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Palladium-Catalyzed Cyclization of Alkynoic Acids To Form Vinyl Dioxanones Bearing a Quaternary Allylic Carbon

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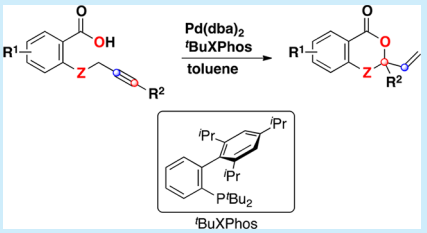
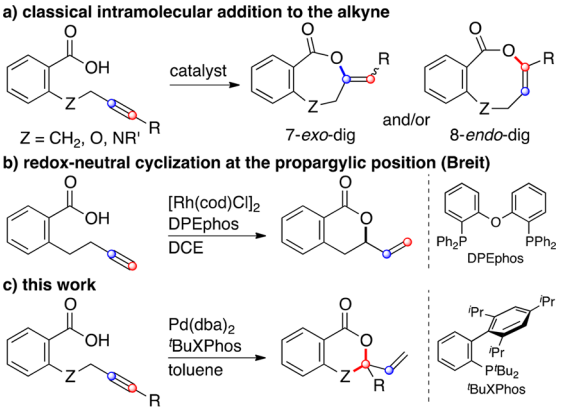
Supporting Information

ABSTRACT: A palladium-catalyzed intramolecular reaction of carboxylic acids and alkynes in a novel cyclization manner was developed. This unique cyclization efficiently provided a wide range of complex ring systems—vinyl dioxanones bearing a quaternary allylic carbon. Mechanistic studies suggest an allenyl carboxylate as an intermediate.



Transition-metal-catalyzed intramolecular cyclization via the addition of heteroatom−hydrogen bonds to carbon−carbon multiple bonds is a powerful synthetic strategy in organic chemistry, because, in principle, the complicated and versatile heterocycles are directly provided starting from readily accessible substrates with 100% atom efficiency.[1] Possibly the most representative and extensively studied of starting molecules for the intramolecular hydrocarboxylation of alkynes are alkynoic acids. Generally, this type of reaction can occur in either an *exo*- or *endo*-cyclization manner, both of which are favored depending on the substrate, e.g. the Baldwin's rules, and/or the choice of catalyst. For example, the cyclization of benzoic acids bearing an alkyne provides alkylidene lactones such as the 7-*exo*-dig and/or 8-*endo*-dig adducts in the presence of appropriate catalysts, such as palladium,[2a] copper,[2b] silver,[2c] and gold[2c] complexes (Scheme 1a). Recently, Breit and co-workers reported a unique cyclization of acids bearing a terminal alkyne by using a Rh(I)/DPEphos catalyst system,[3] in which the cyclization occurs at the propargylic position to form a vinyl lactone instead of alkylidene lactones (Scheme 1b).[3b]

Scheme 1. Transition-Metal-Catalyzed Cyclization of Alkynoic Acids



In contrast to these traditional intramolecular additions and Breit's cyclization, we describe herein an unprecedented type of intramolecular cyclization for alkynoic acids employing a Pd(0)/^{t}BuXPhos system, to afford 4*H*-1,3-benzodioxin-4-one derivatives bearing a vinyl substituent at the quaternary carbon (Scheme 1c). The 6-membered 4*H*-1,3-benzodioxin-4-one frameworks themselves are a core structural unit found in many natural products.[4] In addition, the vinyl substituent at the quaternary carbon is available as a reaction site for further transformations. The products provided by this method, therefore, are considered valuable precursors to diverse, complicated heterocyclic molecules.

To evaluate the cyclization of alkynoic acid **1a**, which is derived from salicylic acid, the reactions in the presence of a catalytic amount of $Pd(dba)_2$ and several phosphine ligands (1:2 Pd/P) were conducted in toluene at 110 °C for 1 h (Table 1). When (2-biphenyl)di-*tert*-butylphosphine (JohnPhos) was used as a ligand, the formation of 6-membered cyclization product vinyl dioxanone **2a** was accomplished in an 80% GC yield, and then the product was isolated in a 68% yield (entry 1).[5] After the screening of a series of dialkylbiarylphosphines (Buchwald-type ligands), such as CyJohnPhos, XPhos, and ^{t}BuXPhos (entries 2−4), ^{t}BuXPhos proved to be the most effective ligand, as shown in entry 4 (95% GC yield, 86% isolated yield). However, triaryl- or trialkylphosphines were less effective for this transformation (entries 5−7). The bidentate ligands Xantphos and NiXantphos were also found to be applicable and resulted in 51% and 70% yields, respectively (entries 8 and 9).

