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# Cycloisomerization of 1,6-Enynes Using Acetate as a Nucleophile under Palladium(II) Catalysis

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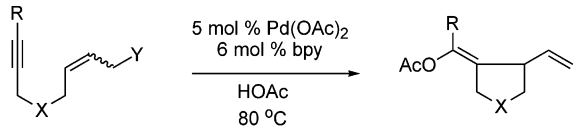


An efficient method for the synthesis of five-membered carbo- and heterocyclic compounds, including fused rings, was reported using acetate as a nucleophile in the cyclization of 1,6-enynes under palladium(II) catalysis. The reaction is initiated by *trans*-acetoxypalladation of the alkynes and quenched by either *trans*- or *cis*-deacetoxypalladation in the presence of 2,2′-bipyridine as the ligand. An example of the catalytic asymmetric cyclization is presented with moderate enantioselectivity using chiral bisoxazoline ligand.

Ring structures abound in naturally occurring or biologically active molecules, and how to construct those respective ring systems is of substantial interest to synthetic organic chemists. Although quite a variety of cyclization methods have been reported to date, the development of new catalytic systems is still valuable in order to enhance synthetic utility and efficiency.[1] Currently, transition metal-catalyzed carbocyclization of α,ω-enynes represents one of the most powerful means to construct cyclic compounds.[2] In terms of carbocyclization, the design of a catalytic protocol centers on the formation of a carbon−metal bond and its subsequent transformations.[2c] In general, the majority of the existing approaches for enyne cyclization involve the initial formation of a vinyl transition metal intermediate. Accordingly, the main cyclization procedures can be categorized according to the pathway by which the vinyl transition metal intermediate is formed:[3] (1) insertion of alkynes into the metal−H(R) species; (2) cyclometalation of enynes; and (3) electrophilic attack of transition metal complexes on the alkynes. On the other hand, it is well-known that nucleophiles may attack alkynes coordinated to high-valent transition metal complexes; however, this has seldom been employed to initiate the enyne cyclization in known procedures.[4] More significantly, reactions catalyzed by high-valent transition metal complexes can be run under air, and a further advantage of introducing nucleophiles is the generation of molecules with additional functional groups and increased versatility. We have developed the palladium(II)-catalyzed synthesis of γ-butyrolactones using acetate as a nucleophile previously.[5] Here, we expand the synthetic scope of the latter method to a number of carbo- and heterocyclic compounds starting from electron-rich alkynes, and in addition, we provide some mechanistic insight into these reactions.

To illustrate the feasibility of the acetoxypalladation-initiated enyne couplings of electron-rich alkynes, we first examined the intermolecular reaction of dimethyl 2-(2-butynyl)malonate with allyl acetate in the presence of $Pd(OAc)_2$ (5 mol %) and 2,2′-bipyridine (bpy, 6 mol %) in acetic acid at 60 °C (Scheme 1). The reaction proceeded smoothly, but a regiochemical issue arose with this nonsymmetrically substituted alkyne, for which a regioisomeric mixture of **1** and **2** was obtained in 63% combined yield.[6] The regioselectivity was not problematic in the coupling reactions of electron-deficient alkynes.[5c] Undoubtedly, it is required to direct the regioselectivity of the addition of acetate to the electron-rich alkynes in order to effect the intramolecular cyclization.

In fact, only the five-membered cyclic compound **4a** was obtained in 82% yield when we conducted the cyclization of (*Z*)-4-(dec-2′-yn-1′-oxy)-but-2-en-1-yl acetate (**3a**) under similar conditions as shown in Scheme 1 (Table 1). No cyclization occurred in the absence of the bpy ligand, and adding extra nucleophile (sodium acetate, 1 equiv) had no effect on either the cyclization rate or the yield. Other representative results are summarized in Table 1. For the oxygen-tethered substrates, the aryl alkyne was equally as effective as the alkyl alkyne. The enyne **5** with an (*E*)-olefin could also be cyclized smoothly, in sharp contrast to the strict geometric demand (only (*Z*)-olefin) for enyne esters.[4c] In addition, benzoate could replace acetate as the leaving group, and this feature should be useful in developing an asymmetric variant, presuming that the allylic leaving group carrying a chiral auxiliary group may induce diastereoselectivity. Introducing a nitrogen atom (sulfonamide) or all carbon in the tether was as effective as the oxygen tether. The stereochemistry of the exocyclic double bond was deduced by NOE

