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Accessing 1,3-Dienes via Palladium-Catalyzed Allylic Alkylation of Pronucleophiles with Skipped Enynes

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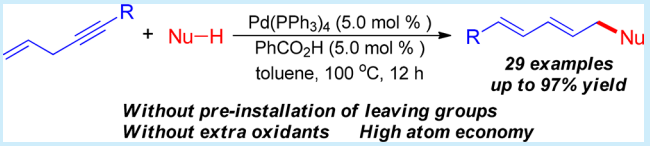
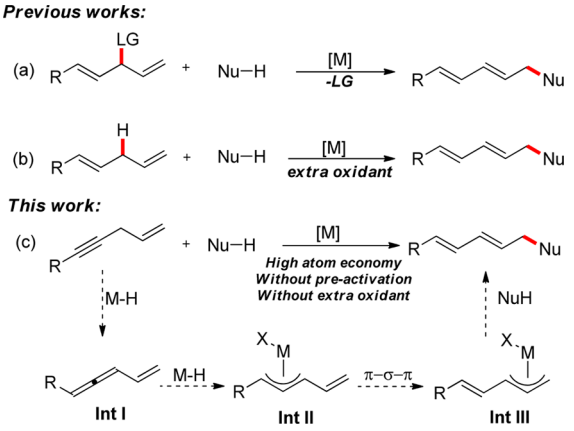
Supporting Information

ABSTRACT: An unprecedented palladium-catalyzed allylic alkylation of pronucleophiles with unactivated skipped enynes has been developed. This method provides a straightforward access to a wide array of 1,3-dienes without the need to preinstall leaving groups or employ extra oxidants. The reaction exhibited high atom economy, good functional group tolerance, excellent regioselectivities, and scalability. With D_2O as cosolvent, deuterium could be incorporated in high efficiency.



1,3-Dienes are crucial skeletons found in numerous natural products and bioactive molecules,[1] such as antiproliferative agent dolatrienoic acid,[2] (−)-zampanolide,[3] antitumor antibiotic anthramycin,[4] and bacteriostatic antibiotic (−)-macrolactin A.[5] Moreover, they also serve as privileged building blocks in organic synthesis.[6] Thus, the development of efficient methods to construct 1,3-dienes has been actively pursued by synthetic chemists. Traditional methods to build 1,3-dienes include the Horner−Wadsworth−Emmons reaction,[7] Wittig reaction,[8] transition-metal-catalyzed (dehydrogenative) cross-coupling,[9] olefin metathesis,[10] and others.[11] As an alternative, transition-metal-catalyzed allylic substitution provides a new method to construct 1,3-dienes (Scheme 1a).[12] Furthermore, the allylic C−H oxidative functionalization of 1,4-dienes has attracted chemists' research interests over the last few decades (Scheme 1b).[13] However, some unavoidable limitations of previous methods still exist with respect to the formation of stoichiometric valueless byproducts, prefunctionalization of substrates, and employment of stoichiometric oxidants. An undeveloped route to 1,3-dienes that is ideal from the perspective of atom economy and sustainable chemistry is redox-neutral allylic alkylation with unactivated skipped enynes because of its inherent advantages of bypassing prefunctionalization of the substrates.

Scheme 1. Transition-Metal Catalyzed Allylic Alkylation To Construct 1,3-Dienes



Since transition-metal-catalyzed redox-neutral allylic alkylation of internal or terminal alkynes has been described,[14] we were drawn to the possibility that skipped enynes[15] could provide a new avenue to develop a general catalyst system for building 1,3-dienes with a range of pronucleophiles (Scheme 1c). Mechanistically, the 1,3-dienes could be produced through the following process: (1) skipped enynes transform to vinyl allene intermediates **Int I** through M−H insertion and subsequent β-hydrogen elimination, which was followed by the addition of M−H species again to deliver vinyl (π-allyl) metal **Int II**; (2) **Int II** converts into **Int III** via $\pi-\sigma-\pi$ isomerization; (3) pronucleophiles capture **Int III** to afford the corresponding 1,3-dienes. With this strategy selected, the regioselectivities and substrate scope are potential issues to be determined. Moreover, the success of this idea depends largely on the isomerization process and the choice of transition-metal catalysts. As a continuation of our previous work on the palladium-catalyzed allylic alkylation of alkynes,[16] herein we describe an unprecedented palladium-catalyzed redox-neutral allylic alkylation of pronucleophiles with skipped enynes to construct 1,3-dienes with high atom economy.

