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# Synthesis of Indole-Substituted Indanones via Palladium(II)-Catalyzed Tandem Reaction of *ortho*-Electron-Deficient Alkynyl-Substituted Aryl Aldehydes with Indoles

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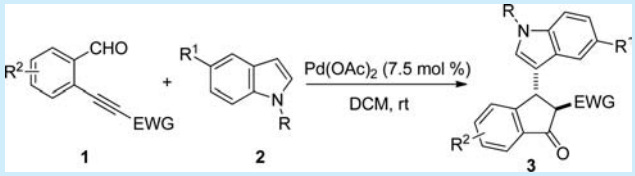
Supporting Information

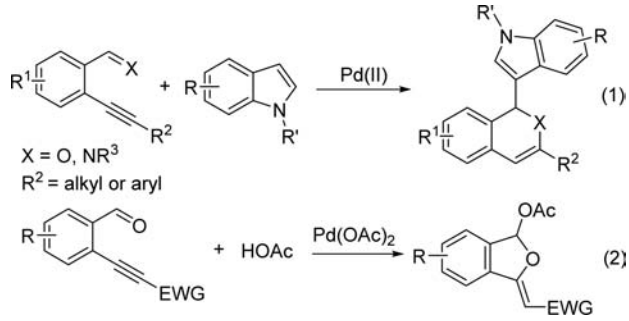
**ABSTRACT:** A $Pd(OAc)_2$-catalyzed cyclization reaction of *ortho*-electron-deficient alkynyl-substituted aryl aldehydes with indoles was accomplished, providing an efficient and economical way to synthesize indole-substituted indanones. The electron-withdrawing group attached to the alkyne and the nucleophilic indole play important roles in the formation of the indanone ring.




Indole derivatives, which ubiquitously exist in pharmaceuticals, agrochemicals, and functional materials, have gained increasing attention in exploring mild and efficient methods to access this kind of heterocyclic compounds.[1] Compared with the enormous effort devoted to the construction of indole rings,[1c] less emphasis has been placed on the functionalization of indole rings.[2] Among the functionalizations of this skeleton, their reactions as nucleophiles with various electrophiles catalyzed by transition metals constitute a convenient approach to polysubstituted indoles.[2,3]

On the other hand, the development of new domino strategies for the synthesis of cyclic compounds has fascinated many researchers.[4] The big advantage of such strategies lies in the fact that the procedure usually starts from easily available building blocks using a single sequential transformation. In the last two decades, the use of *o*-alkynylaryl aldehydes as handy building blocks to react with a variety of nucleophiles for the preparation of carbo- or heterocycles by sequential inter/intramolecular nucleophilic addition cyclization has been well-established.[5] Among these established methods, transition-metal-catalyzed reactions have proved to be more efficient because both the alkyne and the aldehyde group can be activated by transition metals and thus attacked by nucleophiles easily. Indole rings are electron-rich and therefore, they can also act as good nucleophiles to react with *o*-alkynylaryl aldehydes. Recently, Li[6] and our group[7] reported Pd(II)-catalyzed tandem reactions of *o*-alkynylaryl aldehydes with indoles. In the above reactions, the alkynes tethered to the aryl aldehydes were substituted by aryl or alkyl groups on another side, and a 6-endo-dig cyclization was realized to give 1*H*-isochromenes (eq 1).

In our previous work, it was found that a 5-exo-dig cyclization can be successfully achieved to provide dihydroisobenzofurans when *ortho*-electron-deficient alkynyl-substituted aryl aldehydes are reacted with acetic acid under the catalysis of palladium acetate. In this transformation, the electron-withdrawing group attached to the alkyne is the key for the cyclization mode (eq 2).[8] Inspired by this work, we then envisioned using indoles as the nucleophile to synthesize indole-substituted analogues. Our initial attempt explored the reaction of *ortho*-electron-deficient alkynyl-substituted benzaldehyde **1a** with *N*-methylindole (**2a**) in the presence of $Pd(OAc)_2$ (5 mol %) in 1,2-dichloroethane (DCE) at room temperature. Surprisingly, indanone **3aa**[9] was isolated in 61% yield rather than the expected dihydroisobenzofuran **3aa′** (Scheme 1).