(1) For recent contributions, see: (a) Cadran, N.; Cariou, K.; Hervé, G.; Aubert, C.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. *J. Am. Chem. Soc.* **2004**, *126*, 3408. (b) Lee, S. I.; Park, J. H.; Chung, Y. K.; Lee, S.-G. *J. Am. Chem. Soc.* **2004**, *126*, 2714. (c) Mahandru, G. M.; Skauge, A. R. L.; Chowdhury, S. K.; Amarasinghe, K. K. D.; Heeg, M. J.; Montgomery, J. *J. Am. Chem. Soc.* **2003**, *125*, 13481.

(2) For reviews, see: (a) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813. (b) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1. (c) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635.

(3) Fernández-Rivas, C.; Méndez, M.; Echavarren, A. M. *J. Am. Chem. Soc.* **2000**, *122*, 1221 and references therein.

(4) For reviews, see: (a) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067. (b) Lu, X.; Zhu, G.; Wang, Z. *Synlett* **1998**, 115. (c) Lu, X.; Ma, S. New Age of Divalent Palladium Catalysts. In *Transition Metal Catalyzed Reaction*; Murahashi, S.-I., Davies, S. G., Eds.; Blackwell Science: Oxford, UK, 1999; Chapter 6, p 133.

(5) (a) Zhang, Q.; Lu, X. *J. Am. Chem. Soc.* **2000**, *122*, 7604. (b) Lu, X.; Zhang, Q. *Pure Appl. Chem.* **2001**, *73*, 247. (c) Zhang, Q.; Lu, X.; Han, X. *J. Org. Chem.* **2001**, *66*, 7676.

(6) Ratio of compounds **1**:**2** (or **2**:**1**) is calculated according to the signal intensity of the NMR spectra of the mixture, which is inseparable on the silica gel column chromatography, and we did not assign the spectral signal specifically to **1** and **2**.

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**SCHEME 1**

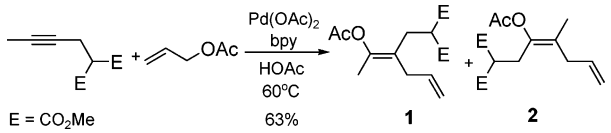
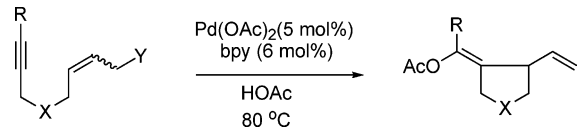



**TABLE 1. Palladium(II)-Catalyzed Cyclization of 1,6-Enynes**[a]




| | substrate X | substrate R | substrate Y | allylic double bond | time (h) | product (yield,[b] %) |
|---|---|---|---|---|---|---|
| **3a** | O | $C_7H_{15}$ | OAc | *Z* | 12 | **4a** (82) |
| **3b** | O | $CH_3$ | OAc | *Z* | 12 | **4b** (94) |
| **3c** | O | Ph | OAc | *Z* | 20 | **4c** (84) |
| **5** | O | $C_7H_{15}$ | OAc | *E* | 11 | **4a** (70) |
| **6** | O | $C_7H_{15}$ | OBz | *Z* | 24 | **4a** (80) |
| **7a** | NTs | $CH_3$ | OAc | *Z* | 4 | **8a** (97) |
| **7b** | NTs | $C_7H_{15}$ | OAc | *Z* | 40 | **8b** (92) |
| **9a** | $C(CO_2Me)_2$ | $CH_3$ | OAc | *Z* | 48 | **10a** (87) |
| **9b** | $C(CO_2Et)_2$ | $C_7H_{15}$ | OAc | *Z* | 48 | **10b** (85) |