We commenced our study with 1-methyl-3-phenylindolin-2-one **1a** and pent-4-en-1-yn-1-ylbenzene **2a** as substrates, and the results are summarized in Table 1. A series of acids typically employed for palladium-catalyzed redox-neutral allylic alkylation were examined (Table 1, entries 1−5), and a good result was observed with $PhCO_2H$ as additive, giving the desired 1,3-

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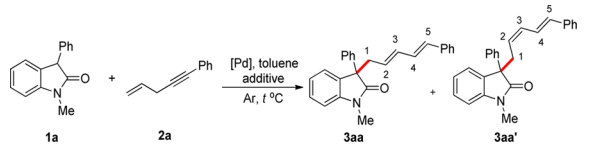
Table 1. Optimization of Reaction Conditions[a]



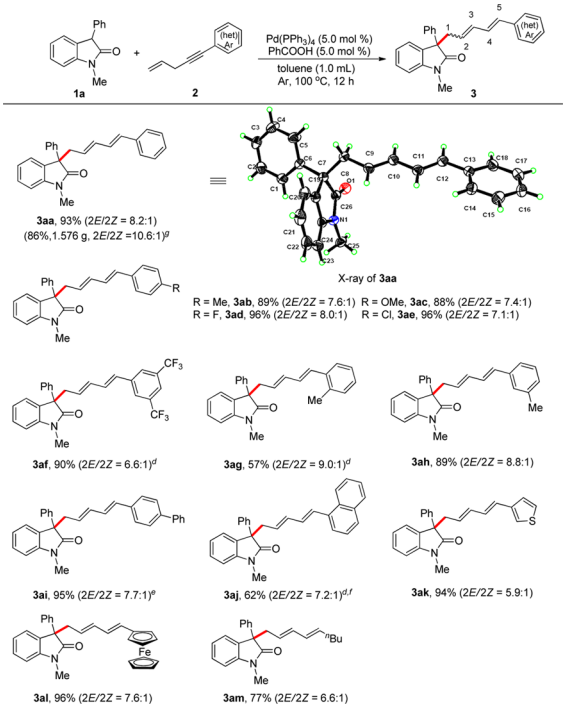
entry	catalyst	T (°C)	additive	yield[b] (%)	ratio (3aa/3aa′)[c]
1	$Pd(PPh_3)_4$	100	$TsOH·H_2O$	trace	
2	$Pd(PPh_3)_4$	100	$(PhO)_2POOH$	38	6.7:1
3	$Pd(PPh_3)_4$	100	Ph_3CCO_2H	86	5.7:1
4	$Pd(PPh_3)_4$	100	CH_3CO_2H	92	6.3:1
5	$Pd(PPh_3)_4$	100	$PhCO_2H$	93	8.2:1
6[d]	$Pd(PPh_3)_4$	100	$PhCO_2H$	84	8.0:1
7[d]	$Pd_2(dba)_3$	100	$PhCO_2H$	<10	
8[d]	$Pd_2(dba)_3·CHCl_3$	100	$PhCO_2H$	<10	
9	Pd/C	100	$PhCO_2H$	nd	
10	$Pd(OAc)_2$	100	$PhCO_2H$	nd	
11		100	$PhCO_2H$	nr	
12	$Pd(PPh_3)_4$	100		39	4.3:1
13	$Pd(PPh_3)_4$	80	$PhCO_2H$	74	5.2:1
14	$Pd(PPh_3)_4$	60	$PhCO_2H$	50	3.9:1
15	$Pd(PPh_3)_4$	40	$PhCO_2H$	nd	

