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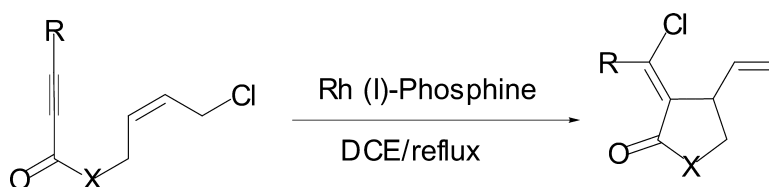
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Novel Rhodium-Catalyzed Cycloisomerization of 1,6-Enynes with an Intramolecular Halogen Shift

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Transition-metal-catalyzed cyclization of 1,6-enyne has been one of the most efficient methods for the synthesis of various types of cyclic compounds.[1] Several transition metals have been reported to catalyze the cyclization reaction under mild conditions.[2] Of all of the transition-metal-catalyzed cyclization reactions, two transformations are especially significant. One process involves oxidative cyclization of unsaturated substrates to form a metallocycle, followed by β-H elimination and reductive elimination to complete the catalytic cycle. The other process includes activation of an alkyne to form a corresponding metal-alkenyl species, followed by insertion of an alkene, and then β-X elimination (X = H, halogen, OAc). Besides these two fundamental processes, it is conceivable that a third process involving formation of a metal π-allyl complex could be possible for the enyne isomerization. However, this type of enyne isomerization is relatively unexplored (Scheme 1).[3] To the best of our knowledge, the cyclization of an enyne involving a π-allyl rhodium complex has not been reported. Herein, we report a new Rh-catalyzed 1,6-enyne cyclization process with a π-allyl rhodium as the key intermediate. It is noteworthy that a halogen shift happened in this process.

Recently, we have developed the first Rh-catalyzed Alder-ene reaction.[4] Under the reaction conditions, a variety of 1,6-enyne substrates with a functional group (OH, OAc, OBz) at the allylic position can be cycloisomerized in excellent yields, regio-, and enantioselectivities.[5] When these functional groups were replaced with a halogen group, we uncovered an unprecedented intramolecular halogen shift, and an α-methylene β-butyrolactone was isolated as the sole product. The configuration of the exo double bond is conformed by the 2D NOESY NMR. To find appropriate conditions to perform this transformation, a number of Rh(I)-species were tested. Our experiment results are summarized in Table 1. Under the optimal reaction condition, a variety of substrates **1** were tested for cycloisomerization with RhCl(PPh₃)₃ as the catalyst (Table 2).

Although we have discovered the new Rh-catalyzed cycloisomerization of 1,6-enynes, identification of the reaction mechanism can be a challenging task. In the following sections, several potential mechanisms (Scheme 1) are discussed.

On the basis of the results of the typical Rh-catalyzed enyne isomerization (path a), we propose that a mechanism through a cyclometalation intermediate[6] may be a possible explanation of the product formation and geometry of the resulting alkenyl halide. Oxidative cyclometalation of the coordinated enyne generates an intermediate (**I**), and β-halide elimination of **I** affords **II**. Reductive elimination of **II** leads to the product with the right alkene geometry.

Although the mechanism through oxidative cyclometalation seems to be reasonable for the cycloisomerization of the enyne, there is a key transformation in the catalytic cycle that has difficulty

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Scheme 1. Proposed Mechanisms of Rh-Catalyzed Cycloisomerization[a]
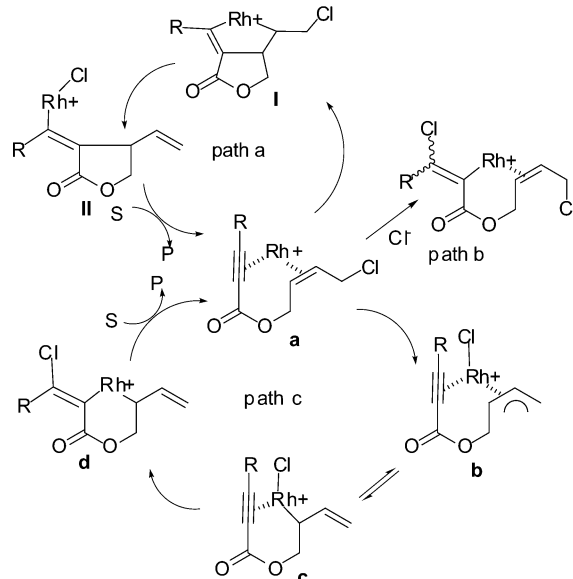
[a] Phosphine ligands are omitted. S = substrate. P = product.

