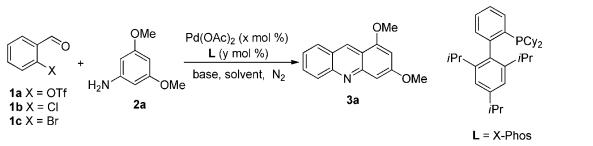


Table 1. Optimization of the Reaction Conditions[a]



entry	*x*	*y*	base	solvent	*t* (°C)	yield (%)[b]
1	10	15	*t*-BuOK	toluene	105	trace
2	10	15	Cs_2CO_3	toluene	105	trace
3	10	15	Na_2CO_3	toluene	105	trace
4	10	15	K_3PO_4	toluene	105	trace
5	10	15	K_2CO_3	toluene	105	99
6	10	15	K_2CO_3	*o*-xylene	105	87
7	10	15	K_2CO_3	*p*-xylene	105	82
8	10	15	K_2CO_3	dioxane	105	trace
9	10	15	K_2CO_3	DMF	105	trace
10	10	15	K_2CO_3	toluene	100	92
11	10	15	K_2CO_3	toluene	120	87
12	5	15	K_2CO_3	toluene	105	76
13	10	10	K_2CO_3	toluene	105	83
14	5	7.5	K_2CO_3	toluene	105	72
15[c]	10	15	K_2CO_3	toluene	105	trace
16[d]	10	15	K_2CO_3	toluene	105	trace
17[e]	10	15	K_2CO_3	toluene	105	trace

[a] Unless otherwise mentioned, the reactions were carried out with **2a** (0.2 mmol), **1a** (0.24 mmol), $Pd(OAc)_2$-**L**, base (2.0 equiv), and solvent (2.0 mL) in a Schlenk tube at 105 °C for 13 h under a N_2 atmosphere. [b] Isolated yield. [c] Air atmosphere. [d] **1b** as the substrate. [e] **1c** as the substrate.

Initially, 2-formylphenyl triflate (**1a**) and 3,5-dimethoxyaniline (**2a**) were chosen as model substrates to explore the domino reaction conditions (Table 1). With $Pd(OAc)_2$-X-Phos as the catalyst, various bases including *t*-BuOK, Cs_2CO_3, Na_2CO_3, K_3PO_4, and K_2CO_3 were examined in toluene at 105 °C (entries 1−5). Surprisingly, the base had great impact on the reactivity of the reaction, and K_2CO_3 could afford the desired acridine **3a** with quantitative yield (99% yield, entry 5). Encouraged by the results, the solvent effect was tested. Changing toluene to *o*-xylene, *p*-xylene, dioxane, and DMF did not produce better results (entries 6−9). Subsequently, the reaction temperature was also examined, and the results showed that 105 °C was the best choice (entries 5 vs 10−11). Then, the ratio of $Pd(OAc)_2$ and X-Phos was examined, and x/y = 1:1.5 was determined to be the suitable ratio (entries 5 vs 12−13). When the catalyst loading was reduced to 5 mol %, the product of **3a** was obtained with 72% yield (entry 14). Meanwhile, when the domino reaction was performed under an air atmosphere, only a trace amount of annulation product **3a** was observed, which indicated that the N_2 was crucial for the domino reaction to occur (entry 15). Last, when 2-chlorobenzaldehyde (**2b**) or 2-bromobenzaldehyde (**2c**) was used to react with 3,5-dimethoxyaniline (**2a**), the reaction could hardly proceed, which means that the triflate group was essential for the reaction to occur (entries 16−17). Thus, the optimal reaction conditions

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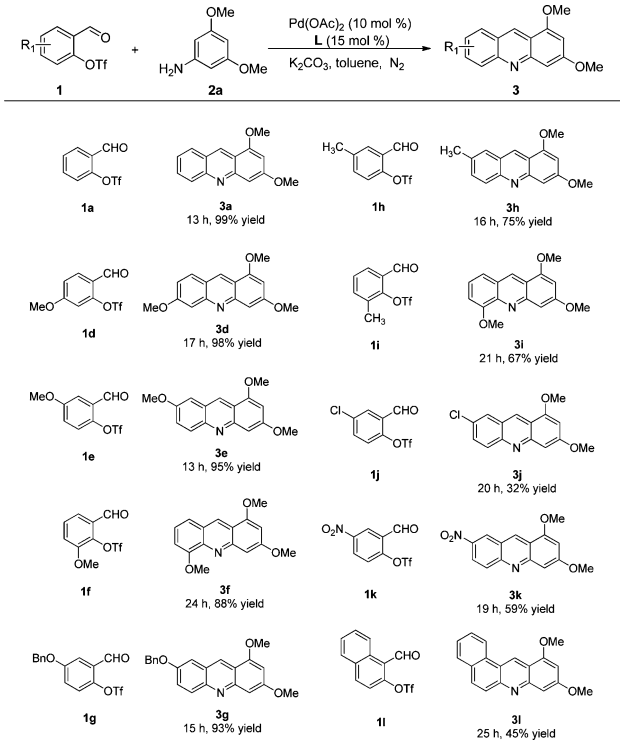
were $Pd(OAc)_2$ (10 mol %), X-Phos (15 mol %), and K_2CO_3 as the base in toluene at 105 °C under N_2 for 13 h (Table 1, entry 15).

