



Facile construction of pyrrolophenanthridone skeleton via a one-pot intramolecular Heck reaction and oxidation



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ABSTRACT

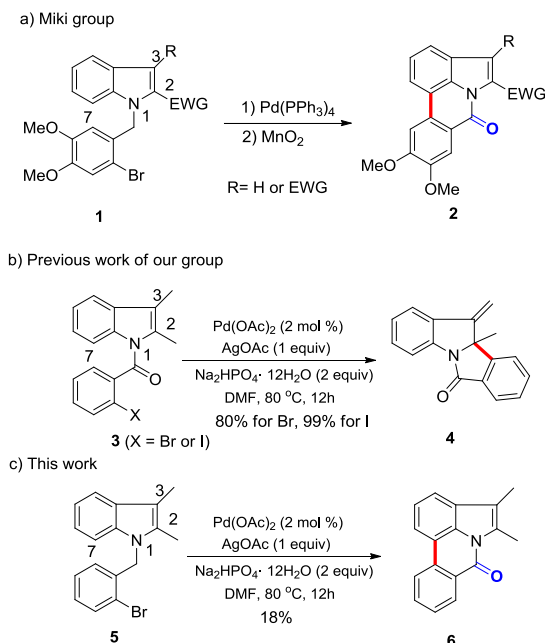
Construction of pyrrolophenanthridone skeleton via a one-pot Pd-catalyzed intramolecular Heck reaction followed by oxidation has been achieved in moderate to good yields. The reaction mechanism has been proposed.

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1. Introduction

Pyrrolophenanthridone is a common structural motif existed in a number of natural alkaloids,¹ many of which exhibit a wide range of biological activities.² The intriguing structural feature and interesting bioactivities have attracted much attention from synthetic communities. In the past decades, several excellent methods have been reported,³ in which intramolecular cyclization through radical⁴ or palladium catalyzed pathway⁵ represents the most straightforward method for construction of this skeleton. In 1999, Miki and co-workers reported a two-step sequence for the preparation of pyrrolophenanthridones.⁶ In this case, *N*-(2-bromobenzyl) indole substrate (**1**) underwent Pd(0) catalyzed intramolecular coupling, followed by the oxidation with MnO₂ to yield the corresponding product (**2**, Scheme 1a). To the best of our knowledge, none of direct construction of pyrrolophenanthridones from *N*-(2-bromobenzyl) indoles was reported.

During the last few years, many transition-metal catalyzed coupling reactions have been developed for the functionalization of arenes.⁷ Among them, palladium-catalyzed intramolecular cyclization of heteroarenes has been proved to be one of the most



Scheme 1. Construction of pyrrolophenanthridone skeleton.

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efficient methods to build diverse polycyclic compounds.⁸ Very recently, we disclosed an efficient construction of fused indoline (**4**) with a 2-quaternary center through a palladium-catalyzed intramolecular Heck reaction of *N*-(2-halobenzoyl)-2,3-disubstituted indoles (**3**, Scheme 1b).⁹ However, when *N*-(2-bromobenzyl) substituted indole (**5**) was used as a substrate under the same reaction conditions, no fused indoline product was observed, but instead, the intramolecular coupling occurred at the C7-position and the methylene was oxidized to a carbonyl group, leading to pyrrolophenanthridone skeleton (**6**) as a major product (Scheme 1c). We herein report the direct construction of pyrrolophenanthridones from *N*-(2-bromobenzyl) indoles via a one-pot intramolecular Heck reaction and oxidation.

2. Results and discussion

We began our investigation using **5a** as a model substrate. The results were summarized in Table 1.¹⁰ When **5a** was treated with 10 mol % of Pd(OAc)₂, 2 equiv of AgOAc, and 2 equiv of K₂CO₃ in DMF at 120 °C for 15 h, we were delighted to find that the desired product **6a** was afforded in about 53% yield with 31% of **5a** recovery (Table 1, entry 1). Encouraged by this result, a variety of catalysts and oxidants were evaluated to optimize the reaction conditions. First screening of oxidants suggested that the yield could be promoted to 66% when Ag₂CO₃ was used (entries 2, 3). Very interestingly, the yield of **6a** was improved when the reaction was carried out under argon atmosphere (entry 5), but remarkably dropped under oxygen atmosphere (entry 4). Next screening on bases suggested that replacing K₂CO₃ with a weaker base, KHCO₃, could slightly promote the yield to 86% (entries 6, 7). Further tests on the loadings of the catalyst and oxidant revealed that the yields of **6a** dropped when the loadings were declined (entries 8, 9). A survey of reaction temperature showed that 120 °C was necessary for full consumption of **5a** (entry 10). Finally, we were pleased to find that the yield of **6a** could be increased to 92% by the use of PPh₃

