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Controllable Pd-Catalyzed Allylation of Indoles with Skipped Enynes: Divergent Synthesis of Indolenines and *N*-Allylindoles

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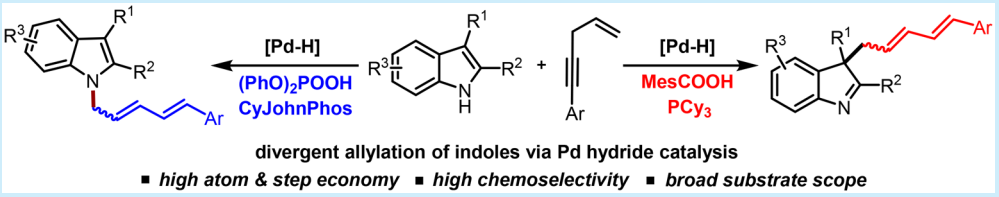
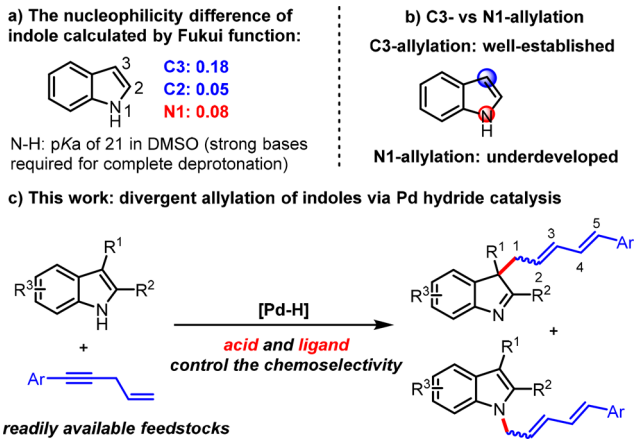
Supporting Information



ABSTRACT: An unprecedented acid- and ligand-controlled divergent allylation of indoles with unactivated skipped enynes via Pd hydride catalysis has been disclosed. This redox-neutral transformation went through multiple hydropalladation insertion, β-hydrogen elimination, $\pi-\sigma-\pi$ isomerization, and allylic substitution steps. This method not only provides a platform for synthesizing indolenines and *N*-allylindoles but also allows facile access to functional 1,3-dienes with high atom and step economy.

The indole scaffolds play a vital role in drug discovery and agrochemical development due to their prevalence in natural products and biologically active structures.[1] They also serve as privileged building blocks in synthetic chemistry.[2] It has been well documented that the C3-position of indole was the most reactive site among the three positions (N1, C2, C3) (Scheme 1a), and the majority of reactions of indoles focused on the C3-position.[3] In contrast, the selective N-functionalization of indoles,[4] especially the direct N-allylation reaction,[5] remains difficult due to the weaker nucleophilicity of N1 relative to that of the C3-position (Scheme 1b). Therefore, developing efficient protocols to control the chemoselectivity and enable divergent synthesis or modification of indoles is still highly desirable, yet challenging, in organic synthesis.[6]

Scheme 1. Chemoselective Allylation of Indoles



The past decades have witnessed great success in the field of transition-metal-catalyzed allylic substitution[7] and allylic C−H oxidation[8] allowing the construction of allyl compounds; however, the catalytic synthesis of versatile 1,3-diene motifs[9] remains underdeveloped.[10] Polyenyl esters[10a,b] and 1,4-pentadienes[10c−f] have been developed to construct 1,3-dienes, while the further development of these synthetic platforms was impeded by the multistep synthesis and prefunctionalization of the allylic substrates, formation of valueless byproducts and/or employment of extra oxidants. Herein, we describe the generality of Pd hydride catalysis for the divergent allylation of indoles (C3 and N1) with unactivated skipped enynes to furnish functional 1,3-dienes, featuring high atom and step economy (Scheme 1c). The high chemoselectivity was made feasible by a delicate choice of acids and ligands.

