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Construction of indoloquinolinones via Pd(II)-catalyzed tandem C—C/C—N bond formation: application to the total synthesis of isocryptolepine

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ABSTRACT

Construction of indoloquinolinone skeleton via Pd-catalyzed tandem C—C/C—N bond formation has been achieved in moderate to good yields. The method was applied toward the total synthesis of the bioactive natural product isocryptolepine in good overall yields.

Indole-containing polycyclic compounds are widely found in natural products and many are clinically used as therapeutic drugs (Fig. 1).[1] Reserpine, an effective hypotensive agent, exists in many species of Rauvolfia Linn.[2] Fumitremorgin C is described as a potent ABCG2/BCRP inhibitor that reverses multidrug resistance.[3] Indoloquinolinones are found in numerous versatile synthetic molecules, many of which exhibit a wide range of biological activities (Fig. 1A1 and A2).[4] Moreover, the indoloquinolinone structure is always employed as an important building block to the synthesis of natural products, such as isocryptolepine.[5] Several methods have been reported for the construction of the indoloquinolinone skeleton.[6]

In the past few years, transition-metal catalyzed tandem C—C/C—N bond coupling reactions have been reported for the formation of nitrogenous compounds.[7] Among them, rhodium or ruthenium catalyzed C—H/N—H cyclization reactions were the mainstream, while most of the reported cases were limited to the substituted phenyl derivatives with alkynes or diazo esters.[8] Recently, the cyclization reactions were extended to indole ring derivatives. In 2010, Jiao's group reported a Pd(II)-catalyzed direct dehydrogenative annulation of indolecarboxamides with internal alkynes via C—H/N—H bond cleavage (Scheme 1a).[9] In 2014, Cui and coworkers developed a Rh(III)-catalyzed tandem coupling of *N*-methoxy-1*H*-indole-1-carboxamide and aryl boronic acids (Scheme 1b).[10] To the best of our knowledge, no example of the construction of indoloquinolinones from *N*-methoxy-1-methyl-1*H*-indole-3-carboxamide has been reported. Continuing our interest in palladium-catalyzed C—H functionalization of indole ring,[11] herein, we will report the Pd(II)-catalyzed tandem C—C/C—N bond formation for the construction of indoloquinolinones and apply our approach toward the total synthesis of the bioactive natural alkaloid isocryptolepine (Scheme 1c).

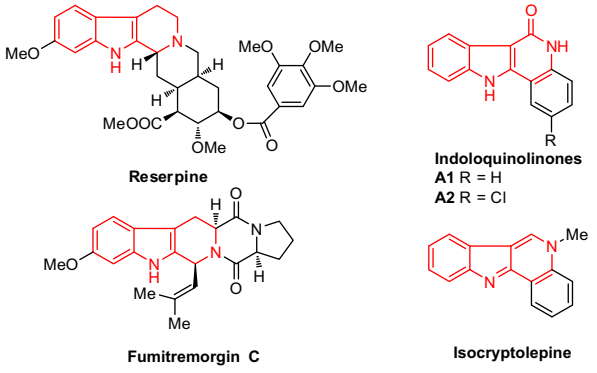

Figure 1. Examples of bioactive indole-containing polycyclic compounds.

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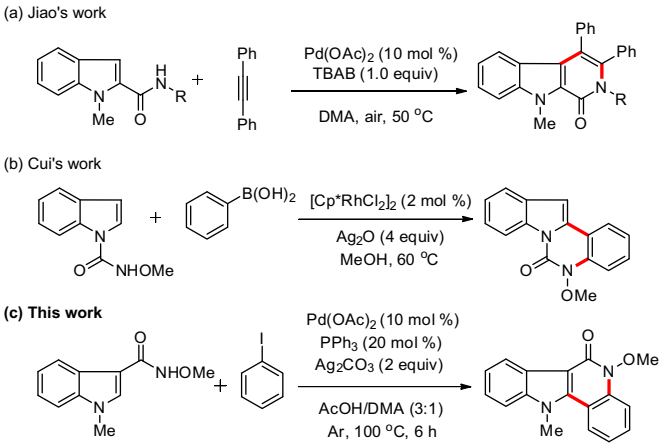
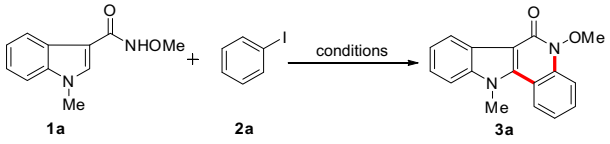


Scheme 1. Transition-metal catalyzed tandem C—C/C—N bond formation.

