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Authors: Zijun Wu , Xinxin Fang, Yuning Leng, Hequan Yao, and Aijun Lin

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Indium-mediated Palladium-catalyzed Allylic Alkylation of Isatins with Alkynes

Zijun Wu, Xinxin Fang, Yuning Leng, Hequan Yao,* and Aijun Lin*

State Key Laboratory of Natural Medicines (SKLNM) and Department of Medicinal Chemistry, School of Pharmacy, China Pharmaceutical University, Nanjing, 210009, P. R. China
Fax: (+86)-25-8327-1042; e-mail: ajlin@cpu.edu.cn and hyao@cpu.edu.cn

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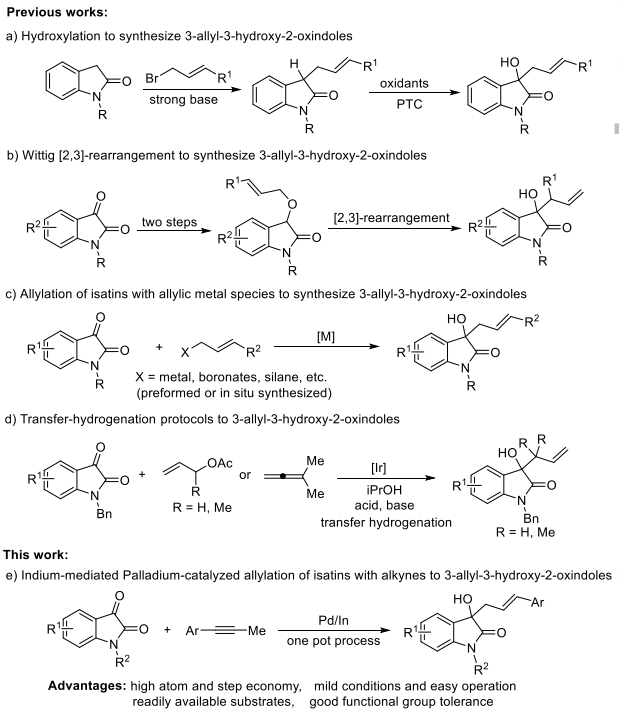
Abstract: An unprecedented indium-mediated palladium-catalyzed allylic alkylation of isatins with alkynes is disclosed. This reaction provides a new, practical, and straightforward route to access 3-allyl-3-hydroxy-2-oxindoles in good yields with broad substrate scope and scalability, exhibiting high atom and step economy. A primary mechanistic study reveals that indium played two roles in the reaction, first as a reductant and second as a Lewis acid. Compared with previous methods, our strategy eliminated the steps for the separation and purification of the reaction intermediates, as well as pre-installing leaving groups to allylic substrates. Moreover, our reaction did not employ moisture-sensitive allylic metal species and stoichiometric oxidants.

Keywords: palladium-catalyzed; indium; 3-allyl-3-hydroxy-2-oxindoles; isatins; allylic alkylation

3-Allyl-3-hydroxy-2-oxindoles as versatile building blocks have been widely utilized for the preparation of alkaloids, bioactive molecules, and clinical pharmaceuticals.[1] Hydroxylation of 3-allyl-2-oxindoles was one of the earliest reported methods to prepare these skeletons (Scheme 1a).[2] However, the preparation of 3-allyl-2-oxindoles under strong basic conditions in low to moderate yields presented a strong limitation. Wittig [2,3]-rearrangement as an alternative method has also been reported to access such skeletons (Scheme 1b).[3] Unfortunately, for the success of the reaction, two or more steps are needed to pre-synthesize 3-cinnamyloxyoxindoles, involving elaborate reaction routes and conditions. Allylation of isatins with allylic metal species,[4,5] which could be either pre-formed or formed in situ, has been the most widely used method to obtain 3-allyl-3-hydroxy-2-oxindoles (Scheme 1c). Nevertheless, the allylic metal species are usually unstable and moisture sensitive, making the reaction conditions difficult. Moreover, the allylic reagents, such as allylic halides, esters, and alcohols, which are mainly used to synthesize the allylic metal species, need to be pre-prepared through one or more extra steps. Transition-metal catalyzed oxidative allylic C-H borylation could also be used to synthesize allylboronates[6] to realize allylation of isatins, while stoichiometric oxidants were required. More recently, the transition-metal catalyzed allylation, crotylation, and prenylation of isatins via isopropanol-mediated transfer hydrogenation provided another unique approach to synthesize 3-allyl-3-hydroxy-2-oxindoles.[7] Again, this protocol suffered from substrate scope limitations, especially with respect to the allylic agents (Scheme 1d). Thus, exploiting new methods to access 3-allyl-3-hydroxy-2-oxindoles from readily available substrates with broad substrate scope under mild conditions is still highly desirable.