Conversion of various alkynoic acids **1** into **2** was then conducted in the presence of $Pd(dba)_2$/^{t}BuXPhos (Table 2). The reactions of methyl-substituted versions at the 3-, 4-, and 5-

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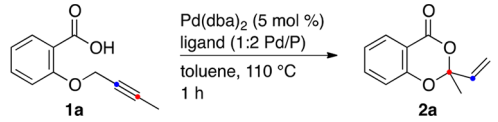
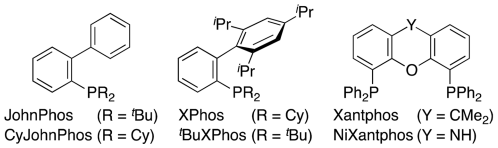
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Ligand Screening for the Pd(0)-Catalyzed Cyclization of 1a to 2a[a]



entry	ligand	yield (%)[b]
1	JohnPhos	80 (68)[c]
2	CyJohnPhos	13
3	XPhos	50
4	^{t}BuXPhos	95 (86)[c]
5	PPh_3	9
6	P^tBu_3	0
7	PCy_3	2
8	Xantphos[d]	51
9	NiXantphos[d]	70



[a]Reaction conditions: **1a** (0.5 mmol), $Pd(dba)_2$ (0.025 mmol), ligand (0.05 mmol), toluene (1 mL), 110 °C, 1 h. [b]GC yield. [c]Isolated yield (1 mmol scale). [d]Ligand (0.025 mmol).

position of the benzene ring, **1b**–**1d**, afforded the expected cyclization products **2b**–**2d** in 79–82% yields (entries 1–3). Substrates bearing a methoxy- and a chlorine-substituent, **1e** and **1f**, provided the products, **2e** and **2f**, in good yields, whereas with the bromine-substituted **1g**, the yield of **2g** was 8% (entries 4–6). Electron-withdrawing substituents, such as an acetyl, a trifluoromethyl, and nitro groups, **1h**–**1k**, were also suitable for the reaction and provided the corresponding heterocycles **2h**–**2k** (entries 7–10). Naphthoic acid derivatives **1l** and **1m** afforded **2l** and **2m** in 72% and 75% yields (entries 11 and 12). The molecular structure of **2m** was confirmed by single crystal X-ray diffraction analysis, and the ORTEP drawings of **2m** are illustrated in Figure 1.[6] Intramolecular reactions of a carboxylic

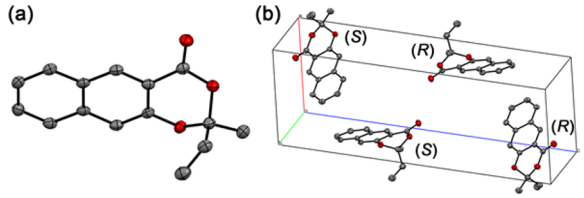
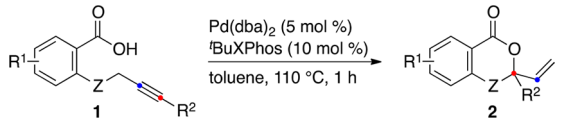


Figure 1. ORTEP drawings of the X-ray crystal structure of (a) (*S*)-**2m** and (b) the packing structure. H-atoms are omitted for clarity.

acid with an internal alkyne substituted by a *n*-butyl, a *tert*-butyl, or a phenyl group, **1n**–**1q**, also proceeded in the same cyclization manner, to form **2n**–**2q** (entries 13–16). The anthranilic acid derivative **1r** was available for this cyclization, giving *N*-containing heterocycle **2r** in a 64% yield (entry 17). On the other hand, the expected cyclization was not observed in the case of an alkynoic acid bearing a methyl substituent at the propargylic position as a starting substrate.

