

# Synthesis of Indoles through Palladium-Catalyzed Three-Component Reaction of Aryl Iodides, Alkynes, and Diaziridinone

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Supporting Information

ABSTRACT: The three-component reaction of aryl iodides, alkynes, and diaziridinone is described. The reaction provides an innovative synthetic approach for indoles. The approach features high efficiency, broad substrate scope, and excellent regioselectivity. C,C-Palladacycles should act as the intermediates. The C,C-palladacycles are obtained from simple aryl halides and alkynes and then reacted with diaziridinone to afford indoles.

he indole ring system is one of the most important and abundant heterocycles in nature, and the indole nucleus is ubiquitous in biologically active molecules and pharmaceuticals. Unsurprisingly, continuous efforts have been made to search for facile and efficient synthetic methods for indoles, and a variety of reactions are available to access this important class of N-containing heterocycles.<sup>2</sup> While the traditional Fischer indole synthesis has been widely used,<sup>3</sup> transition-metal-catalyzed coupling of ortho-halogenated anilines with internal alkynes represents an alternative powerful method (Scheme 1a).4

## Scheme 1. Alkyne-Based Syntheses of Indoles

#### Previous work

a. Cyclization of 2-haloaniline derivatives and alkynes

$$X = I. Br. Cl.$$

$$R^{2} + R^{2}$$

$$R^{3}$$

$$R^{2} + R^{3}$$

$$R^{3}$$

b. Cyclization of aniline derivatives and alkynes through C-H activation

#### This work

c.Three-component reaction of iodobenzenes, alkynes, and diaziridinone

$$R^{3} \stackrel{\text{||}}{=} + \underset{R^{2}}{\stackrel{\text{||}}{=}} + \underset{t-Bu}{\stackrel{\text{||}}{=}} R^{1} \xrightarrow{Pd} R^{3} \stackrel{\text{||}}{=} R^{2}$$

However, the ortho-halogenated anilines have to be presynthesized, and their syntheses often involve multiple steps. Therefore, C-H annulation of anilines with alkynes has gained considerable interest, and diverse reactions of this type have been developed (Scheme 1b).<sup>5</sup>

C,C-Palladacycles have unique structures and may exhibit novel reactivities.<sup>6</sup> Furthermore, the two C-Pd bonds can be manipulated to develop novel reactions. 7 C, C-Palladacycles are generally prepared from aryl halides through oxidative addition and subsequent C-H activation. Although C,C-palladacycles can also be accessed by double aryl C-H bond activation, rare examples are available. 7t,u However, for these methods, the major drawback is that substrates have the same level of structural complexity as the C,C-palladacycles to be formed and have to be presynthesized. Alternatively, C,C-palladacycles can be synthesized through the intermolecular reaction of aryl halides and alkynes. The aryl halides and alkynes are relatively simple starting materials, so this method is more desirable. Several intramolecular cyclization reactions of the palladacycles prepared from aryl halides and alkynes have been developed. However, intermolecular reactions are very rare. One example involves the arylation of C,C-palladacycles by the starting material aryl halides.9 Actually, this reaction implies that the aryl halides could react with C,C-palladacycles and this side reaction must be suppressed to develop intermolecular reactions with other external reagents.

On the other hand, it has been demonstrated that C, C-palladacycles can be aminated by diaziridinone, including the amination of palladacycles obtained from 2-iodobiphenyls. Di-tert-butyldiaziridinone has intriguing reactivities and is a stable compound, so it is an important synthetic intermediate. 10d

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We envisioned that diaziridinone might also react with the *C*,*C*-palladacycles obtained from aryl halides and alkynes. Herein, we report a Pd-catalyzed three-component reaction of aryl iodides, alkynes, and diaziridinone, which represents a facile and efficient approach for the synthesis of indoles. It should be mentioned that aryl iodides that are used as the starting materials are very common and commercially available chemicals.

We commenced our studies by investigating the three-component reaction of 1, 2-diphenylethyne (1a), iodobenzene (2a), and diaziridinone (3). The desired indole product (4aa) was not observed under the conditions as shown in entry 1 (Table 1).

