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Palladium-Catalyzed Dearomative Allylic Alkylation of Indoles with Alkynes To Synthesize Indolenines with C3-Quaternary Centers

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Supporting Information

ABSTRACT: A palladium-catalyzed dearomative allylic alkylation of indoles with alkynes to construct indolenines with C3-quaternary centers was reported. The in situ formed arylallene intermediate omitted the need to install leaving groups on the allylic compounds and employ extra oxidants to oxidize the allylic C−H bonds. The reaction exhibited good functional group tolerance and high atom economy. Moreover, the reaction was further expanded to synthesize pyrroloindolines and furanoindolines.

Indolenine motifs and their derivatives are widely distributed in natural products and bioactive compounds,[1] such as potent monoamine oxidase inhibitor strictamine,[2] (±)-chartelline C,[3] analgesic agent (+)-koumine,[4] and (−)-tubifoline[5] (Figure 1). To construct the indolenine skeletons, the transition-metal-catalyzed dearomative reaction of indoles has been studied intensively over the past few years.[6] However, the dearomative allylic alkylation of indoles at the C3-position represents a significant challenge due to the potential N1/C3 and branch/linear selectivity. To date, three general strategies have been developed as shown in Scheme 1, among which Pd-, Ir-, and Cu-based catalytic systems with allylic agents have been abundantly documented (Scheme 1a).[7] The introduction of leaving groups such as ester, halide, or hydroxyl to the allylic compounds was necessary to complete the transformation. Bandini's group reported the allylic alkylation reactions between indoles and electron-rich allenamides with Brønsted acids or gold as catalysts (Scheme 1b).[8] Very recently, Yang's group developed a palladium-catalyzed dearomative allylic alkylation of indoles with allylbenzene through an C−H activation/dearomatization process employing a stoichiometric Ag_2CO_3 as an extra oxidant (Scheme 1c).[9] Despite the fact that the aforementioned methods were very interesting to achieve the allylic alkylation of indoles at the C3-position, the development of a more efficient method with facile accessible substrates and higher atom economy is still desirable.

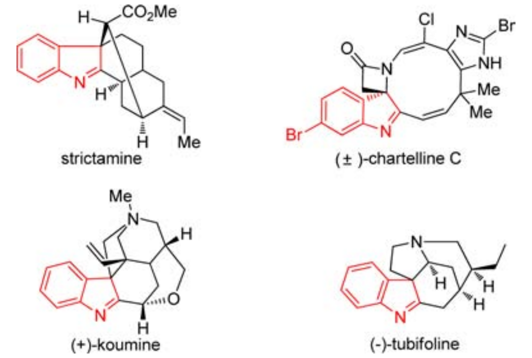
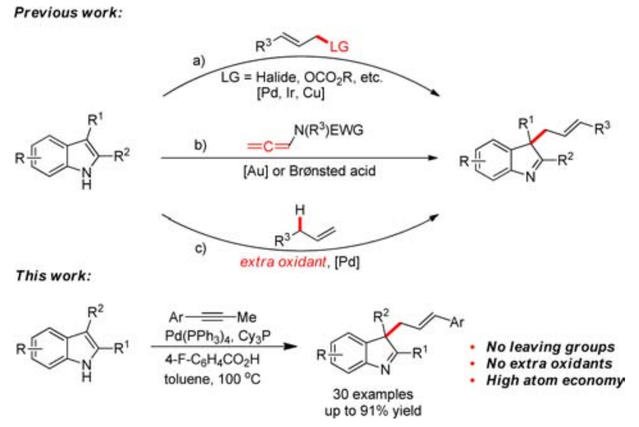


Figure 1. Selected natural products containing indolenine cores.

