0.169, respectively). CCDC-192482 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

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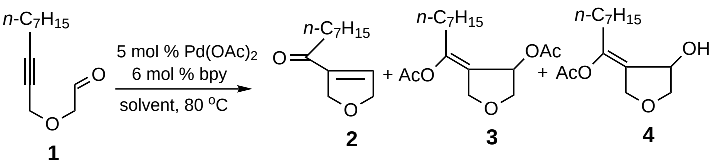
Pd$^{\mathrm{II}}$-Catalyzed Cyclization of Alkynes Containing Aldehyde, Ketone, or Nitrile Groups Initiated by the Acetoxypalladation of Alkynes[**]

Ligang Zhao and Xiyan Lu*

The insertion of carbon–carbon multiple bonds into carbon–transition-metal bonds as a facile method of carbon–carbon bond formation is a very important fundamental reaction in transition-metal organometallic chemistry.[1] However, in contrast to the numerous reports regarding the insertion of carbon–carbon multiple bonds into carbon–transition-metal bonds, direct insertion of carbon–heteroatom multiple bonds, such as carbonyl and nitrile groups, without using stoichiometric organometallic reagents, has received scant attention.[1] The disadvantages of such insertion processes are that the carbon–heteroatom π bond is stronger than the carbon–carbon π bond,[2] and that electrophilic metals tend to form σ complexes with the heteroatom of carbon–heteroatom multiple bonds, instead of π complexes,[3] which makes the insertion unfavorable. Such obstacles make this area of research particularly challenging. Recently, some examples of the insertion of carbonyl groups into late-transition-metal–carbon bonds, for example with Rh[4] and Ni,[5] have been reported, although most of these require the use of stoichiometric organometallic reagents or additives. In palladium chemistry, a limited number of examples catalyzed by Pd^0 have been reported by Vicente,[6] Yamamoto,[7a–d] Yang,[8a–c] and Larock.[8d,e] To the best of our knowledge, there are no examples of the direct insertion of a carbonyl or nitrile group into a carbon–palladium bond by reactions catalyzed by a palladium(II) species through the acetoxypalladation of alkynes.

The fact that a Pd$^{\mathrm{II}}$ species is formed after quenching an oxygen–palladium bond through protonolysis, even in Pd^0-catalyzed reactions, suggests that a redox system must be involved in the reported Pd^0-catalyzed carbonyl insertion reactions. It occurs to us that a Pd$^{\mathrm{II}}$-catalyzed reaction may be advantageous for such insertion reactions. Recently, we reported a Pd$^{\mathrm{II}}$-catalyzed cyclization reaction of enyne esters initiated by the acetoxypalladation of alkynes which utilized bipyridine as a ligand.[9] This novel catalytic system encouraged us to develop new reactions using carbon–heteroatom multiple bonds as insertion species, instead of carbon–carbon double bonds. Herein, we wish to exhibit another mechanism involving the cyclization of alkynes with carbonyl or nitrile groups through the acetoxypalladation of alkynes, followed by the insertion of carbon–heteroatom multiple bonds into the carbon–palladium bond and subsequent protonolysis.

Our investigation of the reaction conditions began by using dec-2-ynyloxyacetaldehyde (**1**, 0.5 mmol), $Pd(OAc)_2$ (5 mol%) as the catalyst, and 2,2′-bipyridine (bpy, 6 mol%) as the ligand in acetic acid (5 mL) at 80 °C (Scheme 1). The reaction afforded products **2**–**4** (**2**:**3**:**4** 20:40:40) in 78% total yield. Control experiments confirmed that **4** can partially transform into either **3** (by acetylation) or **2** (by transformation) in this system. Reactions with ketones gave the corresponding tertiary alcohols as a single product in good yield using acetic acid/dioxane as the solvent, while the reactions of aldehydes proceeded smoothly to afford the sole product **3** in moderate yield (50%) using acetic acid/1,4-



Scheme 1. Pd$^{\mathrm{II}}$-catalyzed cyclization of an aldehyde-containing alkyne.