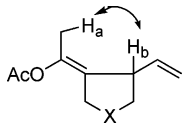
[a] Reaction conditions: substrate (0.5 mmol), $Pd(OAc)_2$ (5 mol %), bpy (6 mol %) in HOAc (2.0 mL) at 80 °C. [b] Isolated yield.

experiments on the cyclization product **4b** and **8a**.[7] It is noteworthy that all the cyclizations are regiospecific and highly stereoseletive, that is, only five-membered cycles were obtained and the acetoxypalladation of alkynes occurred in only the trans attacking mode. The limitation of the current method is that substrates with terminal alkynes cannot be used since no desired cyclization products were obtained.

$Pd(bpy)(OAc)_2$[8] might be the active catalytic species in the reaction, which was supported by the fact that preformed complex of $Pd(bpy)(OAc)_2$ gave the same result as the in situ-formed catalyst. The cylization was proposed to follow a sequence of *trans*-acetoxypalladation of the alkyne, olefinic migratory insertion into the newly formed vinyl-palladium intermediate **II**, and the final deacetoxypalldation as outlined in Scheme 2. Our previous study has shown that the nitrogen-containing ligand is a key factor in the palladium(II)-mediated reactions to promote the $\beta$-heteroatom elimination and inhibit the common $\beta$-H elimination allowing the generation of the catalytic Pd(II) species.[5c]

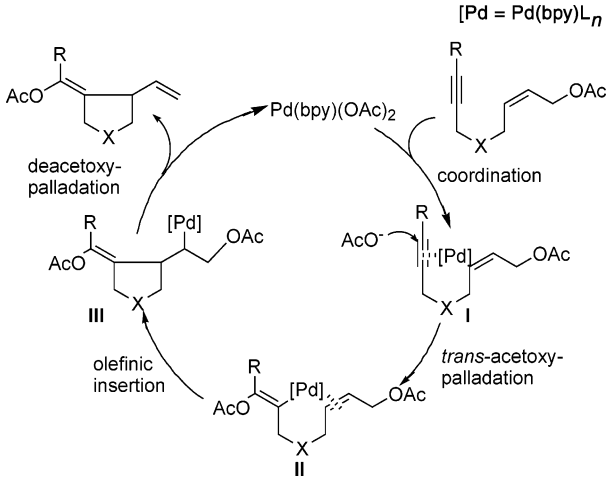
In our previous report in which halide was applied as the nucleophile in the cyclization of enyne esters, the stereochemistry of $\beta$-heteroatom (halide or acetoxy group) elimination was exclusively trans, which demonstrated that the palladium and the leaving group existed in an

(7) $H_a$ and $H_b$ has a NOE correlation in the $^1H$ NMR experiment as shown here.




(8) Stephenson, T. A.; Morehouse, S. M.; Powell, A. R.; Heffer, J. P.; Wilkinson, G. *J. Chem. Soc.* **1965**, 3632.

**SCHEME 2**



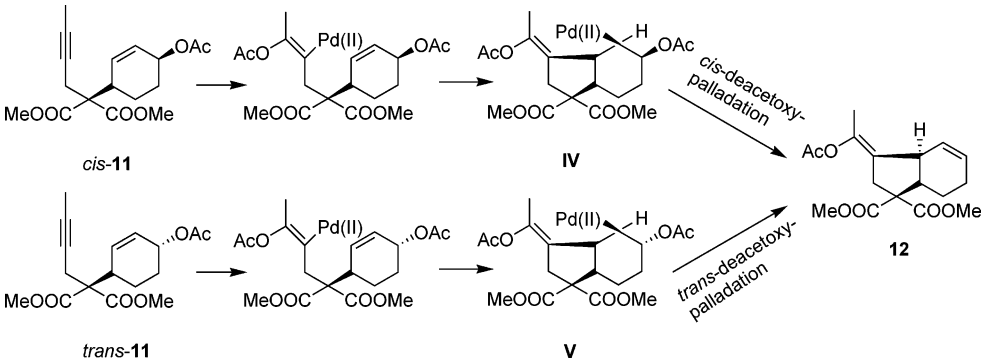

antiperiplanar arrangement.[9] The respective halide ions serve both as nucleophile and ligand, and a large excess of halide was required to ensure a stereoselective and fast reaction.[10] Given that the present acetoxypalladation-initiated cyclization is quite different in terms of the use of only catalytic amounts of nitrogen-containing ligands and the lack of addition of extra nucleophiles (acetate anions), we tried to understand whether the stereochemistry of $\beta$-heteroatom elimination in the current reaction system could also be different from that in the halopalladation-initiated reactions.

