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cis-Chloropalladation of 1,6-Enynes

Gangguo Zhu and Zhaoguo Zhang*

State Key Laboratory of Organometallic Chemistry,
Shanghai Institute of Organic Chemistry,
Shanghai 200032, China

zhaoguo@mail.sioc.ac.cn

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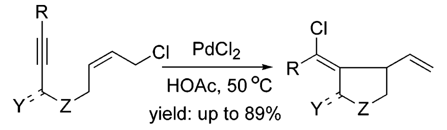

Y= O, H$_2$; Z=O, NTs

A PdCl$_2$-catalyzed *cis*-chloropalladation−cyclization reaction of various 1,6-enyne substrates was developed. This Pd-catalyzed enyne cyclization reaction represents a new route for the synthesis of stereodefined α-halomethylene-γ-butyrolactones, lactams, tetrahydrofurans, and cyclopentanes. A mechanism involving a neighboring coordination group is proposed to explain the experiment results.

Transition metal-catalyzed carbocyclization[1] of alkenes and alkynes is an efficient method for the construction of ring systems because it offers a simple entryway from linear substrates to cyclic compounds with control of stereochemistry.[2] Enyne cyclization reactions[3] have been widely applied in the synthesis of various types of cyclic compounds because these reactions usually proceed under mild reaction conditions with high efficiency and high selectivity.[4]

Lu et al.[5] developed a Pd(II)-catalyzed enyne cyclization reaction in the presence of excess halide, by which the *Z*-isomer, resulting from *trans*-halopalladation, was always the major product. By careful tuning of the concentration of halide ions, pure *trans*-halopalladation product (*Z*-isomer) might be obtained (Scheme 1). Studies in this group revealed that the excess halide in this reaction not only tempers the ratio of the *Z*- and *E*-isomer but also inhibits β-hydride elimination.[6]

Transition metal-catalyzed exclusive *cis*-halometalation of a C−C triple bond has been rarely reported. A palladium-mediated halopalladation of alkynes[7] and a rhodium-catalyzed cycloisomerization of 1,6-enynes[8] are the few examples believed involving the *cis*-halometalation of alkynes. It is also reported that the low concentration[9] of halide favors the *cis*-halopalladation pathway, therefore enhancing the ratio of the *E*-isomer. However, the halide is still in excess compared with the catalyst, otherwise, β-hydride elimination will occur. No research group has ever systemically studied how much halide is sufficient to inhibit a β-hydride elimination while achieving a β-heteroatom elimination. Here, we report a *cis*-chloropalladation reaction by which the *cis*-chloropalladation product is the only product. Through optimization of the reaction conditions by employing substrate **1a**, we chose 50 °C as the reaction temperature, PdCl$_2$ as the catalyst, and HOAc as the solvent. Under these reaction conditions, the reaction afforded the *E*-isomer with excellent selectivity ($E/Z > 99/1$); no *trans*-halopalladation product was detected (Table 1).

This is the first palladium-catalyzed enyne cyclization via *cis*-chloropalladation by which the *E*-**2** is the only product. This reaction also shows that a β-halide elimination is preferential even in the absence of halide.[10] For this reason, further investigation into the scope and synthetic utility of this reaction is appealing. The results

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SCHEME 1. Palladium(II)-Catalyzed Cyclization of 4′-Halo-2′-butenyl-2-alkynoates

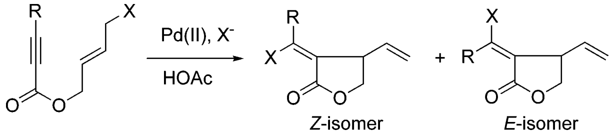
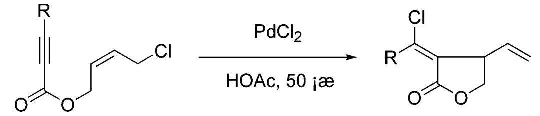


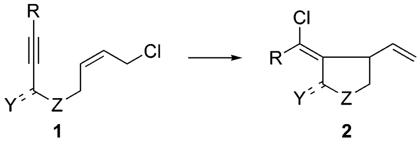
TABLE 1. *cis*-Chloropalladation of Electron-Deficient 1,6-Enynes[a]



entry		R	yield[b]/%
1	**1a**	Me	64
2	**1b**	CH_2OCH_3	70
3	**1c**	*n*−Bu	74
4	**1d**	Ph	69

[a] All the reactions were conducted with **1** (0.25 mmol), $PdCl_2$ (2 mg, 0.0125 mmol), and HOAc (5 mL) at 50 °C for 8 h. [b] Isolated yield; *Z*-isomer was not detected by GC.