Under the optimized conditions (Table 1, entry 5), the substrate scope of the domino reaction was examined (Scheme 2). When the position (4, 5, or 6 position) of 2-formylphenyl triflate was introduced with a methoxy group, the domino reaction proceeded well, affording the corresponding acridines **3d**–**3f** with 88–98% yields. In addition, when the methoxy group was changed with a benzyloxy group, a comparable yield could still be obtained (**3g**, 93% yield). Meanwhile, 4-methyl or 6-methyl substituted substrates could also be tolerated in the reaction to give the acridines **3h** and **3i** in good yields. Next, 4-chloro or 4-nitro substituted substrates could also furnish the target acridines **3j**–**3k**, albeit the yields were somewhat low. Notably, the ring-fused substrate **1l** could also give the product **3l** in moderate yield, providing a useful access for the preparation of the benzo[*a*]acridine derivative.

Scheme 2. Reaction with Various 2-Formylphenyl Triflates[a,b]

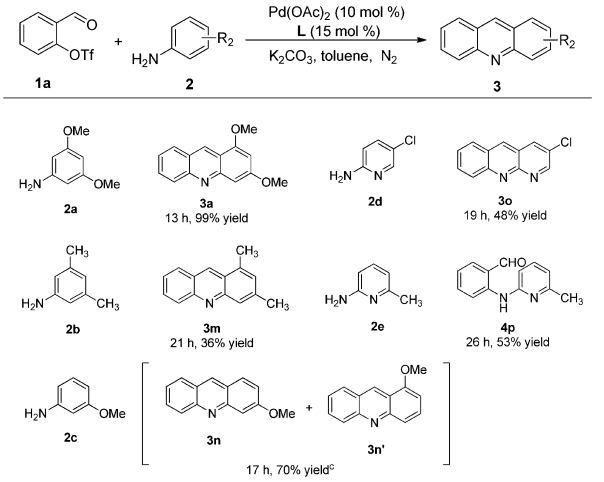


[a] Reaction conditions: **2a** (0.2 mmol), **1** (0.24 mmol), $Pd(OAc)_2$-**L**, K_2CO_3 (2.0 equiv), toluene (2.0 mL) in a Schlenk tube at 105 °C under N_2 atmosphere. [b] Isolated yield.

To further test the generality of the domino reaction, a series of anilines (**2a**–**2f**) were investigated under the optimized reaction conditions (Scheme 3).[10] When

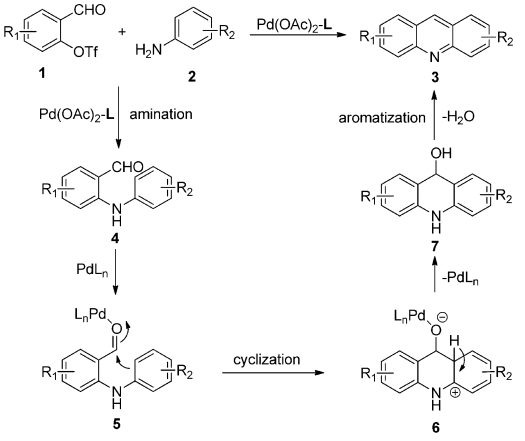
(10) 2-Hydroxyl aniline, 3-hydroxyl aniline, and 3-amino aniline had been tested, and the desired products were not formed. Meanwhile, when 3-isopropoxyaniline, 3-phenoxyaniline, and 3-(benzyloxy)aniline were used, trace products were observed, which were hard to isolate.

Scheme 3. Reaction with Various Anilines[a,b]



[a] Reaction conditions: **2** (0.2 mmol), **1a** (0.24 mmol), $Pd(OAc)_2$-**L**, K_2CO_3 (2.0 equiv), and toluene (2.0 mL) in a Schlenk tube at 105 °C under a N_2 atmosphere. [b] Isolated yield. [c] The ratio of 3-methoxyacridine **3n** to 1-methoxyacridine **3n′** is 2:1.

Scheme 4. Preliminary Proposed Mechanism for the Domino Amination/Cyclization/Aromatization Reaction



3,5-dimethylaniline (**2b**) was used as the aniline component, the yield decreased greatly. Meanwhile, 3-methoxyaniline **2c** could afford the corresponding acridine **3n** with 70% yield, which had a 2:1 regioselective ratio and the annulation occurred at the less hindered site. We were pleased to find that 5-chloropyridin-2-amine **2d** could also give the acridine **3o** in moderate yield. However, when pyridin-2-amines **2e** was used to react with 2-formylphenyl triflate (**1a**), the corresponding acridine could not be formed. The isolated stable 2-amino-benzaldehyde derivative **4p** was obtained, which indicated that the amination reaction is the first step of this domino reaction.

Based on the results and previous work,[11,12] a preliminary mechanism of this domino reaction was proposed as follows (Scheme 4). The first step was the Pd-catalyzed amination reaction to form the diphenylamine intermediate **4**, which

could be isolated for many substrates. Subsequently, the carbonyl group of intermediate **4** was activated by the Pd catalyst. Then, the cyclization occurred with the formation of intermediate **6** through an intramolecular nucleophilic attack from intermediate **5**. After releasing the Pd catalyst, the aromatization reaction occurred with dehydration to generate the final acridine **3**.

In summary, we have developed a Pd-catalyzed one-pot amination/cyclization/aromatization reaction to construct acridines for the first time. With $Pd(OAc)_2$-X-Phos as the catalyst, a series of unsymmetric acridines were obtained in moderate to excellent yields (up to 99% yield). Meanwhile, the diphenylamine intermediate could be isolated, which proved the domino reaction mechanism. Further investigation of the reaction mechanism is in progress in our laboratory.

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Supporting Information Available. Experimental procedure, characterization data, and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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