[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.50 mmol), [Pd] (5.0 mol %), additive (5.0 mol %) in 1.0 mL of toluene at 100 °C under argon for 12 h. [b]Isolated yields and the yields are reported as a mixture of *E* and *Z* isomers. [c]The ratios were determined by ^{1}H NMR. [d]2.5 mol % of catalyst and 2.5 mol % of $PhCO_2H$ were used. nr = no reaction. nd = not detected.

dienes **3aa** and **3aa′** in 93% total yield. Other acids such as $TsOH·H_2O$, $(PhO)_2POOH$, Ph_3CCO_2H, and CH_3CO_2H showed inferior performance with respect to both product yields and ratios of **3aa**/**3aa′**. The structure of **3aa** was assigned by X-ray crystallographic analysis (see the Supporting Information for details).[17] The role of each reactant was further tested. The 1,3-dienes could still be obtained in 84% yield without obvious loss of stereoselectivity when the catalyst loading was reduced to 2.5 mol % (Table 1, entry 6). $Pd(PPh_3)_4$ was critical to this reaction because no product was detected with Pd/C or $Pd(OAc)_2$ as catalysts, and poor yields were obtained with $Pd_2(dba)_3$ or $Pd_2(dba)_3·CHCl_3$ as catalysts (Table 1, entries 7−10). The reaction did not occur under catalyst-free conditions (Table 1, entry 11). Control experiments revealed that $PhCO_2H$ played a vital role in the reaction (Table 1, entry 12). The yields and ratios of **3aa**/**3aa′** were reduced at lower temperatures (Table 1, entries 13 and 14), and no reaction was observed when the reaction temperature was below 40 °C (Table 1, entry 15).

With the optimized conditions in hand, we then investigated the scope and generality of this reaction with a series of skipped enynes, and the results are summarized in Scheme 2. Skipped enynes bearing both electron-donating groups (−Me, −OMe) and electron-withdrawing groups ($-CF_3$, −F, −Cl) on the phenyl group gave the desired products **3ab**−**af** in good yields from 88% to 96%. *Ortho*-substituted skipped enyne **2g** exhibited lower reactivity due to steric hindrance, while *meta*-substituted skipped enyne **2h** afforded **3ah** in 89% yield. When the phenyl group was changed to biphenyl and 1-naphthalenyl groups, the reaction proceeded smoothly to deliver **3ai** in 95% yield and **3aj** in 62% yield, respectively. Moreover, heterocycles and functional groups such as thiophene-3-yl and ferrocenyl

Scheme 2. Substrate Scope of Skipped Enynes[a−c]



[a]Reaction conditions: **1a** (0.25 mmol, 1.0 equiv), **2** (0.50 mmol, 2.0 equiv), $Pd(PPh_3)_4$ (5.0 mol %), and $PhCO_2H$ (5.0 mol %) in toluene (1.0 mL) at 100 °C under argon for 12 h. [b]Isolated yields and the yields are reported as a mixture of *E* and *Z* isomers. [c]The ratios of 2*E*/2*Z* were determined by ^{1}H NMR. [d]24 h. [e]85 °C. [f]120 °C. [g]3.0 mol % of $Pd(PPh_3)_4$ and 3.0 mol % of $PhCO_2H$ were used.

groups could also be tolerated to give **3ak** in 94% yield and **3al** in 96% yield. For **2m** with an alkyl substituent, the allylic alkylation proceeded regioselectively at the terminal position to produce **3am** in good yield. To further test the practicability of this reaction, a gram-scale reaction was conducted with 3.0 mol % of $Pd(PPh_3)_4$ as catalyst, and **3aa** was generated in 86% yield (1.576 g, 2*E*/2*Z* = 10.6:1).