Scheme 1. Strategies for Dearomative Allylic Alkylation of Indoles



π-Allylmetal complexes are very important intermediates in the transition-metal-catalyzed allylic alkylation reaction (namely, the Tsuji−Trost-type reaction).[10] From an atom- and redox-economic point of view, arylpropynes were ideal precursors to form the π-allylmetal complex, and much research has been reported to construct C−C bonds and C−X (X = N, O, S) bonds.[11] To the best of our knowledge, the dearomative allylic alkylation of indoles at the C3-position with arylpropynes has never been reported. As a continuation of our previous work on the transition-metal-catalyzed dearomative reactions of

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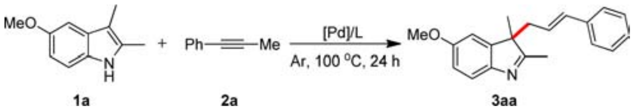
indoles,[12] herein we report a palladium-catalyzed dearomative allylic alkylation of indoles with alkynes to construct indolenines with C3-quarternary centers.

We commenced our reaction with 5-methoxyl-2,3-dimethylindole **1a** and phenylpropyne **2a** as substrates and benzoic acid as an additive in 2.0 mL of anhydrous toluene at 100 °C under argon for 24 h as shown in Table 1. Screening of palladium catalysts revealed that $Pd(PPh_3)_4$ could yield the dearomative allylic alkylated product **3aa** in 69% yield, while no product was obtained with Pd/C, $Pd_2(dba)_3$, or $Pd_2(dba)_3{\cdot}CHCl_3$ as catalysts (entries 1−4). A control experiment indicated that ligand was essential to this reaction (entry 5). Varying different ligands (entries 6−11) showed that Cy_3P could afford **3aa** in 91% yield, while dppp, dppm, and $^tBu_3P$ exhibited inferior performance and Ph_3PO inhibited the reaction completely. Further screening of acids suggested that small aliphatic acids such as AcOH and PivOH furnished **3aa** in 50% and 54% yields (entries 12 and 13). The benzoic acids gave better results, and **3aa** could be finally isolated in 91% yield when 4-fluorobenzoic acid was selected (entries 14−16). Decreasing the amount of $Pd(PPh_3)_4$ influenced the outcome slightly (entries 17 and 18). With the catalyst dislodged, no reaction could be detected (entry 19).

Table 1. Optimization of Reaction Conditions[a,b]

