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Construction of *N*-Heterocyclic Systems Containing a Fully Substituted Allylic Carbon by Palladium/Phosphine Catalysis

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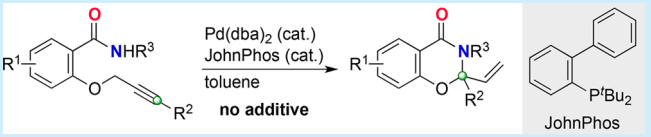
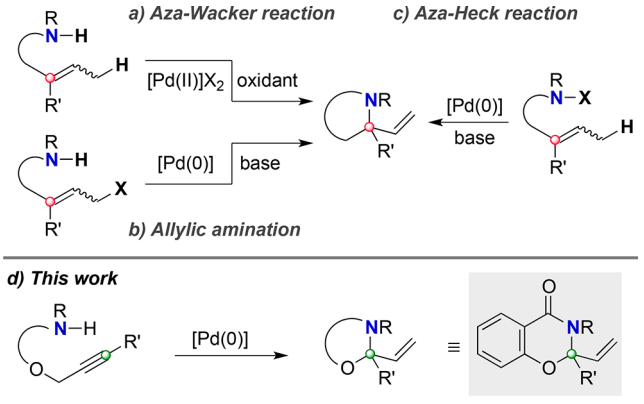
Supporting Information

ABSTRACT: The unique cyclization of benzamide derivatives that contain an alkyne by a Pd(0)/dialkyl(biaryl)-phosphine catalytic system is reported. The reaction efficiently provides a variety of six-membered *N*-heterocyclic compounds that contain a fully substituted carbon center without the need for a stoichiometric additive. Mechanistic studies suggest that this unprecedented cyclization starts with the cleavage of a propargylic C−O bond, and a 1,3-diene has been identified as a relevant intermediate.



The construction of complex *N*-heterocycles is an important topic in synthetic chemistry, given their importance as core structural motifs in potentially bioactive molecules and their role as versatile precursors for more complex ring systems.[1] A significant challenge in this field involves the introduction of a fully substituted carbon center bearing a vinyl substituent in the ring system. The Pd-catalyzed intramolecular cyclization via the formation of carbon−nitrogen bonds is regarded as one of the most reliable routes to such compounds. The aza-Wacker cyclization of alkenes that bear a nitrogen nucleophile by Pd(II) is a well-established process (Scheme 1a).[2,3] To perform the reaction catalytically, an external oxidant is required for the regeneration of the Pd(II) species from the resulting Pd(0) complex. Other approaches are the allylic amination (Tsuji−Trost reaction)[4,5] and the aza-Mizoroki−Heck reaction (Narasaka−Heck cyclization)[6,7] catalyzed by Pd(0) in the presence of a base (Scheme 1b and 1c). The aza-Mizoroki−Heck reaction is a complementary strategy to both the aza-Wacker and the allylic amination reactions, given that the electrophilic nitrogen functions therein as the reaction site.

Scheme 1. Pd-Catalyzed Construction of *N*-Heterocyclic Systems Containing a Tetrasubstituted Allylic Carbon Center



In terms of substrate generality and reaction diversity to access complex *N*-heterocyclic architectures, the development of alternative methods that generate the same motifs from different starting substrates through unprecedented reaction mechanisms is desirable.[8] Our recent studies have examined the Pd-catalyzed cyclization of alkynoic acids, which affords vinyl-substituted *O*-heterocycles with a tetrasubstituted carbon center.[9] This novel synthetic strategy was subsequently exploited to access a variety of *N*-heterocycles. In this communication, we describe the Pd(0)-catalyzed construction of *N*-heterocyclic systems with a fully substituted allylic carbon atom from alkynes bearing a nitrogen nucleophile (Scheme 1d). The present protocol provides in principle no side products and, therefore, avoids the use of stoichiometric additives. Moreover, this transformation involves an unprecedented skeletal rearrangement. Overall, the simple method presented herein allows producing a large variety of novel and complex *N*-heterocyclic compounds.