Next, we turned our attention to explore the generality of the pronucleophiles under the standard conditions and the results are summarized in Scheme 3. Indolinones with electron-donating groups (−OMe, −Me) and an electron-withdrawing group (−F) afforded **3ba**−**da** in 74−83% yields. The nonsteroidal anti-inflammatory drug phenylbutazone was efficiently allylic alkylated at the C3-position to provide **3ea** in 78% yield. Cyano, nitro, and acetyl groups were also compatible with this catalytic system and delivered **3fa**−**ha** in 53−97% yields. Moreover, difluoride product **3ia** was achieved in 72% yield, and the incorporated phosphonate group provided a handle to further derivation. The diketones **1j** and **1k** could be elaborated efficiently to give **3ja** in 67% and **3ka** in 93% yield. Moreover, **3ka** (2.33 g) could be synthesized in 92% yield on a 10.0 mmol scale with the reaction time prolonged to 24 h. To our delight, 1,3-dienoic moiety could also be introduced to the unactivated cyclic ketone with L-proline and $TsOH·H_2O$ as co-catalyst,[16b] delivering **3la** in 60% yield. In addition, heteronucleophiles such as indoline and tetrahydroquinoline could also generate **3ma** and **3na** in 97% and 96% yields through C−N bond formation. It is worth noting that the complex natural product rutecarpine, a COX-2 inhibitor, was modified successfully to provide **3oa** in 57% yield. When

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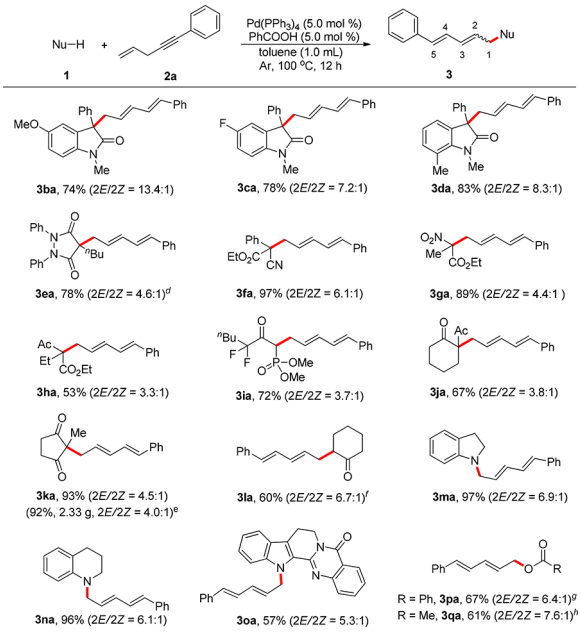
Scheme 3. Substrate Scope of Pronucleophiles[a−c]

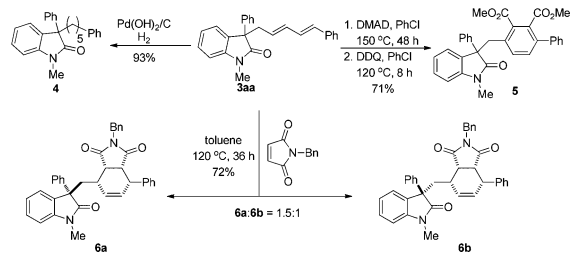


[a]Reaction conditions: **1** (0.25 mmol, 1.0 equiv), **2a** (0.50 mmol, 2.0 equiv), $Pd(PPh_3)_4$ (5.0 mol %), and $PhCO_2H$ (5.0 mol %) in toluene (1.0 mL) at 100 °C under argon for 12 h. [b]Isolated yields and the yields are reported as a mixture of *E* and *Z* isomers. [c]The ratios of 2*E*/2*Z* were determined by ^1H NMR. [d]CH_3CN was used as solvent. [e]10.0 mmol scale, 24 h. [f]$Pd(PPh_3)_4$ (10.0 mol %), $(4-F-C_6H_4)_3P$ (20.0 mol %), $TsOH·H_2O$ (15.0 mol %), and L-proline (30.0 mol %) were used. [g]$PhCO_2H$ (0.25 mmol, 1.0 equiv) was used. [h]CH_3CO_2H (0.25 mmol, 1.0 equiv) was used.

benzoic acid and acetic acid were used as pronucleophiles, **3pa** and **3qa** were obtained in 67% and 61% yields through C−O bond construction, while PhOH or BnOH could not offer the corresponding product.