Table 1. Optimization of Reaction Conditions

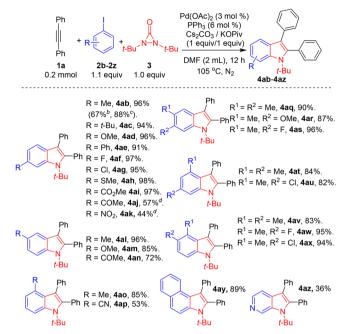
entry	base (2 equiv or 1 + 1 equiv)	solvent	ligand	yield <sup>a</sup> (%)
1	$Cs_2CO_3$	DMF	_	_
2	$Cs_2CO_3$	DMF	$P(o-tol)_3$	62
3	$K_2CO_3$	DMF	$P(o-tol)_3$	56
4	KOAc	DMF	$P(o-tol)_3$	41
5	Cs <sub>2</sub> CO <sub>3</sub> /KOAc	DMF	$P(o-tol)_3$	90
6	K <sub>2</sub> CO <sub>3</sub> /KOAc	DMF	$P(o-tol)_3$	78
7	Cs <sub>2</sub> CO <sub>3</sub> /KOPiv	DMF	$P(o-tol)_3$	98
8	Cs <sub>2</sub> CO <sub>3</sub> /KOPiv	THF	$P(o-tol)_3$	31
9	Cs <sub>2</sub> CO <sub>3</sub> /KOPiv	DMSO	$P(o-tol)_3$	85
10	Cs <sub>2</sub> CO <sub>3</sub> /KOPiv	DMA	$P(o-tol)_3$	94
11	Cs <sub>2</sub> CO <sub>3</sub> /KOPiv	DMF	$PPh_3$	97
12	Cs <sub>2</sub> CO <sub>3</sub> /KOPiv	DMF	$PPh_3$	88 <sup>b</sup>
13	Cs <sub>2</sub> CO <sub>3</sub> /KOPiv	DMF	$PPh_3$	$96^{c} (93^{d})$

 $^a$ The yields were determined by  $^1$ H NMR analysis of crude reaction mixture using CH<sub>2</sub>Br<sub>2</sub> as the internal standard.  $^b$ 1.0 equiv of 3, 1 mol % Pd(OAc)<sub>2</sub>.  $^c$ 1.0 equiv of 3, 1 mol % Pd(OAc)<sub>2</sub>, 105 °C.  $^d$ Isolated yield.

Gratefully, product **4aa** was formed in a yield of 62% in the presence of  $P(o\text{-tol})_3$  as a ligand (entry 2). While other inorganic bases such as  $K_3CO_3$  and KOAc gave lower yields (entries 3 and 4), a 90% yield was obtained using a combination of  $C_2CO_3$  and KOAc (entry 5). The combination of  $K_2CO_3$  and KOAc was less effective (entry 6). However, the yield increased to 98% when KOPiv was used (entry 7). The product was formed in lower yields when the reaction was carried out in other solvents (entries 8–10). PPh<sub>3</sub> was also an effective ligand and gave the same yield as  $P(o\text{-tol})_3$  (entry 11). Notably, the reaction was very efficient, because a yield of 88% was still obtained when 1 equiv of 3 and 1 mol % of  $Pd(OAc)_2$  were used (entry 12). The yield was enhanced to 96% when running the reaction at 105 °C (entry 13).

Having developed a highly efficient approach for the synthesis of indoles, we then investigated the substrate scope of this method. We first examined the performance of various substituted iodobenzenes. As shown in Scheme 2, 4-iodotoluene 2b was allowed to react with 1a and 3 under the optimal conditions. Product 4ab was formed in a much lower yield. However, the yield was improved to 88% by using 3 mol % of Pd(OAc)<sub>2</sub> and furthermore was enhanced to 96% by slightly increasing the amount of 1a to 1.1 equiv. To make sure that the optimal yields were obtained, this new protocol was

Scheme 2. Aryl Iodide Scope



<sup>a</sup>Isolated yield. <sup>b</sup>1.0 equiv of **2b**, 1 mol % Pd(OAc)<sub>2</sub>. <sup>c</sup>1.0 equiv of **2b**, 3 mol % Pd(OAc)<sub>2</sub>. <sup>d</sup>1.5 equiv of **2b**.

used for the reactions of other substrates. The compatibility of common functional groups was probed by investigating the reactions of para-substituted iodobenzenes. The electron-donating groups such as tert-butyl and methoxy and the phenyl group were compatible, and the yields were almost quantitative (4ac-4ae). Notably, fluoro, chloro, and methylthiol groups were well tolerated and did not affect the high efficiency of the reaction (4af-4ah). Whereas the electron-withdrawing ester group gave a high yield (4ai), the presence of a carbonyl or nitro group led to a lower yield even when using 1.5 equiv of iodobenzenes (4ai and 4ak). The compatibility of functional groups at the ortho- or meta-positions was also probed. Both electron-donating and -withdrawing groups were compatible (4al-4ap). Likewise, electron-withdrawing groups (carbonyl and cyano) gave lower yields (4an and 4ap). A range of disubstituted iodobenzenes could also undergo this three component reaction, affording indole products in good or excellent yields (4aq-4ay). Finally, 4-iodopyridine was also suitable; however, the yield was low (4az).