Our studies commenced by employing 5-methoxy-2,3-dimethylindole **1a** and pent-4-en-1-yn-1-ylbenzene **2a** as the model substrates (Figure 1). When the reaction was performed in the presence of $Pd(PPh_3)_4$ (10.0 mol %), PPh_3 (20.0 mol %), and PivOH (20.0 mol %) as a catalytic system in toluene at 100 °C, the C3-allylation of indole was successfully realized through a dearomatizaton process with high chemoselectivity, yielding **3aa** in 15%. To increase the yield of **3aa**, various acids were then tested, and 2,4,6-trimethylbenzoic acid (**A5**, MesCOOH) could provide **3aa** in 62% yield. Further screening of acids revealed that the chemoselectivity was completely switched to the formation of the N-allylation product **4aa** when $(PhO)_2POOH$ or *p*-TsOH·H_2O was used (see the SI for more details). Given that the specific structure

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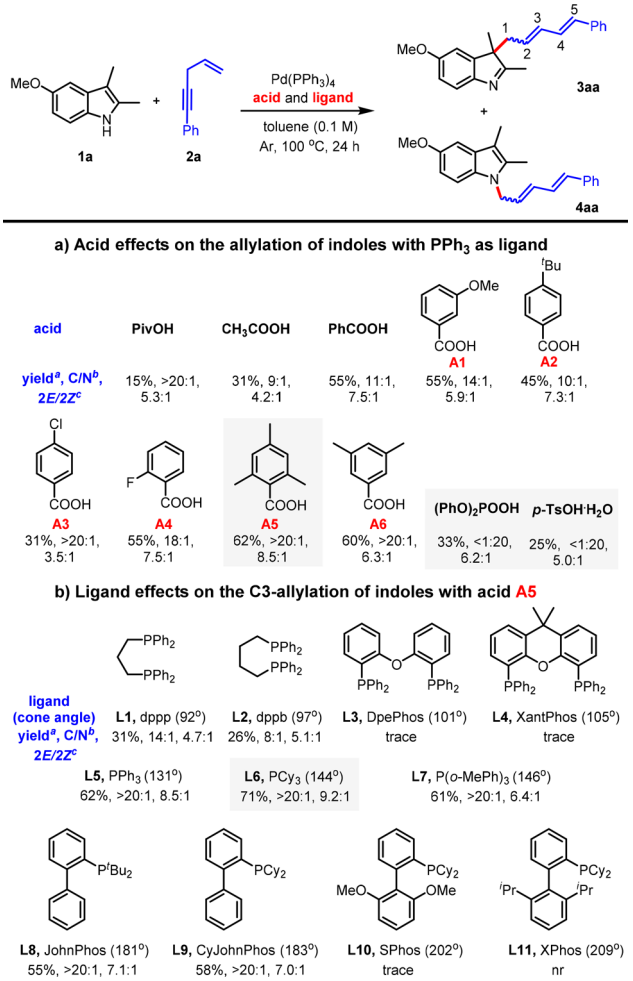
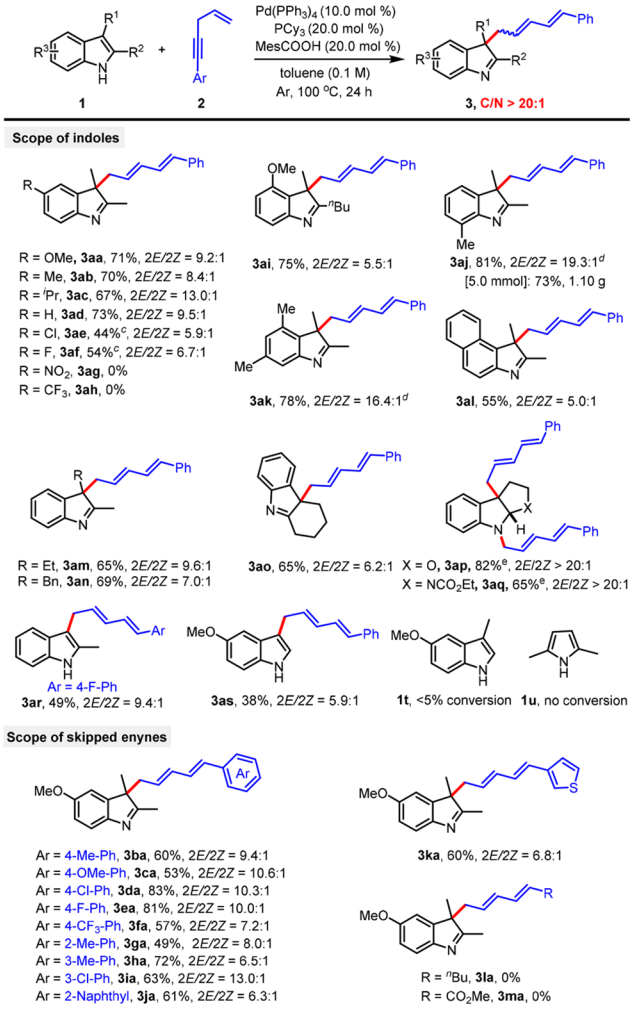