Indanone-containing scaffolds are attractive synthetic targets[10] because of their widespread occurrence in natural products and the biological activity associated with both natural and synthetic indanones.[11] Therefore, intrigued by the formation of compound **3aa** and the possibility of developing this new reaction into a convenient tool for the synthesis of indole-substituted indanones, we turned our attention to optimizing this particular process.

The influence of the catalyst and solvent was first investigated. The catalyst screening showed that cationic palladium salts such as $Pd(TFA)_2$ or $(MeCN)_4Pd(BF_4)_2$ were

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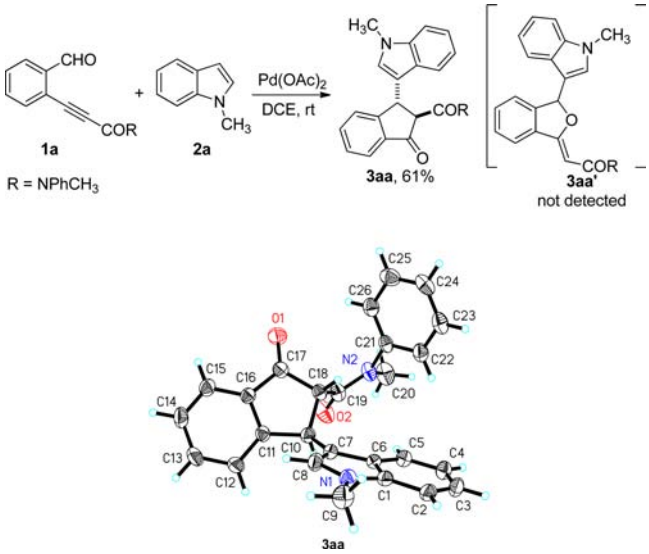
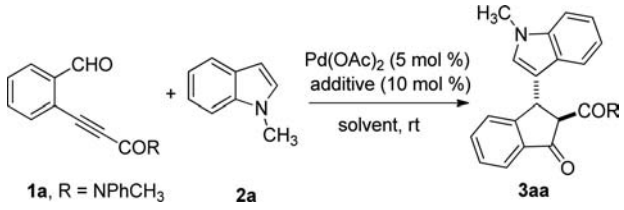
**Scheme 1. Preliminary Results of the Reaction of 1a and 2a Catalyzed by $Pd(OAc)_2$**




less effective, giving the product **3aa** in low yields (Table 1, entries 2 and 3). Increasing the reaction temperature also decreased the yield of **3aa** (entry 4). Further screening of different solvents revealed that 1,4-dioxane and dichloromethane (DCM) gave similar yields as DCE. However, in DCM the reaction time could be diminished to 12 h (entries 5 and 6). Other solvents such as toluene, MeCN, DMSO, and DMF were also tested, and all of them did not work well for this reaction (entries 7−10). Then the effects of additives, the catalyst loading, and the amount of indole **2a** were examined. In the tested reactions, the formation of palladium black was unavoidable because no ligand was present to stabilize the palladium(II) catalyst. Therefore, 2,2′-bipyridine (bpy), pyridine, or DMSO was added. However, the results showed that bpy totally inhibited the reaction and the other two also led to unsatisfactory effects (entries 11−13). To our delight, the yield of **3aa** was improved to 80% when the catalyst loading was increased to 7.5 mol % (entry 14). Further increasing the catalyst loading gave a similar result (entry 15). Increasing or decreasing the amount of indole **2a** did not provide any obvious beneficial effect (entries 16 and 17). It is noteworthy that this transformation did not occur in the absence of the catalyst (entry 18). On the basis of above investigations, the optimized reaction conditions were as follows: **1a** (0.1 mmol), **2a** (1.3 equiv), $Pd(OAc)_2$ (7.5 mol %) as the catalyst, and DCM (2 mL) as the solvent at room temperature.