A deuterium-labeling experiment was next performed as a preliminary mechanistic study. The reaction of **1a**-d_2, deuterated at the propargylic carbon, was carried out under the standard

Table 2. Scope of Alkynoic Acids[a]



entry	alkynoic acid **1**	product **2**, yield (%)[b]
1	**1b** (R^1 = 3-Me)	**2b** (R^1 = 8-Me), 80%
2	**1c** (R^1 = 4-Me)	**2c** (R^1 = 7-Me), 82%
3	**1d** (R^1 = 5-Me)	**2d** (R^1 = 6-Me), 79%
4	**1e** (R^1 = 4-MeO)	**2e** (R^1 = 7-MeO), 80%
5	**1f** (R^1 = 5-Cl)	**2f** (R^1 = 6-Cl), 88%
6	**1g** (R^1 = 5-Br)	**2g** (R^1 = 6-Br), 8%[c,d]
7	**1h** (R^1 = 5-Ac)	**2h** (R^1 = 6-Ac), 86%
8	**1i** (R^1 = 4-CF_3)	**2i** (R^1 = 7-CF_3), 60%
9	**1j** (R^1 = 3-NO_2)	**2j** (R^1 = 8-NO_2), 47%[c,d]
10	**1k** (R^1 = 5-NO_2)	**2k** (R^1 = 6-NO_2), 30%[d]
11	**1l**	**2l**, 72%
12	**1m**	**2m**, 75%
13	**1n** (R^1 = H, R^2 = Bu)	**2n** (R^1 = H, R^2 = Bu), 47%[d]
14	**1o** (R^1 = Me, R^2 = Bu)	**2o** (R^1 = Me, R^2 = Bu), 55%[d]
15	**1p** (R^1 = H, R^2 = ^{t}Bu)	**2p** (R^1 = H, R^2 = ^{t}Bu), 28%[d,e]
16	**1q** (R^1 = H, R^2 = Ph)	**2q** (R^1 = H, R^2 = Ph), 33%[d]
17	**1r**	**2r**, 64%[d]

[a]Reaction conditions: **1** (1 mmol), $Pd(dba)_2$ (0.05 mmol), ^{t}BuXPhos (0.1 mmol), toluene (2 mL), 110 °C, 1 h. [b]Isolated yield. [c]JohnPhos was used as a ligand instead of ^{t}BuXPhos. [d]12 h. [e]20 mol % of $Pd(dba)_2$ (0.2 mmol) and 40 mol % of ^{t}BuXPhos (0.4 mmol) were used.

conditions (Table 3). The reaction proceeded smoothly to provide the cyclization product **2a**-d_2 in a 55% yield after 3 min (entry 1). Then a significant incorporation of deuterium was observed at the terminal vinylic carbon (C^3) of **2a**-d_2 (1.73 D with 0.27 H) by ^{1}H and ^{2}H NMR analyses, along with a small amount of the deuterium incorporation at the methyl carbon (C^1) (0.21 D with 2.79 H). As the reaction time was extended to 1 h (86% isolated yield of **2a**-d_2), the deuterium content at C^3

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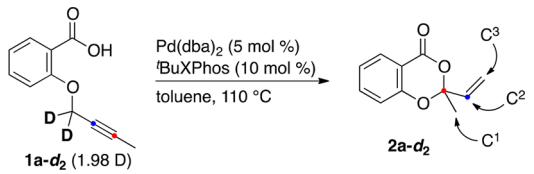
Org. Lett. XXXX, XXX, XXX–XXX

Table 3. Deuterium-Labeling Experiments[a]



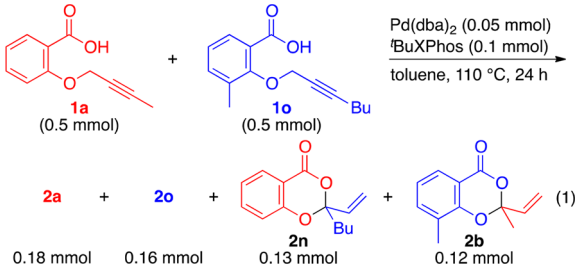
entry	time	yield (%)[b]	D (H) composition[c] at C[n] C[1]	C[2]	C[3]
1	3 min	55	**0.21 D** (2.79 H)	**0.00 D** (1.00 H)	**1.73 D** (0.27 H)
2	1 h	86	**0.66 D** (2.34 H)	**0.03 D** (0.97 H)	**1.26 D** (0.74 H)

[a]Reaction conditions: **1a-d_2** (0.5 mmol), $Pd(dba)_2$ (0.025 mmol), ^{t}BuXPhos (0.05 mmol), toluene (1 mL), 110 °C. [b]Isolated yield. [c]Determined by ^{1}H and ^{2}H NMR analyses of the isolated **2a-d_2**.