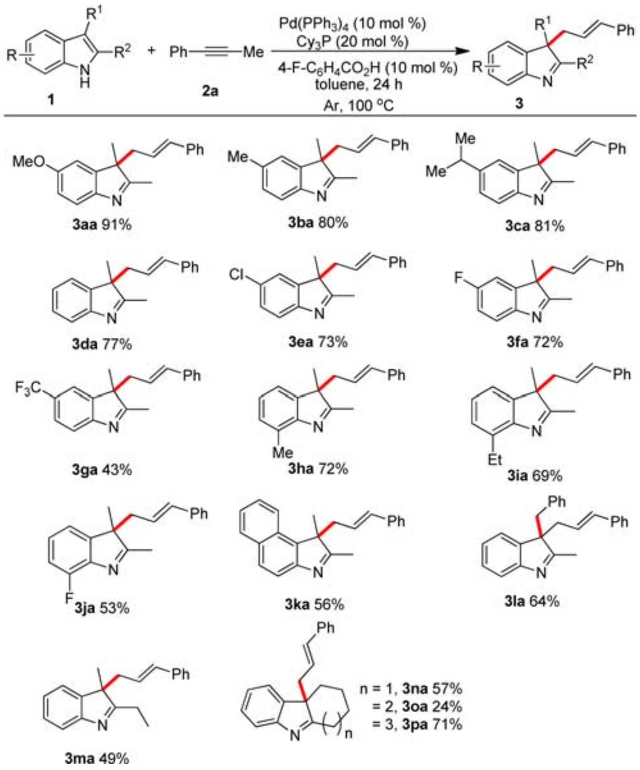


entry	catalyst	additive	ligand	yield (%)
1	$Pd(PPh_3)_4$	$PhCO_2H$	PPh_3	69
2	Pd/C	$PhCO_2H$	PPh_3	nr
3	$Pd_2(dba)_3$	$PhCO_2H$	PPh_3	trace
4	$Pd_2(dba)_3{\cdot}CHCl_3$	$PhCO_2H$	PPh_3	nr
5	$Pd(PPh_3)_4$	$PhCO_2H$		23
6	$Pd(PPh_3)_4$	$PhCO_2H$	Ph_3PO	trace
7	$Pd(PPh_3)_4$	$PhCO_2H$	dppp	51
8	$Pd(PPh_3)_4$	$PhCO_2H$	dppm	79
9	$Pd(PPh_3)_4$	$PhCO_2H$	Cy_3P	91
10	$Pd(PPh_3)_4$	$PhCO_2H$	$^tBu_3P$	64
11	$Pd(PPh_3)_4$		Cy_3P	27
12	$Pd(PPh_3)_4$	AcOH	Cy_3P	50
13	$Pd(PPh_3)_4$	PivOH	Cy_3P	54
14	$Pd(PPh_3)_4$	$4\text{-}MeC_6H_4CO_2H$	Cy_3P	92
15	$Pd(PPh_3)_4$	$4\text{-}FC_6H_4CO_2H$	Cy_3P	95 (91)[c]
16	$Pd(PPh_3)_4$	$4\text{-}MeOC_6H_4CO_2H$	Cy_3P	76
17[d]	$Pd(PPh_3)_4$	$4\text{-}FC_6H_4CO_2H$	Cy_3P	82
18[e]	$Pd(PPh_3)_4$	$4\text{-}FC_6H_4CO_2H$	Cy_3P	73
19		$4\text{-}FC_6H_4CO_2H$	Cy_3P	nr

[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.50 mmol), [Pd] (10 mol %), ligand (20 mol %), and additive (10 mol %) in 2.0 mL of anhydrous toluene at 100 °C under argon for 24 h. [b]The yields were determined by ^1H NMR with dibromomethane as internal standard. [c]Isolated yield. [d]7.5 mol % of $Pd(PPh_3)_4$ and 15 mol % of Cy_3P were used. [e]5 mol % of $Pd(PPh_3)_4$ and 10 mol % of Cy_3P were used. nr = no reaction.

With the optimized conditions in hand, the substrate scope was examined with various indoles (Scheme 2). The indoles with electron-donating groups such as methoxyl, methyl, and isopropyl groups at the C5-position afforded **3aa−ca** in 91%, 80%, and 81% yield, respectively. 2,3-Dimethylindole gave **3da** in 77% yield. The electron-withdrawing groups such as chloro-, fluoro-, and trifluoromethyl groups at the C5-position delivered **3ea−ga** in 73%, 72%, and 43% yields. Besides, 7-Me-, 7-Et-, and 7-F-substituted 2,3-dimethylindoles afforded **3ha−ja** in 53%−72% yields. Moreover, 1,2-dimethyl-3*H*-benzo[*e*]indole **1k** was also tested and furnished **3ka** in 56% yield. By changing the C3-methyl to a benzyl group or the C2-methyl to an ethyl group, **3la** and **3ma** were obtained in 64% and 49% yields. Notably, cyclic olefin-fused indoles were also investigated, and **3na** and **3pa** were obtained in 57% and 71% yields, while **3oa** was only observed in 24% yield due to the disfavored conformation of the seven-membered ring.

Scheme 2. Substrate Scope of Indoles[a,b]

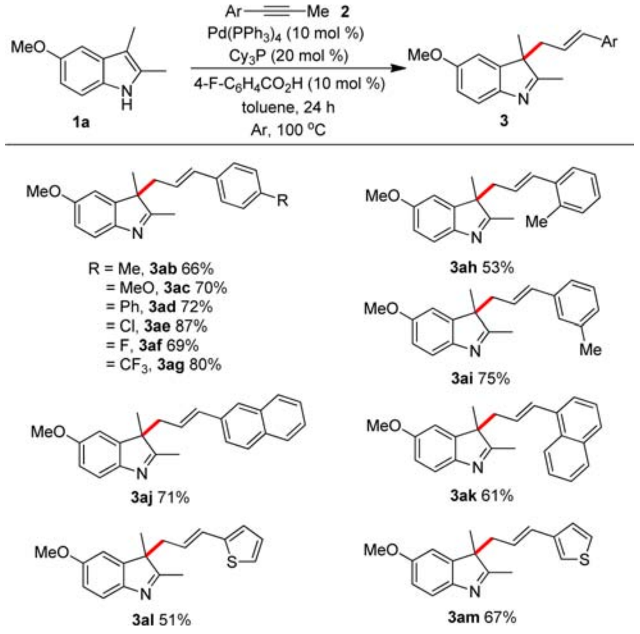


[a]Reaction conditions: **1** (0.25 mmol, 1.0 equiv), **2a** (0.50 mmol, 2.0 equiv), $Pd(PPh_3)_4$ (10 mol %), Cy_3P (20 mol %), and $4\text{-}FC_6H_4CO_2H$ (10 mol %) in anhydrous toluene (2.0 mL) at 100 °C under argon for 24 h. [b]Isolated yields.