Our initial investigation focused on the coupling of *N*-methoxy-1-methyl-1*H*-indole-3-carboxamide (**1a**) with phenyl iodide (**2a**), the results were summarized in Table 1. When **1a** was treated with 10 mol % $Pd(OAc)_2$, 2 equiv of Ag_2O in AcOH at 100 °C for 12 h, we were delighted to find that the desired product **3a** was afforded in 13% yield with the decomposition of **1a** (Table 1, entry 1). Subsequent screening of oxidants suggested that the silver salts were indispensable. Other oxidants such as $K_2S_2O_8$, $PhI(OAc)_2$, $Cu(OAc)_2$ were all ineffective (Table 1, entries 2–4). Phosphine ligands are usually employed to promote the palladium-catalyzed C—H activation reactions,[12] then we added 20 mol % phosphine ligands to the reaction system. Fortunately, the use of PPh_3 or John Phos could increase the yield of the desired product **3a** to 32% and 20%, respectively (entries 5 and 6). Then, some silver salts were screened, and Ag_2CO_3 was the best choice (entry 8). When the reaction time was shortened to 6 h, the reaction could also be completed smoothly and promoted the yield to 55% (entry 9). We found that the strong acidity of solvent leads to the decomposition of the starting material at high temperatures,[13] then we tested our reaction in mixed solvents (entries 10–13). The results showed that the yield of **3a** increased to 83% when the reaction was carried out in AcOH/DMA (3:1) under argon atmosphere (entry 13). Replacing $Pd(OAc)_2$ with other commonly used Pd(II) catalysts gave unsatisfactory results (entries 14 and 15). Without PPh_3, the yield decreased to 20% (entry 16). When phenyl bromide was used instead of phenyl iodide, no product was afforded (entry 17).

With the optimized conditions in hand, we then focused on the substrate scope and generality of the reaction. To our delight, most substrates in Table 2 could react smoothly to provide the desired products **3a**–**3o** in moderate to good yields. The C5-position of the indoles bearing the methoxyl, methyl, or bromine group afforded **3b**, **3c**, and **3d** in 67%, 64%, and 58% yield. The yield of **3e** decreased to 46% due to steric hindrance. Unfortunately, the substrate bearing $-NO_2$ at the C5-position could not generate the

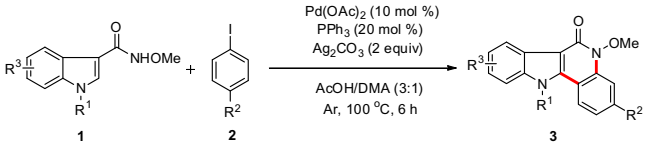
Table 1
Screening of reaction conditions[a]