Initially, we chose the salicylamide derivative *N*-phenylbenzamide **1a**, which bears a propargyl ether moiety at the *ortho*-position, as the starting substrate for the ligand screening (Scheme 2). On the basis of our recent study on the Pd-catalyzed cyclization of alkynoic acids,[9] **1a** was stirred for 1 h in toluene at 110 °C in the presence of $Pd(dba)_2$ (10 mol %) and ^{t}BuXPhos (20 mol %). Under these conditions, the expected intramolecular cyclization afforded *N*-heterocyclic **2a** with a tetrasubstituted allylic carbon atom in 54% GC yield. After screening the reaction conditions,[10] the GC yield of **2a** was improved to 82% when JohnPhos was used as the ligand, and **2a** was isolated in 77% yield.[11]

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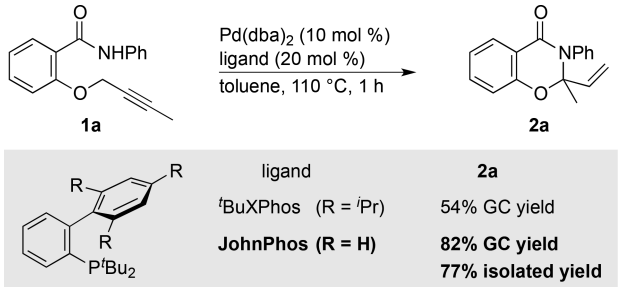
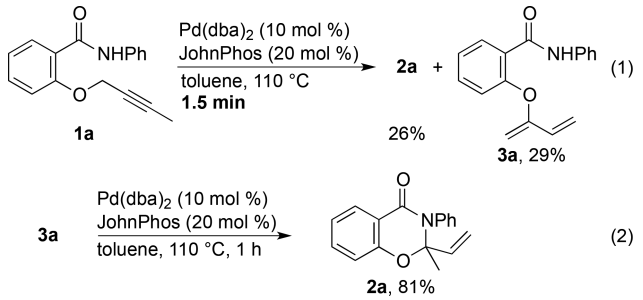
Scheme 2. Ligand Screening



The scope of this cyclization reaction was then explored using the $Pd(dba)_2$/JohnPhos system. As shown in Scheme 3, a variety of substrates **1** underwent cyclization to produce the corresponding products **2** in high yield. Substrates bearing electron-donating and electron-withdrawing substituents on the benzene ring (R^1) or fused-aromatic rings (**1b**–**k**) efficiently provided the corresponding products (**2b**–**k**). Internal alkynes that bear an aryl or an alkyl substituent at their alkynyl carbon atom (R^2) (**1l** and **1m**) also underwent the present cyclization to afford **2l** and **2m**. In contrast, **2n** was not detected using terminal alkyne **1n**; instead, the formation of **2n′** with a seven-membered ring, which is a typical 7-*exo*-*dig* adduct, was observed in 96% yield.[12] The conversion of several *N*-arylbenzamide derivatives (**1o**–**s**; R^3 = Ar) afforded a series of *N*-aryl heterocycles (**2o**–**s**). The unequivocal structural characterization of **2s** was accomplished by a single-crystal X-ray diffraction analysis.[13] Notably, primary amides (**1t**–**v**; R^3 = H) were also transformed into the corresponding products (**2t**–**v**) that contain an unprotected nitrogen atom. On the other hand, *N*-alkylbenzamide derivatives **1w** (R^3 = cyclohexyl) and **1x** (R^3 = butyl) did not provide the corresponding cyclization products **2w** and **2x**, but predominantly generated 1,3-dienes **3w** and **3x**.[14]