Next, the scope of alkynes was investigated, and the results are summarized in Scheme 3. The alkynes with electron-donating groups such as methyl, methoxyl, and phenyl groups at the *para*-position of the phenyl ring delivered **3ab−ad** in 66%, 70%, and 72% yields. The electron-withdrawing groups (−Cl, −F, $-CF_3$) showed higher reactivity and furnished **3ae−ag** in 87%, 69%, and 80% yields. 3-Methyl-substituted alkyne **2i** gave **3ai** in 75% yield, while 2-methyl-substituted alkyne **2h** afforded **3ah** in lower yield due to the steric effect. When the phenyl ring was displaced with a naphthalene ring, the dearomative products **3aj** and **3ak** were obtained in 71% and 61% yields. Moreover, the heterocycles such as thiophene rings were also tolerated under this catalytic system and afforded **3al** in 51% yield and **3am** in 67% yield.

Polycyclic skeletons embedded within pyrroloindoline or furanoindoline frameworks represent important structure motifs in numerous natural products and pharmaceuticals exhibiting interesting biological properties.[13] Therefore, we

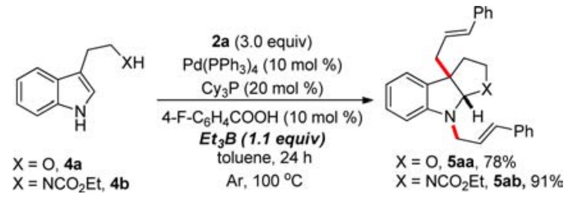
Scheme 3. Substrate Scope of Alkynes[a,b]



[a]Reaction conditions: **1a** (0.25 mmol, 1.0 equiv), **2** (0.50 mmol, 2.0 equiv), $Pd(PPh_3)_4$ (10 mol %), Cy_3P (20 mol %) and $4\text{-}FC_6H_4CO_2H$ (10 mol %) in anhydrous toluene (2.0 mL) at 100 °C under argon for 24 h. [b]Isolated yields.

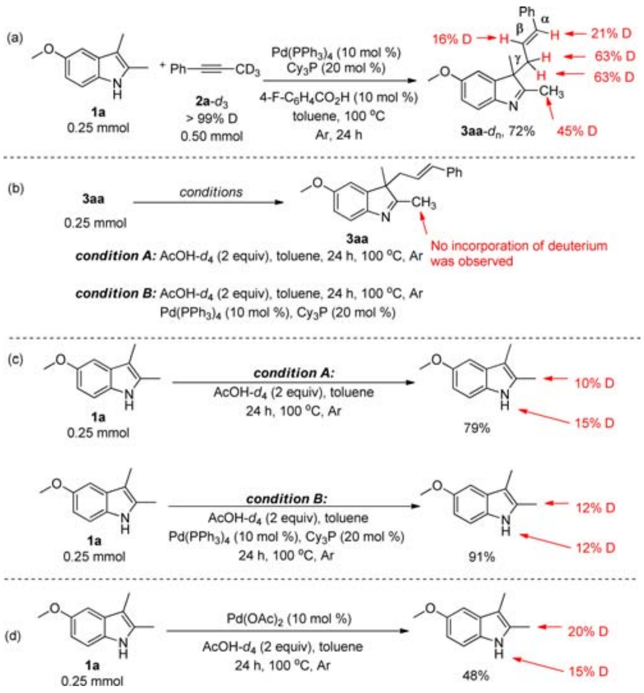
tried to build pyrroloindoline and furanoindoline cores with tryptamine and tryptophol as substrates through cascade dearomatization/allylic alkylation/cyclization process. Unfortunately, no target products were detected under standard conditions. According to our previous work,[14] triethylborane (Et_3B) reacting with indoles could form the *N*-indolyltriethylborate species, which has been proved to be a useful reagent for dearomative C3-alkylation of 3-substituted indoles with both activated and nonactivated alkyl halides due to the enhanced π-nucleophilicity of indoles. Indeed, when 1.1 equiv of Et_3B was added to our catalytic system, **5aa** and **5ab** could be obtained in 78% and 91% yields (Scheme 4).