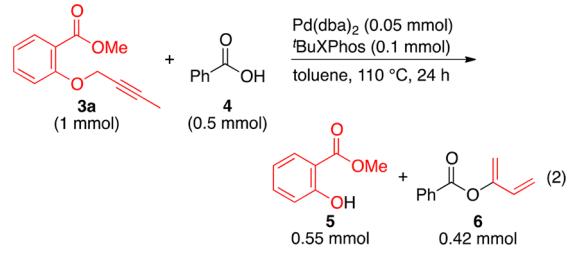
was decreased to 1.26 D (from 1.73 D), and instead small increases were observed (entry 2) in deuterium incorporation at the methyl- (C^1) and at the internal vinylic- (C^2) carbon (from 0.21 to 0.66 D at C^1, from 0 to 0.03 D at C^2). These results indicated that deuterium is transferred from the propargylic carbon of **1a-d_2** into the terminal vinylic carbon (C^3) of **2a-d_2** in the essential conversion process from **1a-d_2** into **2a-d_2**. The changes in the H/D components at the C^1, C^2, and C^3 positions of **2a-d_2** are considered to be caused by the side reactions described in Figure 3 (see below) and H/D scrambling process.[7]

On the basis of the results of the labeling studies, and literature by several research groups,[3,8] pathways involving an allene intermediate were proposed (Figure 2). One of the possible pathways is a reaction between Pd(0) and the carboxylic acid part of **1a** that leads to the formation of palladium carboxylate **A1** (Figure 2, path A). The generation of allene intermediate **B** occurs through either a sequential carboxy-palladation/β-aryloxy elimination or a concerted S_N2'-type substitution. A pathway starting from the propargylic C−O bond cleavage to form **A2** following cyclization is also plausible (Figure 2, path B).[9] Regardless, both of the intermediates result in the production of allenyl carboxylate **B**. The next step involves the insertion of the allene into a Pd(II)−H bond to form the π-allylpalladium species **C**, which finally undergoes reductive elimination of the allylic C−O bond of the vinyl dioxanone **2a**, with return of the Pd(0) to its original state.

A crossover experiment using different alkynoic acids, **1a** and **1o**, as starting substrates was then examined (eq 1). The reaction of 1 equiv (0.5 mmol) each of **1a** and **1o** afforded four kinds of products: the standard intramolecular cyclization products **2a** (0.18 mmol) and **2o** (0.16 mmol), and also **2n** (0.13 mmol) and **2b** (0.12 mmol), produced by annulation via the exchange of the propargyl fragments.



A migration of the propargyl fragment was also observed when methyl ester **3a** (1 mmol) was treated with benzoic acid (**4**, 0.5 mmol) under the standard conditions (eq 2). Along with the production of methyl salicylate (**5**, 0.55 mmol) formed via propargylic C−O bond cleavage of **3a**, it was determined that the cleaved propargyl unit was transferred into benzoic acid (**4**) to form 1,3-butadien-2-yl benzoate (**6**, 0.42 mmol).



Though it is not obvious which pathway proposed in Figure 2 is plausible, these results imply that the mechanism via the intermediate **A2** (path B) is more reasonable than that via **A1** (path A) for the present cyclization. For the intermediate **A2**, three coordination modes are possible; η^1-propargyl, η^3-allenyl/propargyl, and η^1-allenyl palladium species and a reaction at the electrophilic central carbon of **A2** can also occur (Figure 3).[10] In the pathway, after the initial nucleophilic addition of the carboxylic acid to the central carbon, formation of the π-allylpalladium species and β-hydride elimination leads to a palladium complex bearing 1,3-butadien-2-yl benzoate fragment **D**. Subsequently, hydropalladation affords the π-allylpalladium **C′**, which gives the 6-membered product **2a′-d_2** bearing deuterium at the methyl carbon (C^1), not at the terminal vinylic carbon (C^3). Although deuterium was predominantly located at C^3 of **2a-d_2** in the labeling experiments (Table 3), a small amount of the deuterium incorporation at C^1 and formation of diene **6**