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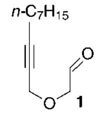
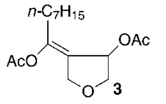
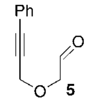
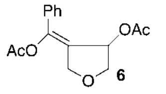
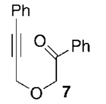
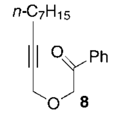
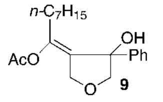
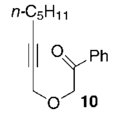
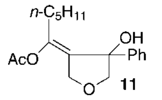
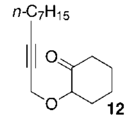
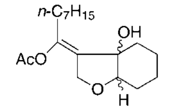
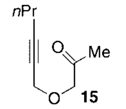
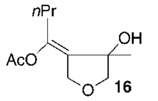
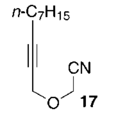
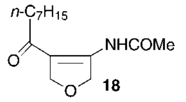
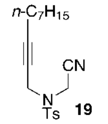
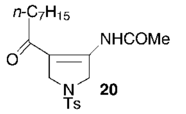
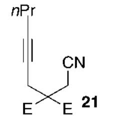
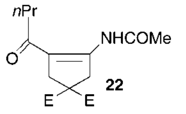
dioxane/acetic anhydride (1:1:1) as the solvent system. When the reaction of **1** was performed in the absence of $Pd(OAc)_2$ or bpy, no cyclization products were obtained. These experiments indicate that both the catalyst and ligand are necessary in these reactions. Employment of 1,10-phenanthroline as the ligand gave similar results to those obtained using bpy. Other ligands such as halide ions, PPh_3, or PBu_3 have no effect in this system. The *Z* configuration of the exocylic double bond, which was assigned by ^{1}H NMR spectroscopy and confirmed by the NOESY spectra of compound **4** and crystal data of compound **9,** indicated a *trans*-acetoxypalladation process in the reaction.[10,11]

The scope and generality of the present reaction is shown in Table 1. Aliphatic aldehydes, ketones, and nitriles are all effective in this catalytic system. The reaction of carbon, oxygen, and nitrogen-tethered alkynyl nitriles proceeded smoothly and five-membered carbocyclic and heterocyclic compounds were obtained in good yields (entries 8–10).[10] The structure of compound **22** was confirmed by X-ray analysis,[11] which indicates that the rearrangement occurred as described in Scheme 2. We believe this represents a rare example of the insertion of a nitrile group into a carbon–palladium bond, catalyzed by a Pd^{II} species without the use of a redox system.

Table 1. Pd^{II}-catalyzed cyclization of alkynes containing aldehyde, ketone, or nitrile groups.[a]

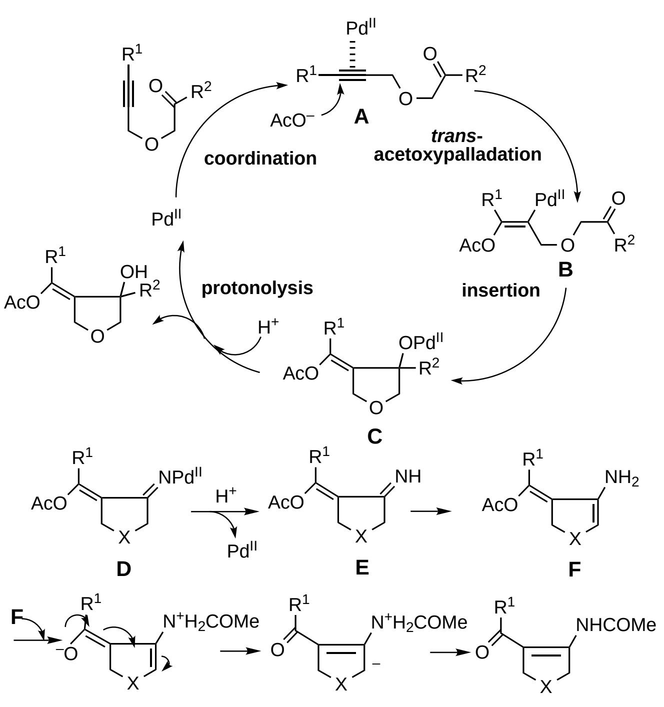
Entry	Substrate	Temperature [°C]	Duration [h]	Product	Yield [%][b]
1	 **1**	80	10	 **3**	50
2	 **5**	80	24	 **6**	22
3[c]	 **7**	100	24	–	–
4	 **8**	80	14	 **9**	71
5	 **10**	80	11	 **11**	80
6[d]	 **12**	80	8	 *cis* **13**: *trans* **14** = 2.2:1	65
7	 **15**	80	11	 **16**	66
8	 **17**	80	16	 **18**	72
9[e]	 **19**	80	16	 **20**	79
10[f]	 **21**	100	16	 **22**	95