Scheme 1. Strategies to the synthesis of 3-allyl-3-hydroxy-2-oxindoles.

Alkynes, as versatile and readily available building blocks,[8] have been employed in allylic alkylations[9] and have drawn increasing interest from synthetic chemists due to their inherent advantages for redox-neutral processes. In conjunction with our ongoing

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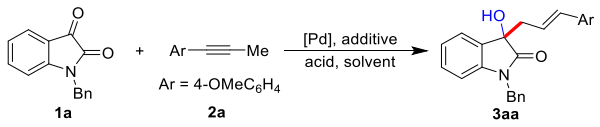
interest in exploring the reaction types of alkynes,[10] herein, we describe our latest work on indium-mediated palladium-catalyzed allylic alkylation of isatins with alkynes to access 3-allyl-3-hydroxy-2-oxindoles, featuring high atom and step economy, and good functional group tolerance. Compared with previous methods, our strategy avoids steps for the separation and purification of the reaction intermediates, as well as pre-functionalization of allylic agents, which addressed the limitations of previous synthetic methods.

Table 1. Optimization of reaction conditions.[a, b]

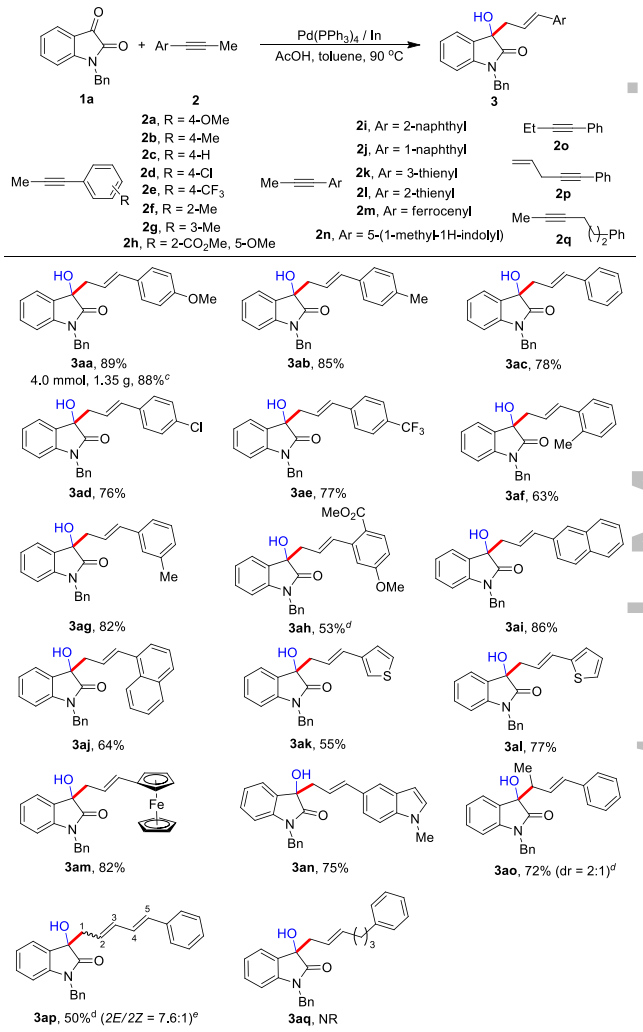


Entry	Additive	Acid	Solvent	Yield
1	In	AcOH	THF	62
2	Zn	AcOH	THF	Trace
3	Mn	AcOH	THF	Trace
4	In	AcOH	toluene	89
5	In	AcOH	1,4-dioxane	71
6	In	AcOH	DMF	Trace
7	In	AcOH	DME	73
8	In	PhCOOH	toluene	58
9	In	HCOOH	toluene	28
10	In	PivOH	toluene	N.D.
11	In	$TsOH·H_2O$	toluene	Trace
12[c]	In	AcOH	toluene	54
13[d]	In	AcOH	toluene	73
14[e]	In	AcOH	toluene	68
15[f]	In	AcOH	toluene	77
16[g]	In	AcOH	toluene	61
17	In		toluene	N.D.
18		AcOH	toluene	N.D.
19[h]	In	AcOH	toluene	N.D.