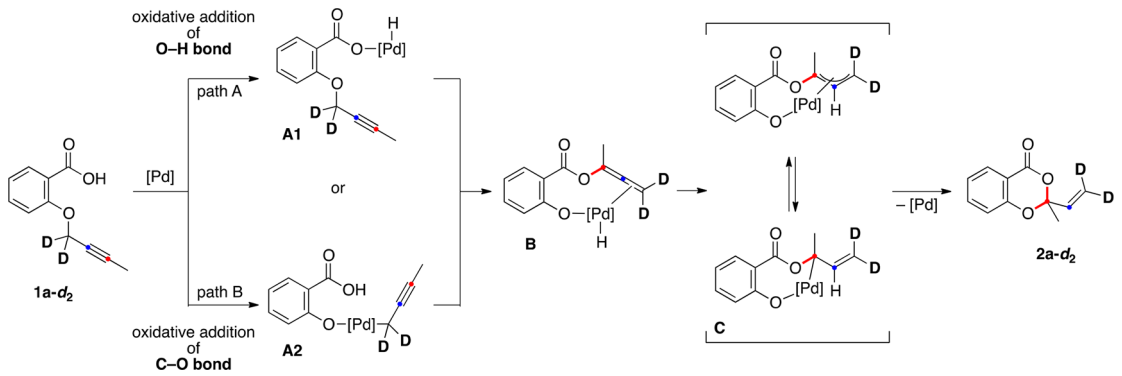


Figure 2. Possible pathways for the palladium-catalyzed conversion of **1a-d_2** into **2a-d_2**.

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Org. Lett. XXXX, XXX, XXX−XXX

(eq 2) indicate that the mechanism in Figure 3 also exists as a minor pathway.

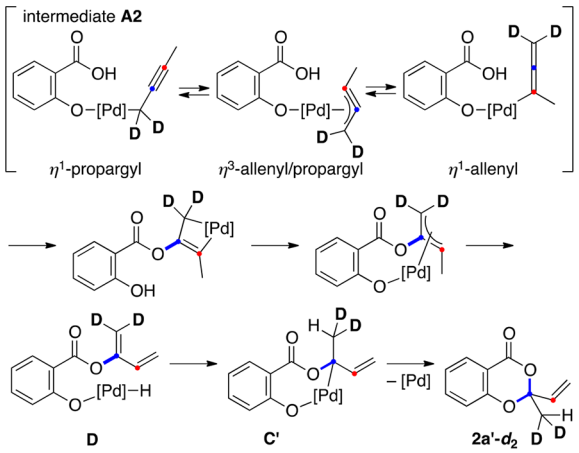

Figure 3. A possible minor pathway.

In summary, we have developed an unprecedented entry for intramolecular cyclization, which involves catalytic conversion of alkynoic acids to 6-membered heterocyclic compounds containing a highly oxidized quaternary allylic carbon in the presence of Pd(0)/^{t}BuXPhos. No stoichiometric additive, such as a base, was required, and therefore, various types of alkynoic acids were available for this transformation. The preliminary mechanistic studies implied that the allene species is a possible intermediate. Further studies of this unique method must involve the following: (i) a detailed mechanistic investigation, (ii) application to other types of substrates such as carboxamides, and (iii) extension to an enantioselective version. These experiments are now underway in this laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02572.

X-ray crystallographic data for **2m** (CIF)

Experimental procedures and characterization data for **1**, **2**, and **3**; X-ray crystallographic data for **2m** (PDF)

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Notes

The authors declare no competing financial interest.

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(5) The structure of **2a** was determined by ^{1}H and ^{13}C NMR, NOESY, ^{1}H-^{1}H COSY, HMQC, and HMBC analyses. The ^{1}H and ^{13}C NMR spectroscopic data of **2a** are also in good agreement with those reported in the following literature. Carrillo-Arcos, U. A.; Rojas-Ocampo, J.; Porcel, S. *Dalton Trans.* **2016**, *45*, 479.

(6) CCDC No. 1569284 (**2m**). The crystallographic data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

(7) Although the details of the H/D exchange are not clear, both intra- and intermolecular mechanisms including β-hydride elimination and reinsertion via [Pd]−H and [Pd]−D species are presumable.

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