Figure 1. Optimization of reaction conditions. Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $Pd(PPh_3)_4$ (10.0 mol %), ligand (20.0 mol %), and acid (20.0 mol %) in toluene (2.0 mL). (a) Isolated yields of two products and the yields are reported as a mixture of *E* and *Z* isomers. (b) C/N refers to the ratio of **3aa**:**4aa**. (c) Ratios of 2*E*/2*Z* were determined by ^{1}H NMR. nr = no reaction.

of ligands may have an enormous impact on stability, reactivity, and selectivity of the transition-metal complexes,[11] an extensive ligand screening for C3-allylation of indoles was examined and is listed in Figure 1b. Diphosphine ligands **L1**−**L4** exhibited low reactivity and selectivity, whereas monophosphine ligands **L5**−**L9** performed well. Based on the evaluation of the monophosphine ligands, we observed a close-knit relationship between the ligand cone angle and the reactivity and selectivity. Monophosphine ligands with cone angles in the range of 131−183° showed good efficiency, and the best result was observed when PCy_3 was adopted with an optimal cone angle of 144°. Further increasing the cone angle of ligands (**L10** and **L11**) resulted in a dramatic decrease in reactivity.

With the optimized conditions in hand, we then examined the substrate scope of C3-allylation of indoles, and the results are shown in Scheme 2. Methoxy, methyl, and isopropyl groups installed at the C5-position of indoles (**1a**−**c**) provided **3aa**−**ac** in 67−71% yields. 2,3-Dimethylindole **1d** gave **3ad** in 73% yield. Products **3ae** and **3af** with halogen groups (−Cl, −F) at the C5-position were achieved in 44% and 54% yields. Indoles bearing strong electron-withdrawing groups (−NO_2 and −CF_3) were found to be incompatible. C4-OMe-substituted indole **1i** afforded **3ai** in 75% yield. In addition, 7-methyl- and 4,6-dimethyl-substituted indoles (**1j** and **1k**) and 1,2-dimethyl-3*H*-benzo[*e*]indole **1l** could furnish **3aj**−**al** in 55−81% yields. The reaction was amenable to scale-up, providing **3aj** in 73% yield on a 5.0 mmol scale. By changing the C3-methyl group to an ethyl group or a benzyl group, **3am** and **3an** were obtained in 65% and 69% yields. 1,2,3,4-Tetrahydrocarbazole **1o** delivered **3ao** in 65% yield. Furanoindoline **3ap** and pyrroloindoline **3aq** were achieved in good yields with tryptamine and tryptophol as substrates via cascade dearomatization/allylation/cyclization.[12] 2-Methylindole **1r** and 5-methoxyindole **1s** could offer C3-allylated indoles in moderate yields. However, 3-methylindole **1t** and 2,5-dimethylpyrrole **1u** gave trace or none products under the standard conditions. Skipped enynes bearing both electron-donating groups (−Me, −OMe) and electron-withdrawing groups (−Cl, −F, −CF_3) on the phenyl ring provided **3ba**−**ia** in moderate to good yields. When the phenyl group was replaced with naphthyl and thiophene groups (**2j** and **2k**), the

Scheme 2. Substrate Scope of C3-Allylation of Indoles[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), $Pd(PPh_3)_4$ (10.0 mol %), PCy_3 (20.0 mol %), and MesCOOH (20.0 mol %) in toluene (2.0 mL). [b]Isolated yields and the yields are reported as a mixture of *E* and *Z* isomers. The ratios of 2*E*/2*Z* were determined by ^{1}H NMR. [c]120 °C. [d]After recrystallization. [e]1.1 equiv of Et_3B was added.