**Table 1. Optimization of the Reaction Conditions**[a]




| entry | equiv of 2a | catalyst | solvent | time (h) | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | 1.3 | $Pd(OAc)_2$ | DCE | 48 | 61 |
| 2 | 1.3 | $Pd(TFA)_2$ | DCE | 48 | 23 |
| 3 | 1.3 | $(MeCN)_4Pd(BF_4)_2$ | DCE | 48 | 36 |
| 4[c] | 1.3 | $Pd(OAc)_2$ | DCE | 48 | 20 |
| 5 | 1.3 | $Pd(OAc)_2$ | dioxane | 48 | 63 |
| 6 | 1.3 | $Pd(OAc)_2$ | DCM | 12 | 58 |
| 7 | 1.3 | $Pd(OAc)_2$ | toluene | 48 | 37 |
| 8 | 1.3 | $Pd(OAc)_2$ | MeCN | 48 | 35 |
| 9 | 1.3 | $Pd(OAc)_2$ | DMSO | 48 | no reaction |
| 10 | 1.3 | $Pd(OAc)_2$ | DMF | 48 | disordered |
| 11[d] | 1.3 | $Pd(OAc)_2$ | DCM | 24 | no reaction |
| 12[e] | 1.3 | $Pd(OAc)_2$ | DCM | 24 | 17 |
| 13[f] | 1.3 | $Pd(OAc)_2$ | DCM | 24 | 43 |
| 14[g] | 1.3 | $Pd(OAc)_2$ | DCM | 12 | 80 |
| 15[h] | 1.3 | $Pd(OAc)_2$ | DCM | 12 | 81 |
| 16[g] | 1.0 | $Pd(OAc)_2$ | DCM | 12 | 78 |
| 17[g] | 2.0 | $Pd(OAc)_2$ | DCM | 12 | 86 |
| 18 | 1.3 | – | DCM | 48 | 0 |

[a]Reaction conditions: **1a** (0.1 mmol, 1.0 equiv) and catalyst (5 mol %) were dissolved in solvent (2 mL). Then **2a** (0.13 mmol 1.3 equiv) was added, and the mixture was stirred at room temperature until **1a** was consumed, as monitored by TLC. [b]Isolated yields. [c]The reaction was conducted at 60 °C. [d]5 mol % bpy was added. [e]10 mol % pyridine was added and 31% **1a** was recovered. [f]10 mol % DMSO was added and 12% **1a** was recovered. [g]7.5 mol % $Pd(OAc)_2$ was used. [h]10 mol % $Pd(OAc)_2$ was used.

To evaluate the scope and limitations of this reaction, diverse substituted indoles were explored under the optimized reaction conditions. When the indole nitrogen atom was protected with an electron-withdrawing group such as acetyl or tosyl, no target product was detected (**3ab** and **3ac**; Scheme 2). In contrast, indoles with N−Bn or unprotected N−H gave moderate yields of the corresponding products (**3ad** and **3ae**; Scheme 2). From the above results, it can be seen that electron-rich indoles are favorable for this tandem reaction. Then the influence of substituents on the indole benzene ring was explored. The results showed that electron-donating groups can provide the corresponding indanones in good yields, while halogen-substituted indoles only gave moderate yields (**3ai−am**; Scheme 2). An indole bearing a nitro group had no reactivity for this transformation, further indicating the superiority of electron-rich indoles in the procedure. Other kinds of electron-rich heteroaromatic compounds were also investigated. Benzofuran did not show any reactivity in this reaction, while benzothiophene and *N*-methylpyrrole gave corresponding products smoothly, albeit in moderate yields (**3af−ah**; Scheme 2).

Next, a series of *ortho*-electron-deficient alkynyl-substituted aryl aldehydes was tried. Generally, the reaction was compatible with both electron-withdrawing and electron-donating groups on the benzene ring, giving the target products in moderate to good yields (**3ba−da**; Scheme 3). When a halogen atom such as F, Cl, or Br was substituted on the benzene ring, the reaction also proceeded successfully (**3ea−ha**; Scheme 3). Not only *N*-methyl-*N*-phenylamide but also other electron-withdrawing groups such as ester or ketone can be substituted on the alkyne to provide the corresponding indole-substituted indanones smoothly (**3ia−ka**; Scheme 3). All of the products obtained in our reactions exhibits *trans* stereochemistry, as shown in Schemes 2 and 3.[12]

According to the literature and our previous work, a proposed mechanism is outlined in Scheme 4. First, substrate **1a** coordinates with $Pd(OAc)_2$ to afford intermediate **I**.[8] Then the carbonyl group of **I** is attacked by indole **2a**, followed by 5-exo-dig cyclization with the intramolecular electron-deficient