Next, the performance of other substituted acetylenes was investigated. As shown in Scheme 3, a variety of symmetrical diphenylacetylene derivatives bearing methyl, tert-butyl, methoxy, or fluoro groups reacted with iodobenzene and diaziridinone, and the reactions were high-yielding (4ba-4ga). 1,2-Di(furan-3-yl)ethyne was also reactive, affording the difuranylated indole in 63% yield (4ha). Notably, dialkylacetylenes underwent the reaction, albeit in lower yields (4ia and 4ja). Subsequently, we studied the reaction of unsymmetrical alkynes. Gratefully, 2-methyl and -propyl phenylacetylenes exhibited high reactivity (4ka and 4la). More importantly, the regioselectivities were excellent, and almost a single product was formed. Other iodobenzenes bearing an electron-donating methoxy or electron-withdrawing carbonyl group also reacted with 2-methylacetylenes efficiently, and the regioselectivities were also very high (4kd and 4kn). Ethyl 3-phenylpropiolate was also highly reactive (4ma). However, two regioisomers were formed in a ratio of 7.3:1. It should be Organic Letters Letter

Scheme 3. Acetylene Scope

<sup>a</sup>Isolated yield.

noted that the two isomers could be separated easily. (For detailed data of regioisomers, see the Supporting Information.)

The *tert*-butyl group of the indole products could be readily removed by treatment with trifluoroacetic acid. <sup>10c</sup> The resulting free amine can be manipulated, which allows easy access to a variety of 1-substituted indole derivatives. Moreover, this three-component reaction can be scaled up to the gram scale in a good yield. (For detailed experiments and results, see the Supporting Information.)

Our reaction represents a facile and efficient approach for the synthesis of 2,3-disubtituted indoles. Notably, it has been reported that the 2,3-disubtituted indoles can be transformed into bioactive and other functional molecules (Scheme 4).

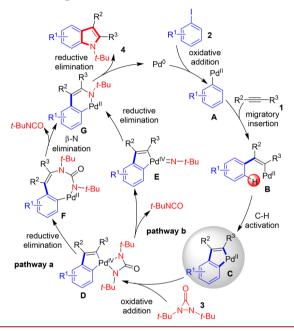
Scheme 4. Transformation of the Indole Products

For example, product **5aa** can be converted to compound **6aa** by dehydrogenative coupling <sup>11</sup> and fused product **7aa** by

Rh(III)-catalyzed annulation with an alkyne. Products **6aa** and **7aa** are promising for organic semiconductors. Furthermore, product **5aa** can also be transformed into compound **9aa**. Compound **9aa** structurally resembles a potent BACE1 inhibitor for the potential treatment of Alzheimer's disease. 13

On the basis of these experimental results and previous reports, <sup>9a,10</sup> we proposed a mechanism, as shown in Scheme 5.

#### Scheme 5. Proposed Mechanism



The catalytic cycle starts with the oxidative addition of iodobenzenes to Pd(0). The resulting aryl Pd(II) species **A** undergoes migratory insertion to form vinyl Pd(II) species **B**. Sa The subsequent intramolecular C–H activation generates *C,C*-palladacycle **C**. Next, **C** inserts into the N–N bond of diaziridinone via oxidative addition to give pallada(IV)cycle **D**. Lightmembered **F** was then formed after the reductive elimination of intermediate **D**. Sinally, the  $\beta$ -N elimination and subsequent reductive elimination led to the product and the regeneration of the Pd(0) catalyst (pathway a). Lic It should be mentioned that a Pd(IV)-nitrene pathway cannot be ruled out (pathway b).

In conclusion, we have developed a palladium-catalyzed protocol for the synthesis of indoles. Unlike previous approaches from anilines or their derivatives, this reaction starts from aryl iodides, which react with alkynes and diaziridinone under palladium catalysis to form indoles. The reaction is highly efficient and has broad substrate scope. Notably, regioselectivity is excellent for unsymmetrical alkynes. *C,C-Palladacycles*, generated through cascade reactions of aryl halides and alkynes, should act as the key intermediates and react with diaziridinone to form indoles.

## ASSOCIATED CONTENT

## **S** Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02750.

Detailed experimental procedures, spectroscopic data of authentic compounds, and characterization of products (PDF)

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#### **Notes**

The authors declare no competing financial interest.

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