Table 1
Screening of reaction conditions^{a, 10}

Entry	Catalyst (10 mol %)	Ligand (mol %)	Oxidant (2 equiv)	Base (2 equiv)	Yield (%) ^b
1	Pd(OAc) ₂		AgOAc	K ₂ CO ₃	53
2	Pd(OAc) ₂		Ag ₂ CO ₃	K ₂ CO ₃	66
3	Pd(OAc) ₂		Cu(OAc) ₂	K ₂ CO ₃	19
4	Pd(OAc) ₂		Ag ₂ CO ₃ /O ₂	K ₂ CO ₃	31
5	Pd(OAc) ₂		Ag ₂ CO ₃ /Ar	K ₂ CO ₃	79
6	Pd(OAc) ₂		Ag ₂ CO ₃ /Ar	CS ₂ CO ₃	4
7	Pd(OAc) ₂		Ag ₂ CO ₃ /Ar	KHCO ₃	86
8^c	Pd(OAc) ₂		Ag ₂ CO ₃ /Ar	KHCO ₃	80
9^d	Pd(OAc) ₂		Ag ₂ CO ₃ /Ar	KHCO ₃	72
10^e	Pd(OAc) ₂		Ag ₂ CO ₃ /Ar	KHCO ₃	81
11	Pd(OAc) ₂	PPh ₃ (40)	Ag ₂ CO ₃ /Ar	KHCO ₃	92 ^f
12	Pd(PPh ₃) ₄	PPh ₃ (40)	Ag ₂ CO ₃ /Ar	KHCO ₃	60
13	Pd ₂ (dba) ₃	PPh ₃ (40)	Ag ₂ CO ₃ /Ar	KHCO ₃	58
14	Pd(OAc)₂	PPh₃(20)	Ag₂CO₃/Ar	KHCO₃	92^f
15	None		Ag ₂ CO ₃ /Ar	KHCO ₃	NR

Bold value signifies the optimized conditions.

^a Reaction conditions: **5a** (0.5 mmol) in DMF (2 mL) at 120 °C for 15 h.

^b ¹H NMR yields using dibromomethane ($\delta=4.80$) as an internal standard.

^c Pd(OAc)₂ (5 mol %) was used.

^d Ag₂CO₃ (1 equiv) was used.

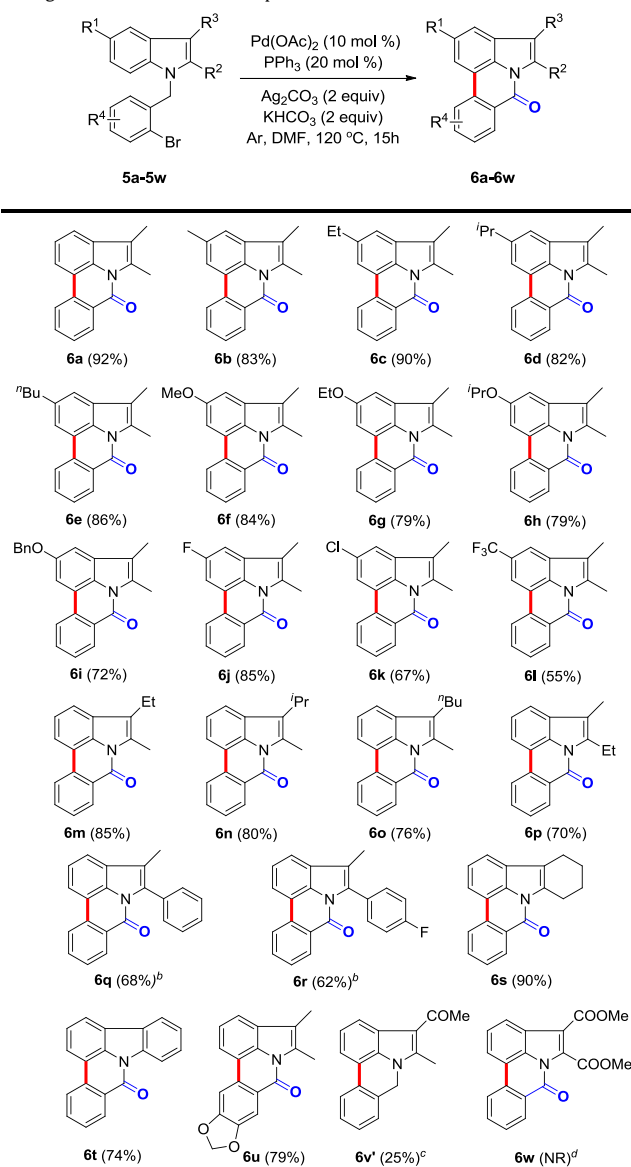
^e 100 °C.

^f Isolated yields.

as a ligand (entries 11, 14). Replacing Pd(OAc)₂ with other commonly used Pd(0) catalysts gave no further improved results (entries 12, 13). A control experiment confirmed that palladium catalyst was necessary in this process (entry 15).

With the established conditions in hand, we then focused on the investigation of the substrate scope. We were delighted to find that most substrates in Table 2 could undergo the cross-coupling reaction under the optimized conditions, resulting in the corresponding products (**6a–u**) in moderate to excellent yields. We first examined the substituent effect on the benzene ring of the indole part. A variety of functional groups, such as hydrogen, electron-donating, and -withdrawing groups, and halogen on the benzene ring of the indole part were compatible. The substrates bearing

Table 2
Investigation on the substrate scope^{a, 10}



^a Reaction conditions: **5** (0.5 mmol), Pd(OAc)₂ (0.05 mmol, 10 mol %), PPh₃ (0.1 mmol, 20 mol %), Ag₂CO₃ (1 mmol, 2 equiv) and KHCO₃ (1 mmol, 2 equiv), in DMF (2 mL) under argon atmosphere at 120 °C for 15 h. Isolated yields.

^b 24 h.

^c None of oxidation product was observed and 57% of **5v** was recovered.

^d No reaction and 82% of **5w** was recovered.

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