TABLE 2. *cis*-Chloropalladation of 1,6-Enynes[a]



entry	1	Y	Z	R	yield[b]/%
1	**1e**	O	O	$C(CH_3)_2OCH_3$	68
2	**1f**	O	NTs	Me	89
3	**1g**	H_2	O	Me	52[c]
4	**1h**	H_2	O	Bu	55[c]
5	**1i**	H_2	O	Bu^t	59
6	**1j**	H_2	O	Ph	87
7	**1k**	H_2	O	1-cyclohexyl	70
8	**1*l***	H_2	O	4-OMe-C_6H_4	76
9	**1m**	H_2	NTs	Bu	82
10	**1n**	H_2	NTs	Ph	84
11	**1o**	$-(CH_2)_5-$	O	Ph	0[d]
12	**1p**	H_2	O	CH_2OCH_3	trace[c]
13	**1q**	H_2	O	CH_2OBn	26[c]
14	**1r**	H_2	$C(CO_2Et)_2$	Me	30[c,e]

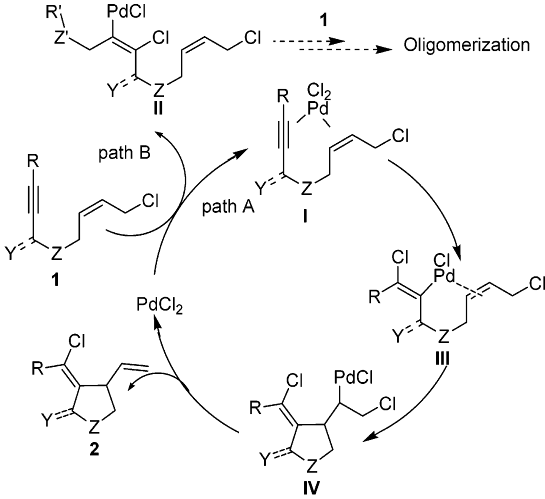
[a] All reactions were conducted with **1** (0.25 mmol), $PdCl_2$ (2 mg, 0.0125 mmol), and HOAc (5 mL) at 50 °C for 8 h. [b] Isolated yield. [c] The reaction was conducted at 35 °C. [d] Substrate **1o** was recovered. [e] Some oligomers were isolated.

obtained with other types of substrates were summarized in Table **2**.

Under the catalytic conditions, most 1,6-enynes substrates smoothly afford the products **2** in good to excellent yields (up to 89%). For the substrate **1o** with a bulkier substituent, the reaction does not occur under the reaction conditions and the substrate was recovered (entry 11, Table 2). When we use an electron-rich enyne substrate, the product **2** was the only isolated product, which was confirmed by comparing with an authentic sample.[8]

The addition of a palladium−halogen bond to a triple bond[7,9d,11] is affected by many factors. The direction is dramatically affected by the substituents attached to the triple bonds.[12] The addition of a Pd−Cl bond to an unsymmetrical disubstituted acetylene may result in two regioisomers if the electronic difference was small.[7] However, we found the product **2** was still the only isolated product even when the electron-rich enyne was employed as substrate.