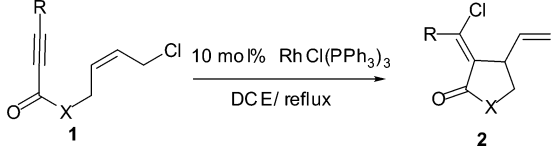**Table 1.** Rh-Catalyzed Cycloisomerization of **1a** and **1b**[a]

entry	sub	Rh(I)	time (h)	% yield[d]
1	**1a**	[Rh(COD)Cl]₂ [b]	2	87
2	**1b**	[Rh(COD)Cl]₂ [b]	6	78
3	**1a**	[Rh(COD)₂]SbF₆ [c]	24	trace
4	**1a**	Rh(CO)Cl(PPh₃)₂	24	0
5	**1a**	RhCl(PPh₃)₃	1	92
6	**1b**	RhCl(PPh₃)₃	3	87

[a] **1a**, R = CH₃; **1b**, R = Ph. [b] dppb as the ligand and AgSbF₆ as the additive. [c] dppb as the ligand. [d] Isolated yield.

occurring. Despite that oxidative cyclometalation of an enyne and β-halide elimination are well-documented transformations, reductive elimination of the rhodium(alkenyl)chloride (**II**) is rare, and the transformation requires harsh conditions.[7] In general, rhodium-(alkenyl)halides will undergo further reactions instead of reductive elimination.[8] Under these considerations, we believe that path a in Scheme 1 is an unlikely pathway for the transformation. A mechanism involving halorhodiation-insertion−β-halogen-elimination (path b) is also impossible under the reaction conditions (vide infro).[9]

Table 2. Cycloisomerization Catalyzed by RhCl(PPh₃)₃

entry	sub	R	X	time (h)	% yield[a]
1	**1a**	CH₃	O	1	92
2[b]	**1a**	CH₃	O	1	90
3	**1b**	Ph	O	2	87
4	**1c**	C₄H₉	O	2	90
5	**1d**	CH₂OMe	O	2	72[c]
6	**1e**	CH₃	NBn	3	89
7	**1f**	Ph	NBn	6	85
8	**1g**	CH₃	NTs	4	83
9[d]	**1a**	CH₃	O	24	85
10[d]	**1e**	CH₃	NBn	24	81

[a] Isolated yield. [b] The trans isomer was used. [c] With an unidentified byproduct. [d] 10 equiv of BnN(CH₃)₃Cl was added.

We speculate on another mechanism involving a π-allyl rhodium complex for the enyne substrates in this study. This is based on a precedent for the oxidative addition of an allyl chloride with RhCl-(PPh₃)₃ to generate a Rh(PPh₃)₂Cl₂(π-C₃H₅) species.[10] If oxidative addition of an allylic halide is a faster step than the oxidative cyclometalation in path a, an enyne coordinated Rh(I) species (**a**) reacts with the allylic chloride to form an π-allyl rhodium complex (**b**). After $\eta^3 - \eta^1$ isomerization of the π-allyl, intermediate (**b**) converts to species (**c**).[11] The rhodium(III) complex (**c**) undergoes nucleophilic attack of the alkyne by the coordinated chloride to another intermediate (**d**).[12] Reductive elimination of the Rh(III) intermediate (**d**)[13] gives the product and regenerates the catalytic Rh(I) species.

To further investigate the mechanistic pathway outlined in Scheme 1, we have designed a new substrate **1a′**. Under the same reaction conditions for the isomerization of **1a**, **1a′** is transformed into **2a** in good yields (eq 1).

(Eq 1)

[Rh(COD)Cl]₂/dppb/AgSbF₆,	50% yield
RhCl(PPh₃)₃	73% yield
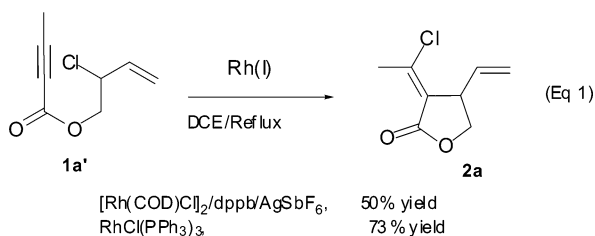
This experiment shows that formation of the common intermediate for both substrates **1a** and **1a′** is possible in the catalytic reaction. Because oxidative cyclometalation of **1a′** is unlikely, path c through intermediate (**c**) is the proposed pathway. Furthermore, we found that enyne **1a** with a cis alkene moiety and the corresponding enyne with a trans alkene moiety transformed to the same product smoothly with the Wilkinson catalyst (Table 2, entry 2). These results again indicate that formation of a π-allyl rhodium species is probably the key step in the catalytic reaction. With this Rh-

catalyzed cycloisomerization, we can prepare a variety of γ-lactones with a halo-alkenyl side chain. It is conceivable that transformation of the halo-alkenyl species to other groups can occur through metal-catalyzed carbon−carbon bond forming reactions.

In summary, we have found that Rh(I)-species can catalyze the enyne cycloisomerization reaction through a π-allyl rhodium intermediate. This Rh-catalyzed enyne cyclization reaction represents a new process for the synthesis of stereodefined α-halo-methylene γ-butyrolactones. Further studies on the reaction mechanism and asymmetric catalysis are ongoing in our laboratories and will be reported in due course.

Supporting Information Available: Experimental details and analytical data for **2** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA034096J