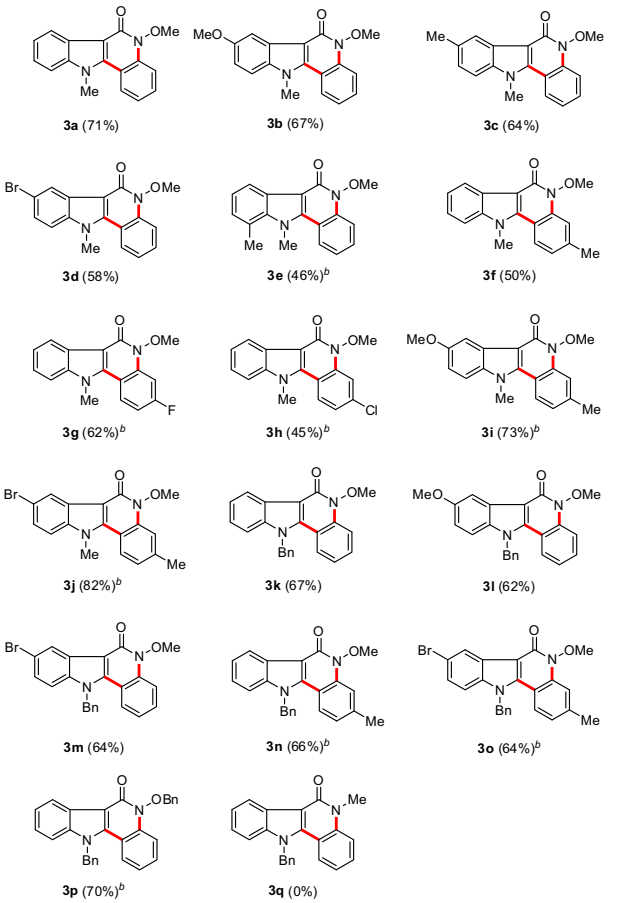


Entry	Catalyst	Ligand	Oxidant	Solvent (3:1)	Yield[b] (%)
1	$Pd(OAc)_2$	None	Ag_2O	AcOH	13[d]
2	$Pd(OAc)_2$	None	$K_2S_2O_8$	AcOH	Trace
3	$Pd(OAc)_2$	None	$PhI(OAc)_2$	AcOH	Trace
4	$Pd(OAc)_2$	None	$Cu(OAc)_2$	AcOH	Trace
5	$Pd(OAc)_2$	PPh_3	Ag_2O	AcOH	32
6	$Pd(OAc)_2$	John Phos	Ag_2O	AcOH	20
7	$Pd(OAc)_2$	PPh_3	AgOAc	AcOH	36
8	$Pd(OAc)_2$	PPh_3	Ag_2CO_3	AcOH	50
9[c]	$Pd(OAc)_2$	PPh_3	Ag_2CO_3	AcOH	55
10[c]	$Pd(OAc)_2$	PPh_3	Ag_2CO_3	AcOH/Tol	49
11[c]	$Pd(OAc)_2$	PPh_3	Ag_2CO_3	AcOH/DMF	58
12[c]	$Pd(OAc)_2$	PPh_3	Ag_2CO_3	AcOH/DMSO	53
13[c]	**$Pd(OAc)_2$**	**PPh_3**	**Ag_2CO_3/Ar**	**AcOH/DMA**	**83(71)[d]**
14[c]	$PdCl_2$	PPh_3	Ag_2CO_3/Ar	AcOH/DMA	29
15[c]	$Pd(TFA)_2$	PPh_3	Ag_2CO_3/Ar	AcOH/DMA	36
16[c]	$Pd(OAc)_2$	None	Ag_2CO_3/Ar	AcOH/DMA	20
17[c]	$Pd(OAc)_2$	PPh_3	Ag_2CO_3/Ar	AcOH/DMA	0[e]

[a] Reaction conditions: Catalyst (10 mol %), Ligand (20 mol %), **1a** (0.5 mmol), **2a** (1.5 mmol) in AcOH (3 mL) at 100 °C for 12 h.
[b] ^1H NMR yields using dibromomethane ($\delta = 4.80$) as an internal standard.
[c] The reaction time was 6 h.
[d] Isolated yields.
[e] Phenyl bromide was used.

Table 2
Investigation on the substrate scope[a]



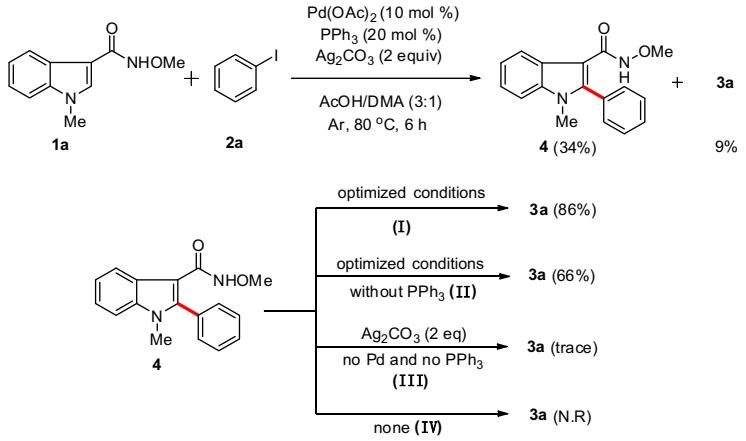


[a] Reaction conditions: **1** (0.5 mmol), **2** (1.5 mmol), $Pd(OAc)_2$ (0.05 mmol, 10 mol %), PPh_3 (0.1 mmol, 20 mol %), Ag_2CO_3 (1 mmol, 2 equiv) in AcOH (3 mL)/DMA (1 mL) under argon atmosphere at 100 °C for 6 h. Isolated yields.
[b] 110 °C.

desired product. Aryl iodides bearing the methyl group offered **3f**, **3i**, and **3j** in 50%, 73%, and 82% yield, respectively. Aryl iodides bearing the halogen group, such as –F and –Cl gave **3g** and **3h** in 62% and 45% yields. *N*-benzyl substituted indoles could also be compatible in the reaction and offered **3k**–**3o** in 62–67% yields. Replacing the methoxy group with the benzyloxy group on the amide yielded the product **3p** in 70%, while *N*-methyl-1-methyl-1*H*-indole-3-carboxamide could not offer the corresponding product **3q** under optimized conditions.

During the screening of the reaction temperature, we observed that when the reaction was carried out at 80 °C, the reaction furnished **3a** in 9% yield with **4** in 34% yield (Scheme 2). This phenomenon suggested that **3a** may be generated from **4**. Under optimized reaction conditions, the **3a** could be obtained in 86% yield from **4** (Scheme 2, I). Without PPh_3, a decreased yield (66% vs 86%) was achieved (Scheme 2, II). Without $Pd(OAc)_2$ and PPh_3, only a trace product was monitored (Scheme 2, III). Without any catalysts and additives, no reaction occurred (Scheme 2, IV). Based on these results and previous reports,[13,8a,8d] here, we proposed a plausible mechanism for our tandem C—C/C—N bond formation reaction as illustrated in Figure 2. The reaction of **1a** with $Pd(OAc)_2$ formed the five-membered palladacycle **A**, which was oxidized to the Pd^{IV} species **B** by phenyl iodide.[14] Reductive elimination gave arylated product **4**. Subsequent deprotonation of the N—H and C—H activation of **4** led to the seven-membered palladacycle **C**. Reductive elimination of **C** afforded **3a** and a Pd^0 species, which was oxidized by Ag_2CO_3 to regenerate the active Pd^{II} species for the next catalytic cycle (Fig. 2).