Two diastereomeric substrates, *cis*- and *trans*-**11**, were synthesized to probe the $\beta$-elimination stereochemistry. Presumably, we could establish the elimination stereochemistry by monitoring the two reactions (Scheme 3). The only possible cis fusion of five- and six-membered rings directs the olefin insertion into the vinyl palladium intermediate. As outlined in Scheme 3, the arrangement of the palladium atom and the acetoxy group will be syn (intermediate **IV**) starting from *cis*-**11** and anti (intermediate **V**) from *trans*-**11**. Consequently, product **12** could be afforded by *cis*-deacetoxypalladation from intermediate **IV** or *trans*-deacetoxypalladation from intermediate **V**. However, as a matter of fact, the same product **12** was obtained starting from either *trans*-**11** or *cis*-**11** in a similarly high yield (89% from *cis*-**11** and 88% from *trans*-**11**). The structure of **12** was further confirmed by X-ray crystallography. These results indicated that the $\beta$-acetoxy elimination is nonstereospecific, occurring readily when the palladium atom and the acetoxy group are in both syn and anti arrangements, which differs from the halopalladation-initiated reactions reported previously.[9] The nonstereoselectivity of the $\beta$-elimination in the current study might be attributed to the coordination of the acetate carbonyl oxygen with palladium in *cis*-**11**.[11]

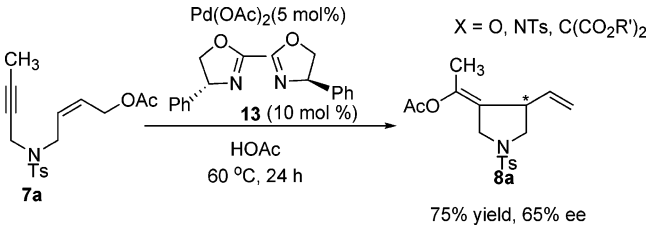
On the basis of the above results, a preliminary attempt was made to unravel the catalytic enantioselective cyclization. We could establish a moderate enantioselectivity (65% ee of **8a**) for the cyclization of **7a** using

(9) Zhu, G.; Lu, X. *Organometallics* **1995**, *14*, 4899.
(10) Ma, S.; Lu, X. *J. Org. Chem.* **1991**, *56*, 5120.
(11) Bäckvall, J. E. *Tetrahedron Lett.* **1977**, 467.

**SCHEME 3**




**SCHEME 4**




the bisoxazoline ligand **13** (Scheme 4).[12] Further optimization of the catalytic enantioselectivity is currently being scrutinized in our laboratory.

In summary, the acetoxypalladation-initiated cyclization of 1,6-enynes provides an efficient method to synthesize functionalized five-membered carbo- and heterocyclic compounds. The reaction proceeds in an acetoxypalladation−insertion−$\beta$-acetoxy elimination sequence to recycle catalytic palladium(II) species. Using the two designed diastereomers **11** as substrates for the cyclization, we could determine that the $\beta$-acetoxy elimination was nonstereoselective in this reaction. Using chiral bidentate nitrogen-containing ligands, this reaction also opens up a way to its catalytic asymmetric version, as illustrated by our preliminary result.[13]