SCHEME 2. The Plausible Reaction Mechanism



Coordination of neighboring groups[11b,13] to palladium can also play a significant role in directing the conversion of an η^2-alkyne-$PdCl_2$ intermediate into the chloropalladation adducts. In essence, they tend to influence the formation of vinylic adducts in such a way that the added palladium ends up closer to the coordinating group. Therefore, the possible that coordination of the linking atom (Z) to palladium may stabilize the intermediate thereby facilitates the insertion of the Pd−Cl bond to the carbon−carbon triple bond and enhances the reaction rate and selectivity of the intramolecular cylization. It is also possible that introducing a heteroatom at the other end of the triple bond may result in competative coordination, and this coordination will lead to regioisomers during the chloropalladation. When we employ electron-deficient alkyne as substrate, the reaction gives the product at reasonable yield; however, the electron-rich alkyne gives very poor yield (entry 12, Table 2 vs entry 2, Table 1). If we use another electron-rich alkyne without any heteroatom (possible coordination atom) at the other end of the alkyne, the reaction gives fair yield (entry 4, Table 2). Although it is not clear whether the heteroatom coordinates to palladium, we could not exclude this possibility especially when we use electron-rich alkyne as substrate. On the basis of the above results and the previous literature reports, we propose the possible reaction mechanism shown in Scheme 2. Coordination of

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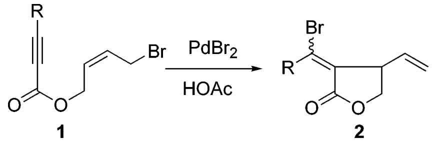
SCHEME 3. PdBr$_2$-Catalyzed Halopalladation of 1,6-Enynes[a]



1 **2**

	R	E/Z[b]	yield[c]
1s	Me	94/6	73
1t	Ph	91/9	82

[a] All the reactions were conducted with **1** (0.25 mmol), PdBr$_2$ (3 mg, 0.0125 mmol), and HOAc (5 mL) at 35 °C. [b]Determined by GC. [c]Combined yield of **2**.

enyne substrate to palladium, followed by *cis*-chloropalladation of alkyne, affords a vinylpalladium intermediate **III**. Then an intramolecular insertion of the allylic carbon−carbon double bond into the carbon−palladium bond in the vinylpalladium intermediate **III**, followed by the dehalopalladation of intermediate **IV**, yields the product **2** and regenerates the catalyst.

When the alkyne is electron-rich and structurally symmetric, the chloropalladation of alkyne may give another vinylpalladium intermediate **II** (path B), where the intramolecular cyclization is obviously not favored. This intermediate may undergo the insertion of another enyne substrate, resulting in dimerization or polymerization of substrate and the decrease of the yield (for substrate **1r**, some oligomers were isolated).

Because of the ease of chemical transformations of the bromo-substituted compounds, we also tried the PdBr$_2$-catalyzed halopalladation reaction of 1,6-enynes in the absence of halide. The results obtained are outlined in Scheme 3.

The reaction also proceeds smoothly under the reaction conditions; however, both *Z*- and *E*-isomers were obtained. Although the *E*-isomer is the main product (*E*/*Z* up to 94/6), the selectivity shows an obvious decrease compared with the results when PdCl$_2$ was employed as the catalyst. The dissimilarity between Pd−Cl and Pd−Br may be responsible for the difference: the increase of polarity of Pd−Br leads to partial cleavage of the Pd−Br bond, and the free bromide favors the formation of the *trans*-halopalladation product resulting in the decline of the selectivity.

In summary, we have developed a stereodefined cycloisomerization reaction of various 1,6-enynes catalyzed by PdCl$_2$ in the absence of halide with the following features: first, the *cis*-chloropalladation product was the only product under the reaction conditions; second, a neighboring coordination group plays a key role in determing the regioselectivity.

Experimental Section

General Method for the *cis*-Chloropalladation Reaction of 1,6-Enynes with PdCl$_2$. Under argon or air atmosphere, a 25-mL Schlenk tube was charged with enyne substrate **1** (0.25 mmol), PdCl$_2$ (0.0125 mmol), and HOAc (5 mL). The mixture was stirred at 50 °C and the reaction was monitored by TLC. After the reaction was completed, the reaction mixture was diluted by ether (100 mL) and washed with water, saturated NaHCO$_3$, and saturated brine, then dried over MgSO$_4$, followed by column chromatography on silica gel to give the product **2**.

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Supporting Information Available: Experimental details, NMR spectra, and analytical data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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