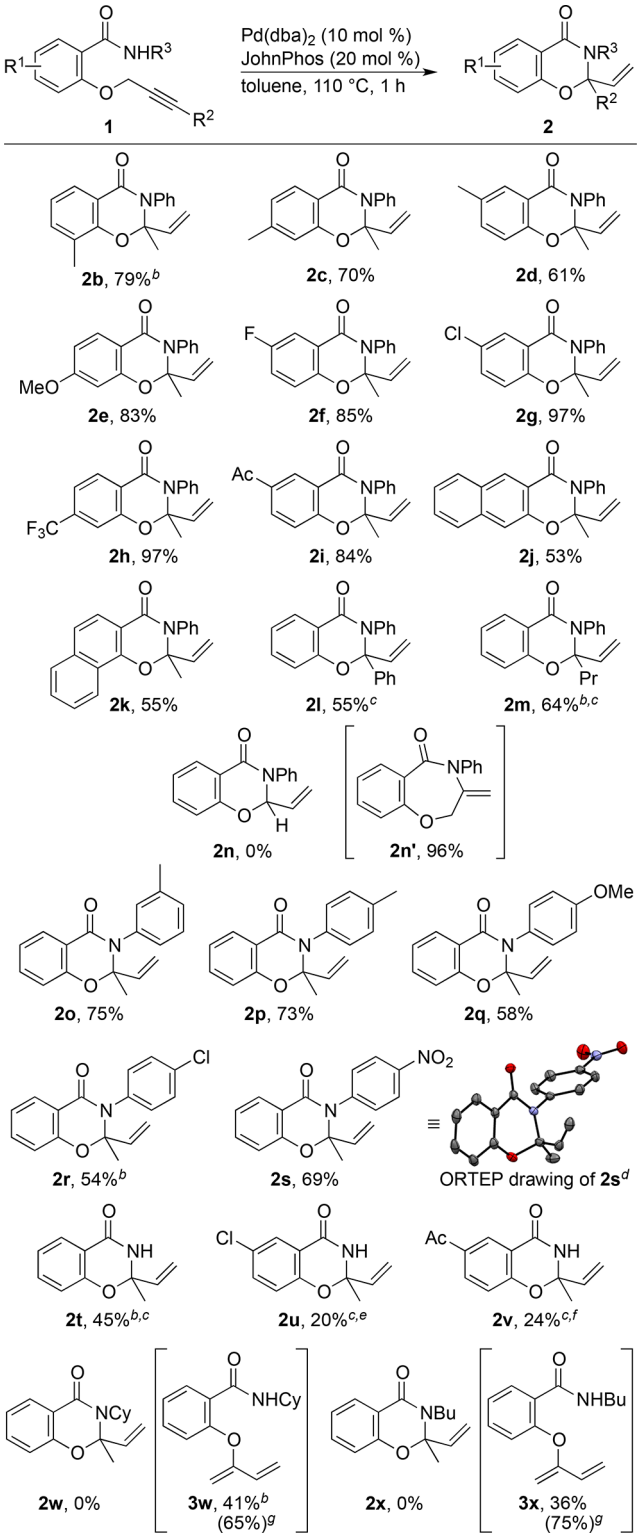
The formation of 1,3-dienes **3** was also observed in the case of the model substrate, i.e., *N*-phenylbenzamide derivative **1a**. When the reaction of **1a** with catalytic amounts of $Pd(dba)_2$/JohnPhos in C_6D_6 at 70 °C was monitored by ^1H NMR spectroscopy, the transient formation of 1,3-diene **3a** was observed (Figure 1a). The plots for the concentrations of the starting substrate [**1a**], cyclization product [**2a**], and 1,3-diene [**3a**] as a function of time are shown in Figure 1b. At the initial stage of the reaction (0–30 min), **3a** is generated predominantly. Subsequently, cyclization product **2a** is formed as diene **3a** is consumed.