## Experimental Section

**General Procedure for the Palladium(II)-Catalyzed Cyclization of 1,6-Enynes.** To a solution of $Pd(OAc)_2$ (6 mg, 0.027 mmol) and 2,2′-bipyridine (5 mg, 0.032 mmol) in HOAc (2 mL) at 80 °C was added **3a** (0.5 mmol) with stirring. The reaction was monitored by TLC. After the reaction was complete, ethyl ether (50 mL) was added. The mixture was washed with saturated $NaHCO_3$ solution (2 × 20 mL), and the aqueous phase was extracted again with ether (30 mL). Then, the organic solutions were washed with brine (20 mL), dried over anhydrous $Na_2SO_4$, and concentrated in vacuo. The residue was submitted to column chromatography on silica gel (petroleum ether/ethyl acetate 8:1), affording the product **4a** in 82% yield. Oil. IR (neat): $\nu$ 3082, 2957, 2929, 2857, 1758, 1638, 1370, 1203 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 5.86−5.77 (m, 1H), 5.17 (dd, $J$ = 17.0, 1.0 Hz, 1H), 5.10 (d, $J$ = 10.1 Hz, 1H), 4.29 (dd, $J$ = 13.1, 1.0 Hz, 1H), 4.22 (d, $J$ = 13.1 Hz, 1H), 3.98 (dd, $J$ = 8.6, 6.6 Hz, 1H), 3.72 (dd, $J$ = 8.6, 4.0 Hz, 1H), 3.44−3.37 (m, 1H), 2.24 (t, $J$ = 7.6 Hz, 2H), 2.12 (s, 3H), 1.40−1.26 (m, 10H), 0.88 (t, $J$ = 6.8 Hz, 3H). MS (*m/z*): 266 ($M^+$), 223(100), 151, 136, 123, 109, 95, 57, 43. Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found C, 71.71; H, 9.44. Characterization data for other products in Table 1 were shown in Supporting Information.

**Cyclization of *cis*-11 or *trans*-11.** Procedure similar to that above gave product **12** as a solid. IR (neat): $\nu$ 2954, 1751, 1736, 1436, 1231, 1064 $cm^{-1}$. $^1H$ NMR (300 MHz $CDCl_3$): $\delta$ 5.83−5.81 (m, 2H), 3.73 (d, $J$ = 5.8 Hz, 6H), 3.41−3.39 (m, 1H), 3.05 (d, $J$ = 6.8 Hz, 1H), 2.92 (dd, $J$ = 5.1, 12.5 Hz, 1H), 2.69 (d, $J$ = 7.0 Hz, 1H), 2.11 (s, 3H), 2.05−2.01 (m, 2H), 1.88 (s, 3H), 1.75−1.11 (m, 2H). MS (*m/z*): 291 ($M^+ - MeO^-$), 281, 249, 202 (100), 161, 143, 135, 117, 43. HRMS: calcd for $C_{17}H_{22}O_6$ 322.1416, found 322.1399.

**Palladium(II)-Catalyzed Enantioselective Cyclization of 7a.** In a manner similar to that described for the palladium-(II)-catalyzed cyclization of enynes, the reaction of **7a** (0.5 mmol) was carried out in the presence of 5 mol % $Pd(OAc)_2$ and 10 mol % bis-oxazoline chiral ligand **13** in HOAc (5 mL) at 60 °C to afford the product **8a**. The ee value of **8a** was determined by chiral HPLC using the chiralcel OD column eluting with hexane/2-propanol (100:1) ($\lambda$ = 214 nm).

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**Supporting Information Available:** Experimental procedure and characterization data, copies of $^1H$ NMR spectra of new compounds, and X-ray crystallography of **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Ee of **8a** was determined by chiral HPLC using the Chiralcel AD column eluting with 9:1 hexane/2-propanol ($\lambda$ = 214 nm). Absolute stereochemistry of the chiral center in product **8a** has not been determined.

(13) For recent contributions to enantioselective enyne cyclizations, see: (a) Hatano, M.; Mikami, K. *J. Am. Chem. Soc.* **2003**, *125*, 4704. (b) Chakrapani, H.; Liu, C.; Widenhoefer, R. A. *Org. Lett.* **2003**, *5*, 157. (c) Lei, A.; Waldkirch, J. P.; He, M.; Zhang, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 4526. (d) Cao, P.; Zhang, X. *Angew. Chem., Int. Ed.* **2000**, *39*, 4104.