To take advantage of the 1,3-dienes, **3aa** was further transformed to various attractive structures (Scheme 4).

Scheme 4. Derivation of the Allylic Alkylated Product 3aa



Through catalytic hydrogenation, indolinone **4** containing a long-chain alkyl group could be obtained in 93% yield. Moreover, through a tandem Diels−Alder/oxidation process, indolinone **5** with a polysubstituted phenyl group was achieved in 71% yield. When *N*-benzylmaleimide was selected as dienophile, polycyclic compounds **6a** and **6b** were isolated in 72% total yield (**6a**/**6b** = 1.5:1). The structure of **6a** was assigned by X-ray crystallographic analysis (Figure 1; see the SI for details).[17]

To gain insight into the mechanism of this reaction, a deuteration reaction was conducted (Scheme 5a). When D_2O was used as a cosolvent, deuterated product **3aa-*d*$_n$** could be

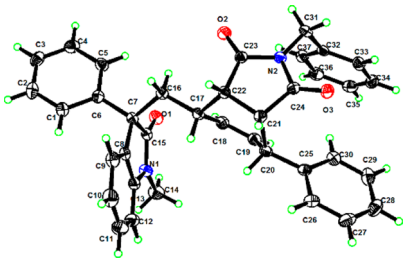
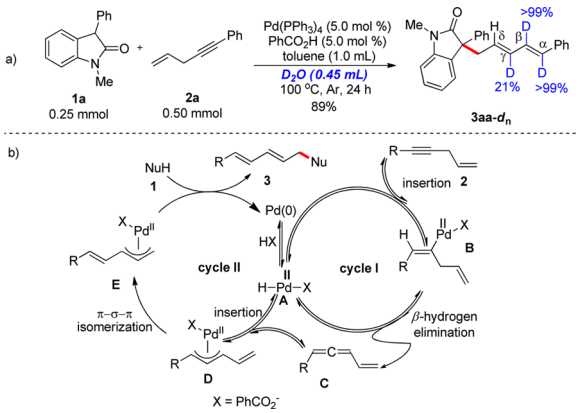


Figure 1. X-ray structure of **6a**.

Scheme 5. Proposed Mechanism



obtained in 89% yield. The deuterated ratios at the *α*,*β*,*γ*-positions were >99%, >99%, and 21%, respectively, which indicated that the *β*-hydrogen elimination of intermediate **B** to vinyl allene **C** was reversible as shown in **Cycle I** of Scheme 5b (see the SI for details).[18] On the basis of previous reports,[19] a plausible catalytic cycle is proposed as shown in Scheme 5b. First, oxidation of $Pd(PPh_3)_4$ with benzoic acid initiates the catalytic cycles and affords the hydridopalladium species **A**. Hydropalladation of **2** 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** delivers the vinyl (*π*-allyl)palladium species **D** (catalytic **cycle II**), which delivers intermediate **E** through *π*−*σ*−*π* isomerization. Capture of intermediate **E** with pronucleophiles **1** affords the allylic alkylated products **3** in addition to Pd(0), which can reenter the next catalytic cycle.

In summary, we have developed a novel palladium-catalyzed allylic alkylation of various pronucleophiles with unactivated skipped enynes to construct 1,3-dienes through C−C, C−N, and C−O bond formation. Various functionalized 1,3-dienes were obtained in good yields with high atom economy in excellent regioselectivities, which also provided a platform to streamlining the synthesis of complex molecules. The in situ formed vinyl allene intermediate bypassed preinstallation of leaving groups to the nucleophilic partner bearing the dienophile in allylic substitution and employment of extra oxidants in allylic C−H oxidation functionalization.

■ ASSOCIATED CONTENT

Supporting Information

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^{1}H and ^{13}C NMR spectra for all new compounds (PDF)
X-ray crystallographic data for **3aa** (CIF)
X-ray crystallographic data for **6a** (CIF)

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Notes

The authors declare no competing financial interest.

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