The isolation of 1,3-diene **3a** was possible by shortening the reaction time to 1.5 min (eq 1). Then isolated diene **3a** was



used as the starting substrate and catalyzed using $Pd(dba)_2$/JohnPhos to furnish the expected cyclization product **2a** in 81% GC yield (eq 2). In their entirety, the kinetic profiles and control experiments suggest that **1a** is initially converted into

Scheme 3. Substrate Scope[a]



[a]Reaction conditions: **1** (1.0 mmol), $Pd(dba)_2$ (0.1 mmol), and JohnPhos (0.2 mmol) in toluene (1 mL) at 110 °C for 1 h. Isolated yields are shown. [b]0.5 mmol scale. [c]12 h. [d]ORTEP drawing of **2s** with thermal ellipsoids set to 50% probability; hydrogen atoms are omitted for clarity. [e]0.5 mmol scale, toluene (1 mL). [f]0.4 mmol scale, toluene (0.8 mL). [g]^1H NMR yield.

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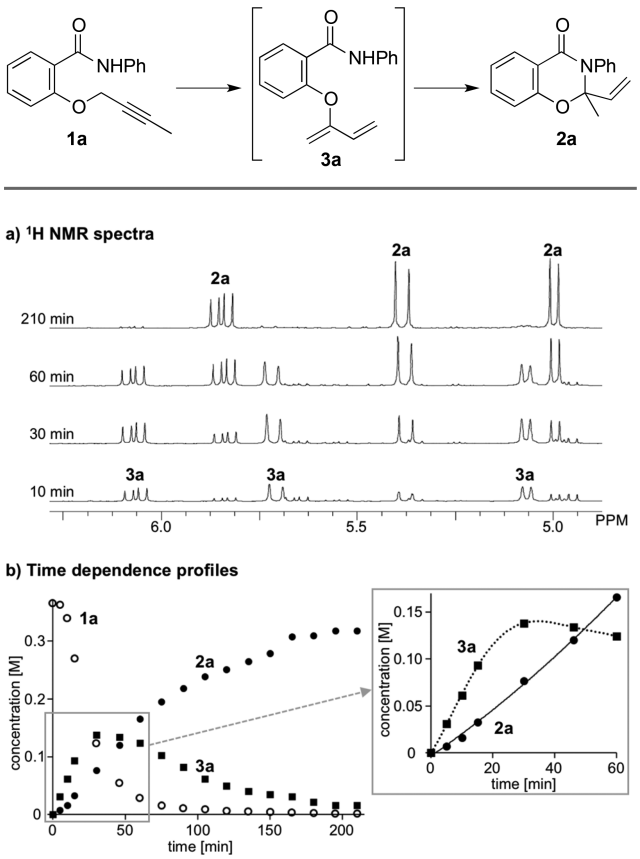
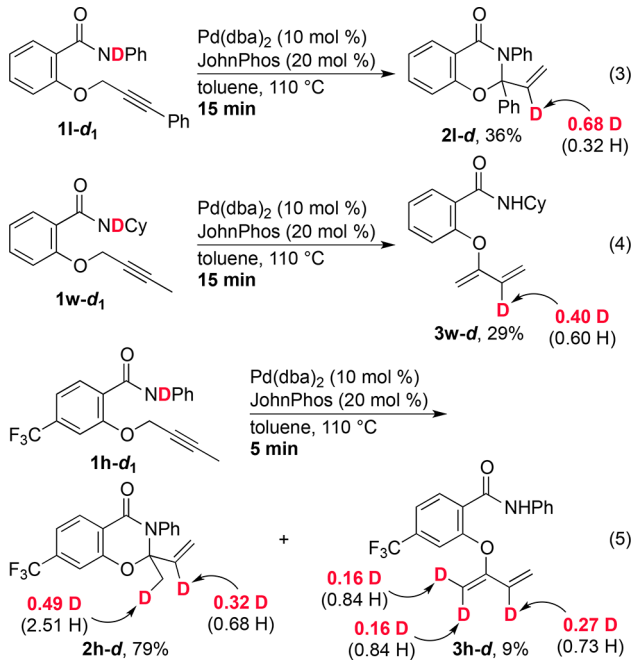