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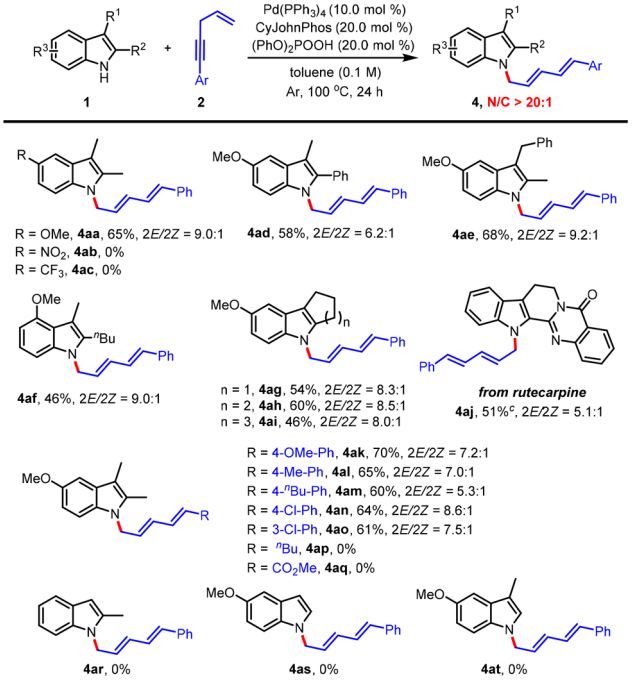
reaction could also proceed efficiently as well. Alkyl- or ester-substituted skipped enynes (**2l** and **2m**) were invalid.

After examining the scope of C3-allylation of indoles, we then turned to the selective N-allylation of indoles (Scheme 3).

Scheme 3. Substrate Scope of N-Allylation of Indoles[a,b]



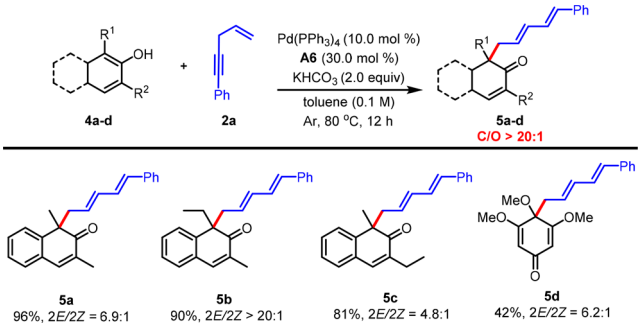
[a]Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), $Pd(PPh_3)_4$ (10.0 mol %), CyJohnPhos (20.0 mol %), and $(PhO)_2POOH$ (20.0 mol %) in toluene (2.0 mL). [b]Isolated yields and the yields are reported as a mixture of *E* and *Z* isomers. The ratios of 2*E*/2*Z* were determined by ^1H NMR. [c]120 °C.

The combination of $(PhO)_2POOH$ and CyJohnPhos was found to be an ideal catalytic system (see the SI for more details). Various N−H indoles bearing sterically modified substituents could efficiently convert into *N*-allylindoles **4aa** and **4ad**−**ai** with high chemoselectivity. Moreover, natural product rutecarpine could be successfully modified to provide **4aj** in 51% yield. Aryl-substituted skipped enynes were competent reagents, which offered **4ak**−**ao** in good yields, while alkyl- or ester-substituted skipped enynes were unsuccessful substrates (**4ap** and **4aq**). Indoles bearing strong electron-withdrawing groups, 2-methylindole, 5-methoxyindole, and 3-methylindole failed to give the desired *N*-allylindoles (**4ab**, **4ac**, and **4ar**−**at**).

Naphthols are readily available materials and possess multiple reactive sites. Recently, the dearomatization of naphthols has received great attention because this transformation represents an ideal method for the rapid construction of functionalized cyclohexadienones.[13] In our Pd hydride catalysis, the cyclohexadienones **5a**−**d** bearing 1,3-diene motifs could be easily accessed through the addition of various *β*-naphthol and phenol derivatives to skipped enyne **2a** with high chemoselectivity (C/O > 20:1) (Scheme 4).

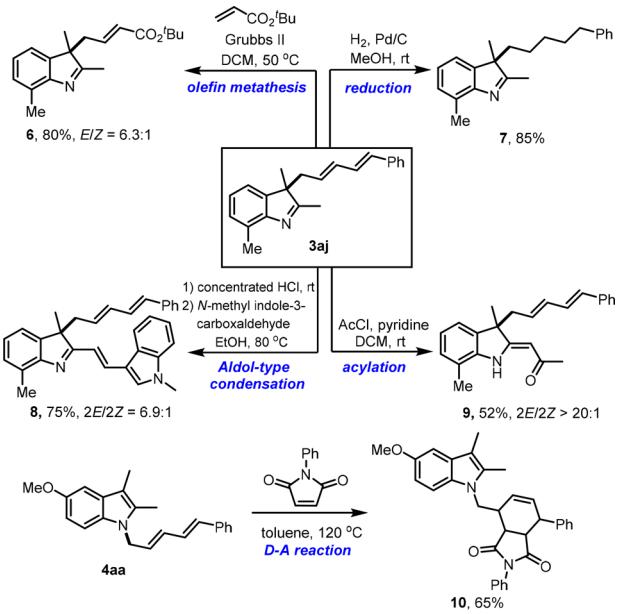
To demonstrate the utility of the reaction, further transformations of the products were carried out. An olefin cross-metathesis of **3aj** with *tert*-butyl acrylate in the presence of Grubbs II catalyst occurred smoothly to furnish indolenine **6** in 80% yield (Scheme 5). Indolenine **7** bearing a long-chain alkyl