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $Pd(PPh_3)_4$ (10 mol%), In (0.4 mmol), acids (0.42 mmol) in solvent (2.0 mL) were stirred at 90 °C under argon atmosphere for 8 h. DME = 1,2-dimethoxyethane. N.D. = not detected.
[b] Isolated yield.
[c] 70 °C.
[d] $Pd_2(dba)_3$ (5.0 mol%), PPh_3 (30 mol%)
[e] $Pd_2(dba)_3·CHCl_3$ (5.0 mol%), PPh_3 (30 mol%)
[f] $Pd(PPh_3)_4$ (7.5 mol%).
[g] $Pd(PPh_3)_4$ (5.0 mol%).
[h] Without $Pd(PPh_3)_4$.

In order to identify an efficient catalyst system for the synthesis of 3-allyl-3-hydroxy-2-oxindoles, we focused our initial study on the reaction between *N*-benzyl isatin **1a** and 1-methoxy-4-(prop-1-yn-1-yl)benzene **2a** (Table 1). Gratifyingly, preliminary attempts led to the desired product **3aa** in 62% yield when the reaction was treated with $Pd(PPh_3)_4$, indium and acetic acid in tetrahydrofuran (THF) at 90 °C under argon atmosphere (Table 1, entry 1). Other tested metal additives (Zn and Mn) gave poor results (Table 1, entries 2 and 3). Optimizing the solvents revealed that toluene performed best and delivered **3aa** in 89% yield (Table 1, entries 4-7). Further screening of acids suggested that acetic acid is the best choice (Table 1, entries 4 and 8-11). Decreasing the temperature resulted in low yield (Table 1, entry 12). $Pd_2(dba)_3$ or $Pd_2(dba)_3·CHCl_3$ with extra PPh_3 could offer **3aa** in 73% and 68% yield (Table 1, entries 13 and 14).[11] Further decreasing the catalyst loadings impacted the reaction efficiency (Table 1, entries 15-16). Control experiments indicated that $Pd(PPh_3)_4$, indium and acetic acid were all essential to this reaction (Table 1, entries 17-19).

Table 2. Substrate scope of alkynes.[a, b]



[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), $Pd(PPh_3)_4$ (10 mol%), In (0.4 mmol), AcOH (0.42 mmol) in toluene (2.0 mL) were stirred at 90 °C under argon atmosphere for 8 h.
[b] Isolated yields.
[c] 4.0 mmol scale.
[d] 100 °C
[e] The dr value and the ratio of 2*E*/2*Z* were determined by ^1H NMR spectra.

With the optimized conditions in hand, we then examined the substrate scope of alkynes and the results

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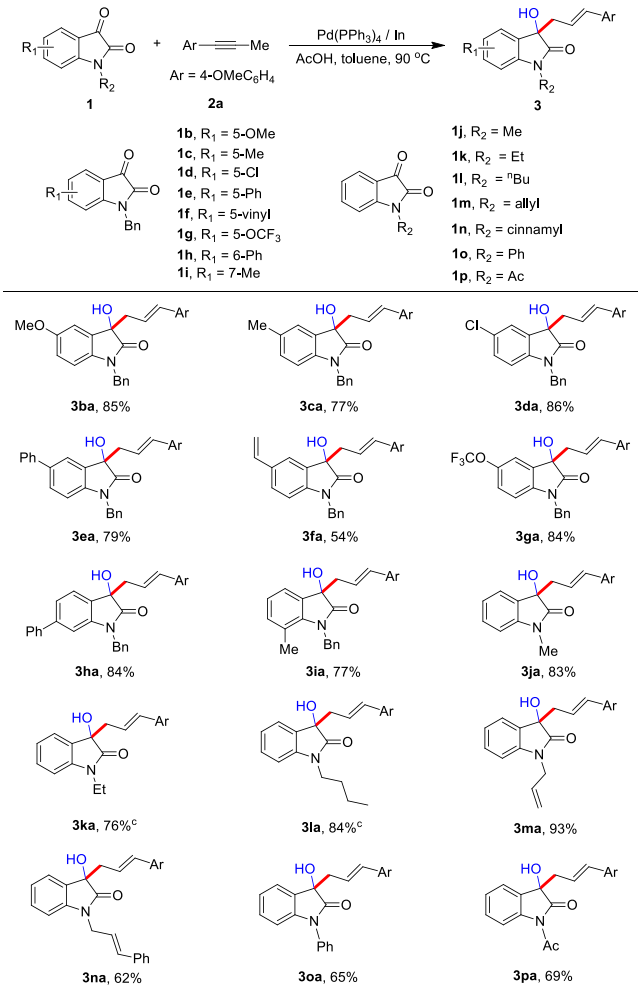
are summarized in Table 2. The alkynes with electron-donating or electron-withdrawing groups at the *para*-position of the benzene ring provided **3aa-3ae** in 76%-89% yields. The steric hindrance of alkyne influenced the reactivity and offered **3af** in 63% yield, while *meta*-methyl-substituted **2g** afforded **3ag** in 82% yield. Replacing the phenyl group with naphthyl, thienyl, ferrocenyl and indolyl groups, the reaction proceeded smoothly, leading to **3ai-3an** in good yields. 1-Phenyl-1-butyne **2o** participated well to deliver **3ao** in 72% yield (dr = 2:1). Moreover, pent-4-en-1-yn-1-ylbenzene (**2p**), a skipped enyne, performed well, offering **3ap** in moderate yield. Aliphatic alkynes, e.g. **2q**, were unreactive under the standard conditions. Gram-scale experiment could also be carried out conveniently and **3aa** (1.35 g) was obtained in 88% yield on 4.0 mmol scale.