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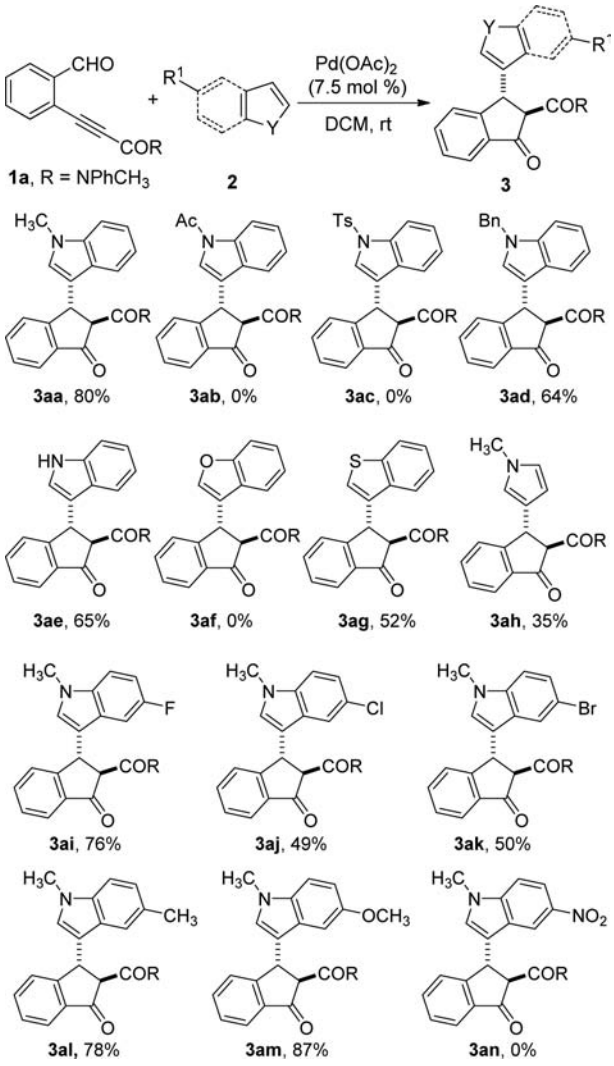
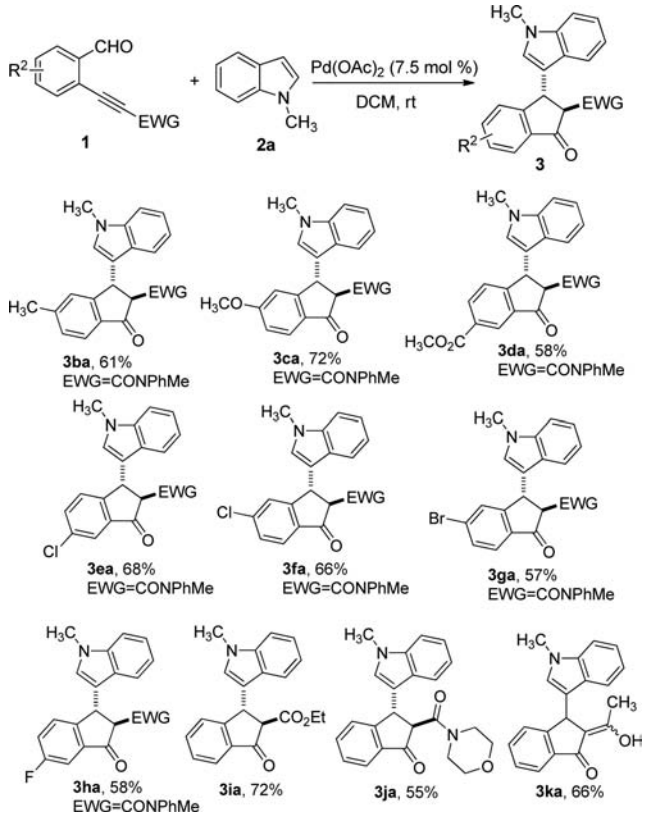
**Scheme 2. Reaction Scope of Heteroaromatics 2**[a,b]




[a]Reaction conditions: **1a** (0.1 mmol, 1.0 equiv) and $Pd(OAc)_2$ (7.5 mol %) were dissolved in DCM (2 mL). Then **2** (1.3 equiv) was added, and the mixture was stirred at room temperature until **1a** was consumed, as monitored by TLC. [b]Isolated yields are shown.