Scheme 4. Construction of Fused Indolines



To gain insight into the mechanism of this reaction, a deuterated-labeling experiment with **2a**-d_3 was conducted (Scheme 5a). The observed incorporation of hydrogen at the γ-position of **3aa**-d_n indicated the procedure of insertion of **2a** to intermediate **A** and β-hydrogen elimination of intermediate **B** during the formation of allene was reversible.[11e] It was noteworthy that the C2-methyl was deuterated in 45% ratio, and further experiments were conducted to explore this phenomenon. When **3aa** was stirred with AcOH-d_4 under conditions A or B, no incorporation of deuterium was observed (Scheme 5b), suggesting that the deuterium at the C2-methyl was not incorporated with **3aa**. With **1a** as substrate, 10% and 12% deuterium incorporation of C2-methyl was detected under conditions A and B, respectively (Scheme 5c). According to this result, we could conclude that $4\text{-}FC_6H_4CO_2D$ was produced when the reaction was conducted with **2a**-d_3, suggesting the oxidation procedure of $Pd(PPh_3)_4$ with 4-fluorobenzoic acid was reversible. Moreover, when **1a** was stirred with 10 mol % of $Pd(OAc)_2$ and AcOH-d_4 (Scheme 5d), a slightly higher deuterated ratio of C2-methyl in 20% was measured, which hinted that the existence of Pd(II) could promote the deuterated procedure of C2-methyl and Pd(II) should be involved in the total catalytic cycle.

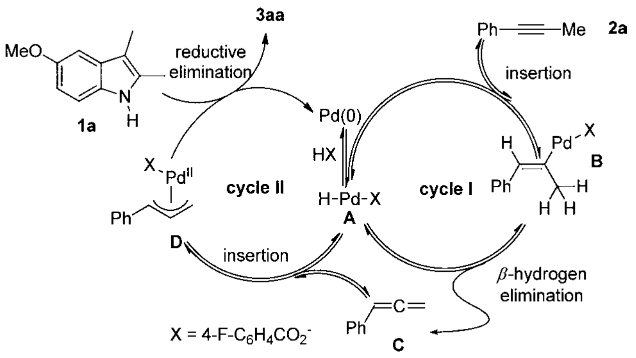
Scheme 5. Deuterated-Labeling Experiments[a]



[a]The extent of deuterium incorporation was determined using ^1H NMR spectroscopy.

On the basis of previous reports[11,15] and our deuterated labeling experiments, a plausible catalytic cycle is proposed as shown in Scheme 6. First, oxidation of $Pd(PPh_3)_4$ with 4-fluorobenzoic acid initiates the catalytic cycles and affords the hydridopalladium species **A**.[15a] Hydropalladation of **2a** with **A** generates to the vinylpalladium intermediate **B**. β-Hydrogen elimination of **B** produces the phenyl allene **C** and intermediate **A** (catalytic cycle I). Next, hydropalladation of **A** with phenyl

Scheme 6. Proposed Mechanism



allene **C** delivers the π-allylpalladium species **D**, which reacts with substituted indole **1a** to give the dearomative product **3aa** together with Pd(0) (cycle II).

In summary, we have developed a palladium-catalyzed dearomative allylic alkylation of indoles with alkynes to construct indolenines with C3-quarternary centers. The in situ formed arylallene intermediate omitted the need of installing leaving groups to the allylic compounds and employing extra oxidants to oxidize the allylic C−H bonds. The reaction exhibited good functional group tolerance as well as high atom economy. Moreover, our protocol was expanded to synthesize pyrroloindoline and furanoindoline frameworks. Further studies on the asymmetric synthesis are currently 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.6b01947.

^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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