Table 3. Substrate scope of isatins.[a, b]

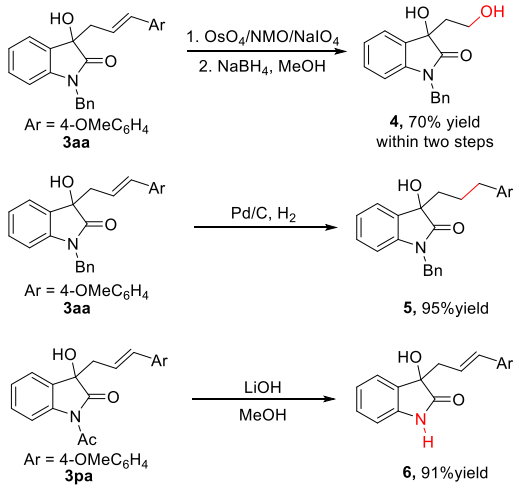


[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $Pd(PPh_3)_4$ (10 mol%), In (0.4 mmol), AcOH (0.42 mmol) in toluene (2.0 mL) were stirred at 90 °C under argon atmosphere for 8 h.

[b] Isolated yields.

[c] 100 °C.

After checking the generality of alkynes, we then turned our attention to the substrate scope of isatins (Table 3). Isatins with various substituents at the 5-position of the benzene ring provided **3ba-3ga** in good yields. The steric hindrance of isatins did not influence the reactivity, offering **3ha** and **3ia** in 84% and 77% yields. Delightedly, isatins with various groups on the *N* atom performed well, offering **3ja-3pa** in 62%-93% yields.



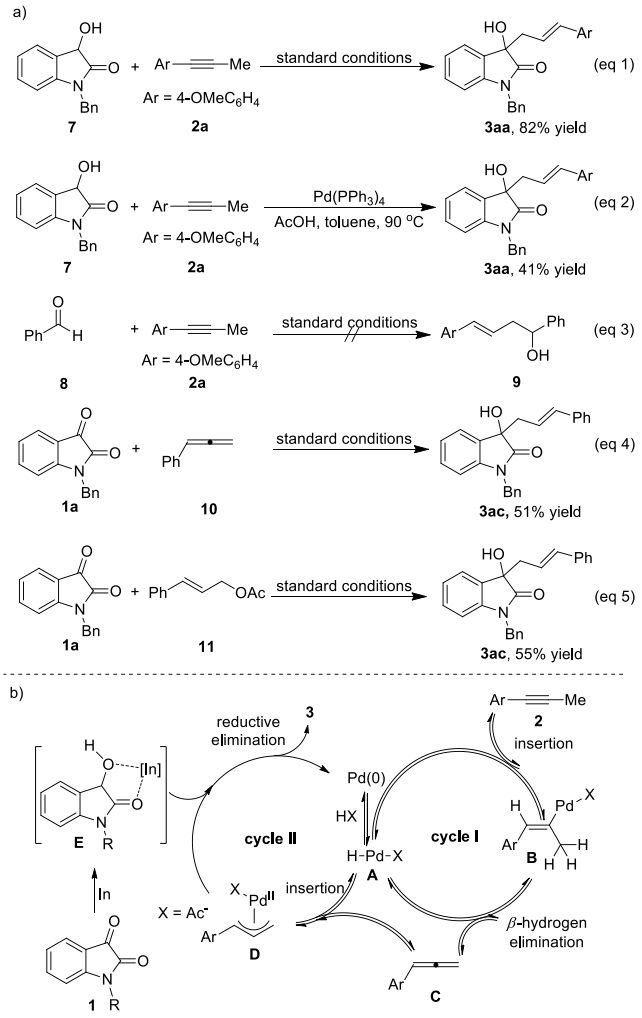
Scheme 2. Transformation of products **3**.