Scheme 4. Substrate Scope of Naphthols[a,b]



[a]Reaction conditions: **4** (0.2 mmol), **2a** (0.4 mmol), $Pd(PPh_3)_4$ (10.0 mol %), **A6** (30.0 mol %), and $KHCO_3$ (2.0 equiv) in toluene (2.0 mL). [b]Isolated yields and the yields are reported as a mixture of *E* and *Z* isomers. The ratios of 2*E*/2*Z* were determined by ^1H NMR.

Scheme 5. Synthetic Applications



group could be obtained through catalytic hydrogenation. Bisindole **8**, a structural motif known for its presence in potent antitumor agents,[14] could be easily obtained by Aldol-type condensation. Treatment of **3aj** with acetyl chloride in the presence of triethylamine provided the corresponding *β*-enaminone **9** in 52% yield.[15] The *N*-allylindole **4aa** underwent a cycloaddition reaction with *N*-phenylmaleimide, producing polycyclic compound **10** in 65% yield.

To gain some insight into the mechanism of this reaction, we prepared phenyl allene **11** and tested its reactivity with **1a** under slightly modified conditions,[16] which delivered **3aa** in 61% yield (Scheme 6a). This result indicated that the phenyl allene could be involved in the reaction process. On the basis of previous reports,[17] the above result, and deuterium-labeling experiment (see the SI for details), a plausible catalytic cycle for the C3-allylation of indoles was proposed as shown in Scheme 6b. First, oxidation of $Pd(PPh_3)_4$ with MesCOOH initials the catalytic cycles and affords the hydridopalladium species **A**. Hydropalladation of **2a** with **A** affords the vinyl palladium intermediate **B**. *β*-Hydrogen elimination of **B** produces the phenyl allene **C** and intermediate **A** (catalytic cycle I). Next, hydropalladation of **A** with phenyl allene **C**

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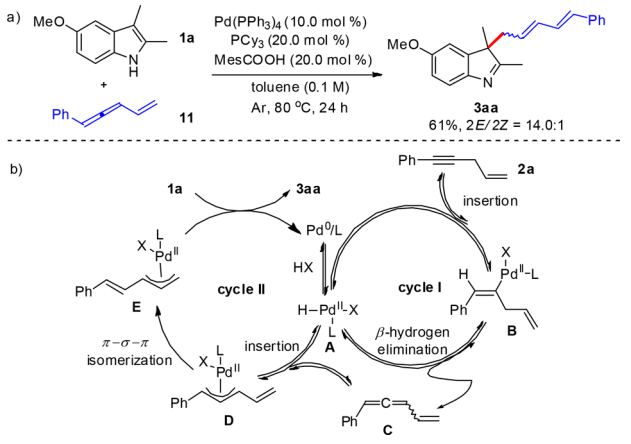
Scheme 6. Mechanism Study



delivers the vinyl π-allyl palladium species **D** (catalytic cycle II), which delivers intermediate **E** through $\pi-\sigma-\pi$ isomerization. Capture of the intermediate **E** with **1a** affords **3aa** together with Pd(0) to enter the next catalytic cycle. Moreover, the chemoselectivity could be switched to the formation of N-allylation product **4aa** when $(PhO)_2POOH$ and CyJohnPhos were employed.

In summary, we have uncovered a divergent allylation of indoles with skipped enynes via Pd hydride catalysis. The chemoselectivity could be well controlled by a suitable combination of acids and ligands. This strategy provided straightforward entry to indolenines and *N*-allylindoles and also allowed facile access to functional 1,3-diene motifs. Moreover, the reaction could be further expanded to the dearomatization of naphthols to synthesize functionalized cyclohexadienones with 1,3-diene motifs. The in situ formed π-allyl metal intermediate bypassed preinstallation of the leaving groups and employment of extra oxidants, featuring excellent atom and step economy. Future studies are warranted to better understand the origin of this unique selectivity.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for all new compounds (PDF). Experimental procedures and spectroscopic characterization data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02481.

Experimental procedures and spectroscopic characterization data; ^{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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