[a] Reaction conditions: substrate (0.5 mmol), $Pd(OAc)_2$ (0.025 mmol), and bpy (0.03 mmol) in solvent (5 mL). Entries 1 and 2 using acetic acid/1,4-dioxane/acetic anhydride (1:1:1) as solvent, entries 3–9 using acetic acid/1,4-dioxane (1:4) as solvent, entry 10 using acetic acid as solvent. [b] Yield of isolated product. [c] Compound **7** was recovered in 80% yield; the reaction did not lead to the isolation of the expected product. [d] *cis*:*trans* = 2.2:1. The assignment of the relative configurations of **13** and **14** was based on their NMR spectra and NOE experiments (entry 6). [e] 0.25 mmol of substrate. [f] E = CO_2Me.

The mechanism shown in Scheme 2 is proposed for this reaction. First, the *trans*-acetoxypalladation of the carbon–carbon triple bond affords vinylpalladium species **B**, followed by insertion of the carbonyl or nitrile group into the carbon–palladium bond of **B** to give oxypalladium species **C** or iminopalladium species **D**, respectively; protonolysis of the intermediate **C** or **D** then gives the corresponding products and imines **E** in the presence of an acid medium, with regeneration of the original palladium species. The unstable intermediate imine **E** may isomerize to the amine products **F**, followed by an intermolecular aminolysis of the acetoxy group to give further products. It is noteworthy that bidentate nitrogen-containing ligands are important in this reaction, possibly for their ability in stabilizing vinylpalladium intermediates that allow the catalytic reaction to proceed.[9]

Vicente et al. provided straightforward evidence for the above possible mechanism through stoichiometric reactions.[6] Moreover, similar species to intermediate **C** have been isolated by treating a cyclopalladated phenyl 2-pyridyl ketone complex with alkynes, which was a direct observation of carbonyl group insertion into a carbon–palladium bond.[12] It should be noted that Hartwig recently reported the direct insertion of an aldehyde into the rhodium–carbon bond,[4i] which provides strong evidence for this mechanism.

In conclusion, we have developed a Pd^{II}-catalyzed cyclization reaction of alkynes with carbon–heteroatom multiple



Scheme 2. Proposed mechanism of the reaction.

bonds under mild conditions, where the insertion of carbon–heteroatom multiple bonds into the carbon–palladium bond is the key step. This is a reaction with high atom economy, which does not require the use of organometallic reagents, additives, or redox systems. This acetoxypalladation/carbon–heteroatom multiple-bond-insertion/protonolysis catalytic system may extend the scope of transition-metal-catalyzed reactions pertaining to the insertion of carbon–heteroatom multiple bonds into metal–carbon bonds, and provide a new methodology in organic synthesis.

Experimental Section

Typical procedure for the cyclization of substrate **8** (Table 1, entry 4): Under nitrogen atmosphere, substrate **8** (136 mg, 0.5 mmol) was added to a mixture of $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), bpy (4.5 mg, 0.030 mmol), acetic acid (1 mL), and 1,4-dioxane (4 mL). The solution was stirred at 80 °C for 14 h until the reaction was complete, which was confirmed by thin-layer chromatography. On cooling, the reaction mixture was neutralized with saturated $NaHCO_3$ and extracted with Et_2O. The combined Et_2O solutions were washed with saturated NaCl, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (ethyl acetate/petroleum ether 1:4) to give the product **9** as a white solid in 71 % yield, mp. 73–74 °C.

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[10] Spectroscopic and analytical data for all new compounds, NOESY spectra of **4**, ^{1}H NMR and ^{13}C NMR spectra of compounds **1**, **2**, **4–6**, **13–18**, **21**, and **23** are available in the Supporting Information.

[11] CCDC-188743 (**9**) and CCDC-188742 (**22**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit @ccdc.cam.ac.uk).

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