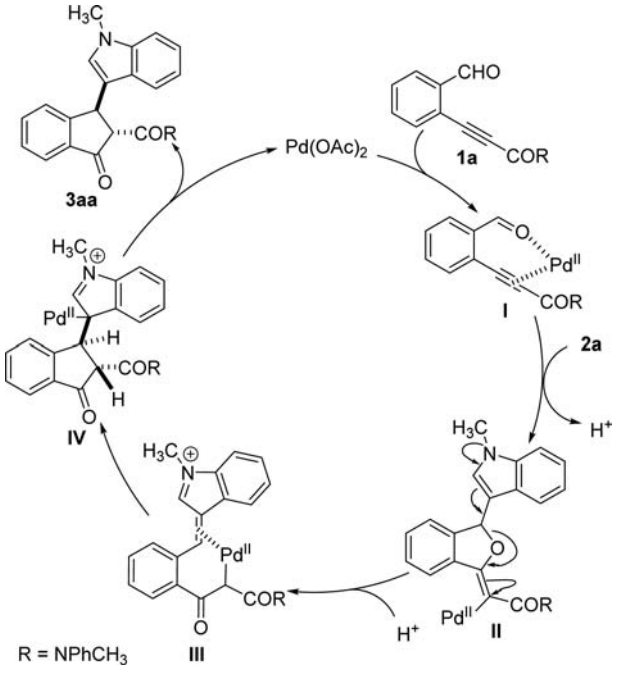
alkyne to produce intermediate **II**. Subsequently, this intermediate is transformed into intermediate **III** with the assistance of the electron-rich indole ring and the electron-withdrawing group on the alkyne. Intermediate **III** undergoes alkene insertion to produce intermediate **IV**. Finally, cleavage of the carbon−palladium bond in **IV** followed by isomerization furnishes the product **3aa** and regenerates the Pd(II) species. From the mechanism, it can be seen that this new tandem reaction is an atom-economical process. We believe that the excellent *trans* selectivity of this reaction originates from the stereochemistry of the alkene insertion step and the stability of the products.[10b,e,13] The electron-withdrawing group attached to the alkyne has a great influence on this transformation, as it not only controls the ring size of cyclization (**I** to **II**) but also promotes the electron transfer in the ring-opening step (**II** to **III**). In addition, the electron-rich indole also has dual functions. First, it is a good nucleophile to react with the aldehyde group. Second, the electronic property of the indole ring facilitates the transformation of intermediate **II** to **III**.

**Scheme 3. Reaction Scope of 2-Alkynylbenzaldehyes 1**[a,b]




[a]Reaction conditions: **1** (0.1 mmol, 1.0 equiv) and $Pd(OAc)_2$ (7.5 mol %) were dissolved in DCM (2 mL). Then **2a** (0.13 mmol, 1.3 equiv) was added, and the mixture was stirred at room temperature until **1** was consumed, as monitored by TLC. [b]Isolated yields are shown.

**Scheme 4. Proposed Mechanism**




In conclusion, we have accomplished a $Pd(OAc)_2$-catalyzed tandem reaction of *ortho*-electron-deficient alkynyl-substituted benzaldehydes with indoles to afford indole-substituted



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indanones. The electron-withdrawing group attached to the alkyne and the nucleophilic indole play important roles in the formation of the indanone ring. Exploration of an enantioselective version of the procedure and work on other applications of the catalytic system are underway in our laboratory.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01240.

Experimental procedures and $^{1}H$ and $^{13}C$ NMR spectra for all new compounds (PDF)
Crystallographic data for **3aa** (CIF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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(9) The relative stereochemistry of **3aa** was assigned as *trans* on the basis of X-ray diffraction.

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(12) The relative stereochemistry of the products was assigned by comparison of the coupling constant of two hydrogens located $\alpha$ and $\beta$ to the carbonyl group on the indanone ring (see the Supporting Information), which was also confirmed by X-ray crystallography of compound **3aa**.

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