Application of this method was demonstrated with the synthesis of the bioactive natural alkaloid isocryptolepine **6**, which has been isolated in 1995 from the West African plant *Cryptolepis sanguinolenta*. Compound **3k** was an appropriate platform for conversion into isocryptolepine in two additional steps as shown in Scheme 3. The removal of methoxyl, N-methylation of amide and N-debenzylation of **3k** could be completed in one pot to offer compound **5** in 77% yield.[6a,8f] Reduction of **5** with $NaBH_4$ and $BF_3{\cdot}Et_2O$ furnished isocryptolepine **6** in 84% yield smoothly (Scheme 3). Compared with other methods,[15] our strategy represented the



Scheme 2. Studies on reaction mechanism.

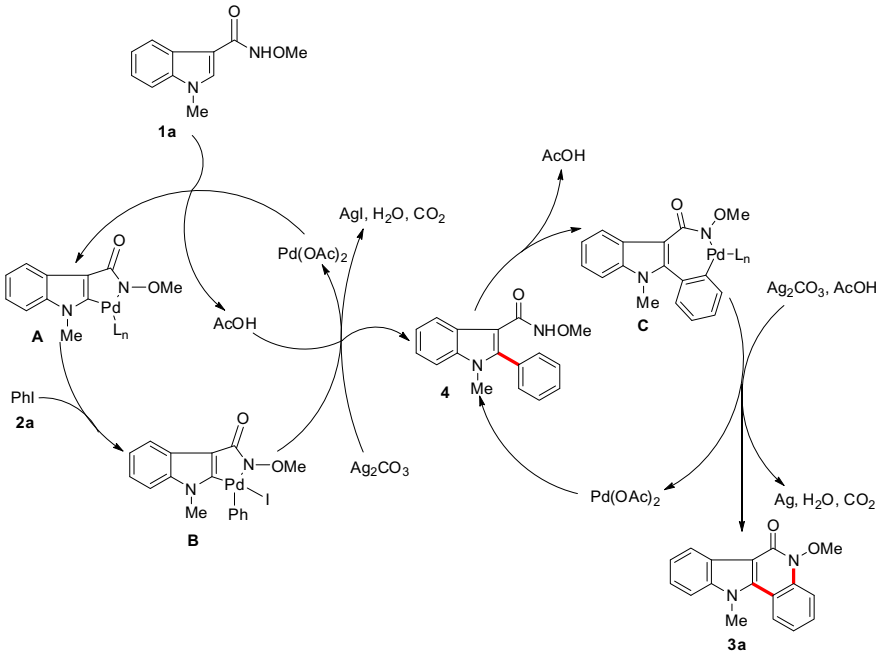
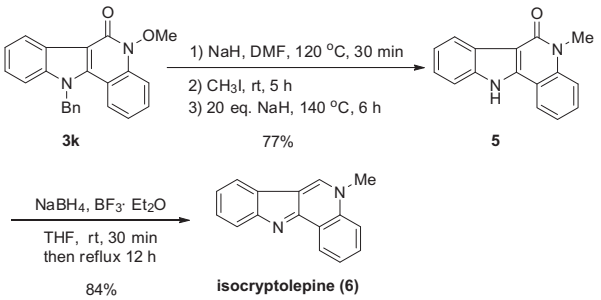


Figure 2. Plausible reaction mechanism. Ln = Ligand.



Scheme 3. Synthesis of isocryptolepine.

shortest and cheapest route to prepare isocryptolepine in 43% overall yield from *N*-methoxy-1-benzyl-1*H*-indole-3-carboxamide.

In conclusion, we have developed a facile method for the construction of indoloquinolinones via Pd(II)-catalyzed tandem C—C/C—N bond formation in good yields and functional group tolerance. In addition, the application of the method to the total synthesis of natural product isocryptolepine highlighted the potential utility of this method in the synthesis of complex natural compounds. Further detailed mechanism research and application in other natural products synthesis are in progress in our laboratory.

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Supplementary data

Supplementary data (detailed results of reaction condition screening and general experimental procedures, along with ^{1}H NMR and ^{13}C NMR spectra of **3a**–**3p**, **4**–**6**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.11.008.

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