To illustrate the synthetic utility of this reaction, further transformations of products **3** were conducted (Scheme 2). Oxidation of the C=C double bond of **3aa** with osmium tetroxide and *N*-methyl-morpholine N-oxide (NMO), followed by $NaIO_4$, an unstable aldehyde was formed, which could be used directly without purification in the following step. Reduction of the aldehyde with $NaBH_4$ gave compound **4** in 70% total yield within two steps. Compound **5** was obtained in 95% yield through Pd/C catalytic hydrogenation. Removing the *N*-acetyl group of **3pa** could be readily achieved with lithium hydroxide in MeOH at room temperature, and compound **6** was obtained in 91% yield.

Control experiments were then conducted to gain insights into the mechanism of the reaction (Scheme 3a). When 1-benzyl-3-hydroxyindolin-2-one **7** reacted with 1-methoxy-4-(prop-1-yn-1-yl)benzene **2a** under the standard conditions, **3aa** was obtained in 82% yield (Scheme 3a, eq 1). When the same reaction was carried out in the absence of indium, **3aa** was only obtained in 41% yield (Scheme 3a, eq 2). These results demonstrated that indium might play two roles in the reaction, one is as a reductant and the other is as a Lewis acid to promote the transformation. When benzaldehyde **8** was used as the substrate, no desired compound **9** was detected (Scheme 3a, eq 3)[12, 13]. This result suggests that the allylic indium species was not formed in this reaction. Additionally, we prepared phenyl allene **10** and cinnamyl acetate **11**, and tested them with **1a** under the standard conditions; **3ac** was delivered in 51% and 55% yield, respectively (Scheme

3a, eq 4 and eq 5). These results indicate that phenyl allene and cinnamyl acetate could be intermediates in the reaction. [15]

On the basis of the above results and previous work,[9,14] a plausible mechanism of our reaction is proposed as shown in Scheme 3b. First, oxidation of $Pd(PPh_3)_4$ with acetic acid initials the catalytic cycles and affords the hydridopalladium species **A**. *syn*-Migratory insertion of **A** to alkynes **2** delivers the intermediate **B**. β-Hydrogen elimination of **B** produces the aryl allene **C** and regenerates **A** (cycle I). Next, migratory insertion of **A** to aryl allene **C** offers the key π-allylpalladium species **D**,[15] which reacts with intermediate **E** to give the allylic products **3** and regenerates the palladium catalyst to the next catalytic cycle (cycle II). On the other hand, it is thought that with the help of indium, isatins could be reduced to form compound **7**, which coordinates with indium salt to form intermediate **E**.



Scheme 3. Control experiments and proposed mechanism.

In summary, we have developed an unprecedented indium-mediated palladium-catalyzed allylic alkylation of isatins with alkynes under mild reaction conditions. This reaction provided a practical and straightforward method to access 3-allyl-3-hydroxy-2-oxindoles in good yields with broad substrate scope and scalability, exhibiting high atom and step economy. The employment of alkynes as allyl equivalents in this reaction avoided pre-installing leaving groups to allylic substrates and employing moisture sensitive allylic metal species. Primary mechanism study revealed that the indium played both as reductant and Lewis acid in this reaction. Further transformation of the products to functional compounds highlighted the potential application prospect of this reaction.

Experimental Section

General procedure of allylation of isatins: A sealed tube was charged with isatins **1** (0.2 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (0.02 mmol, 10 mol%), indium (0.40 mmol, 2.0 equiv), acetic acid (0.42 mmol, 2.1 equiv), alkynes **2** (0.4 mmol, 2.0 equiv) and toluene (2.0 mL). The reaction mixture was vigorously stirred at 90 °C (oil temperature) under argon atmosphere for 8 h. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (20 mL) and filtered through a plug of Celite. The mixture was concentrated *in vacuo* and purified by flash chromatography on silica gel with PE/EA (*v*/*v* = 8:1 to 4:1) to afford the allylic alkylated products **3**.

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[15] At the present stage, we are not sure if it is going to generate cinnamyl acetate, although it could offer the desired product in moderate yield under optimized conditions. In our proposed mechanism, the π-allylpalladium species is the key intermediate of the reaction, which could be formed *via* migratory insertion of A to aryl allene C.

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UPDATE

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