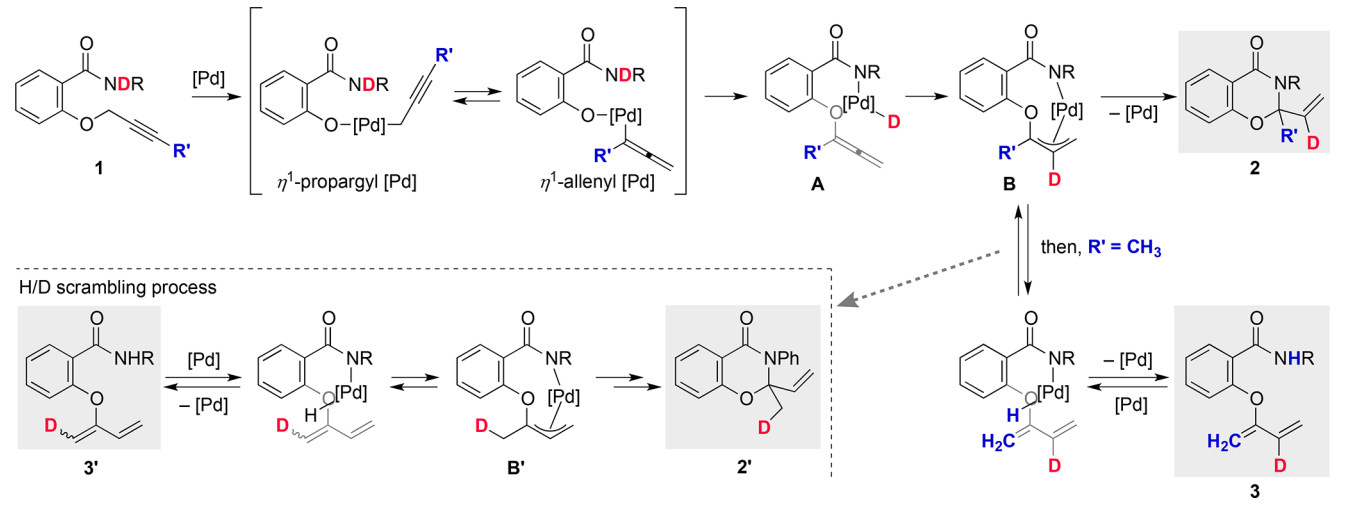
Figure 1. ^{1}H NMR monitoring for the detection of intermediate **3a**. Reaction conditions: **1a** (0.3 mmol), $Pd(dba)_2$ (0.03 mmol), and JohnPhos (0.06 mmol) in C_6D_6 (0.6 mL) at 70 °C. The concentrations of **1a** (○), **2a** (●), and **3a** (■) were calculated from the ^{1}H NMR spectra using 1,3,5-trimethoxybenzene as the internal standard.

intermediate **3a**, which subsequently undergoes cyclization into **2a**.

We then conducted deuterium-labeling experiments employing **1l-*d*$_1$**, **1w-*d*$_1$**, and **1h-*d*$_1$** as the starting substrates, which were deuterated at the nitrogen atom of their amide moieties (eqs 3–5). At the initial stage (15 min) of the reaction of **1l-*d*$_1$** under standard conditions, cyclization product **2l-*d*** was isolated in 36% yield (eq 3). ^{1}H and ^{2}H NMR spectral analyses of the product revealed deuterium incorporation only at the internal vinylic carbon atom of **2l-*d*** (0.68 D, 0.32 H). The reaction of deuterated *N*-alkylbenzamide derivative **1w-*d*$_1$**, which did not afford the cyclization product, proceeded to form 1,3-diene **3w-*d*** in 29% isolated yield with selective deuterium incorporation at the internal diene carbon atom, although the deuterium content was moderate (0.40 D, 0.60 H) (eq 4). When the reaction of **1h-*d*$_1$** was carried out for 5 min, both the cyclization product **2h-*d*** and 1,3-diene **3h-*d*** were isolated in 79% and 9% yield, respectively (eq 5). For the cyclization product **2h-*d***, deuteration of the methyl carbon atom next to the tetrasubstituted carbon atom was also observed (0.49 D, 2.51 H), in addition to that at the internal vinylic carbon atom (0.32 D, 0.68 H). Furthermore, the deuterium incorporation in diene **3h-*d*** occurred at the internal diene carbon atom (0.27 D, 0.73 H) and at the terminal diene



Scheme 4. Possible Pathway for the Pd-Catalyzed Conversion of 1 into 2 and 3



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carbon atom (0.16 D, 0.84 H) next to the oxygen-substituted carbon atom.

On the basis of these mechanistic investigations and our previous experiments employing carboxylic acids,[9] a possible pathway is proposed in Scheme 4. Oxidative addition of the propargylic C−O bond of **1** to Pd(0) would form η^1-propargylpalladium, which would be in equilibrium with η^1-allenyl species. From η^1-allenylpalladium complex, the generation of "*O*-allenyl" palladium intermediate **A** could occur through the formation of a C−O bond and oxidative addition of the N−D bond to Pd(0). Intramolecular hydropalladation of the allene moiety in **A** would proceed to afford π-allylpalladium **B**, which would finally undergo a reductive elimination of the allylic C−N bond of cyclization product **2**, accompanied by deuterium migration from the nitrogen of **1** to the internal vinylic carbon of **2**. In the case of a substrate bearing a methyl substituent at the alkynyl carbon **1** (R′ = Me), the corresponding 1,3-diene **3** would be the observable intermediate, which can be generated from π-allylpalladium **B** via reversible β-hydride elimination and N−H reductive elimination of **3**.

The deuterium incorporation shown in eq 5 for **2h-*d*** and **3h-*d*** implies that rapid H/D scrambling exists in the overall catalytic system. Although the detailed mechanism of the exchange process remains unclear at this stage, assuming a reversible equilibrium between 1,3-diene **3′** and π-allylpalladium **B'** seems feasible.

In summary, we have developed a Pd-catalyzed cyclization of amide derivatives to access challenging nitrogen heterocycles that contain a fully substituted allylic carbon center. The addition of a stoichiometric reagent, such as a base or an oxidant, is not necessary for this reaction to proceed efficiently. This transformation works well on a wide variety of substrates, including primary amides, to produce lactam derivatives. The ^{1}H NMR analyses, deuterium-labeling experiments, and product characterization results revealed that 1,3-diene species are relevant intermediates in a relatively complicated reaction mechanism. Further studies to develop an enantioselective version of this cyclization reaction by asymmetric catalysis and computational studies on the reaction mechanism are currently in progress in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03127.

Experimental procedures and characterization data for all compounds; X-ray crystallographic data for **2s** (PDF)

Accession Codes

CCDC 1571311 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(10) See the Supporting Information for details.

(11) All reactions were carried out under a nitrogen atmosphere; however, they can also be carried out in air, even though this affords slightly diminished yields (69% of **2a** under optimal conditions).

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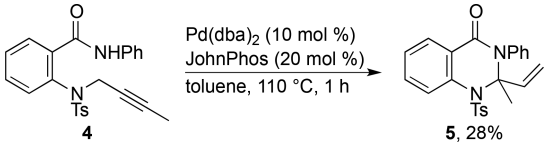
(13) CCDC No. 1571311 (**2s**). The crystallographic data can be obtained free of charge from the Cambridge Crystallographic Data Centre.

(14) The nitrogen linker connecting the aryl and propargyl fragments in substrate **4** was also tolerated, although the yield of the cyclization product **5** was relatively low (28%).



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