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# Rh(I)-Catalyzed Formal [6 + 2] Cycloaddition of 4-Allenals with Alkynes or Alkenes in a Tether

Yoshihiro Oonishi,* Akihito Hosotani, and Yoshihiro Sato*

Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan

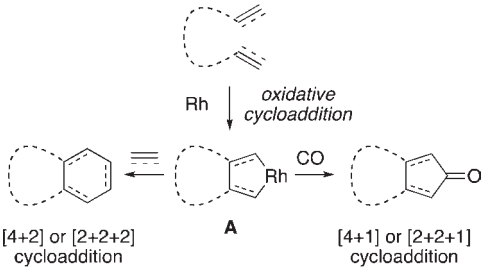
Supporting Information

**ABSTRACT:** Rh(I)-catalyzed formal [6 + 2] cycloaddition of allenal **6** having an alkyne or alkene in a tether proceeded smoothly, giving 5−8- and 6−8-fused bicyclic ketone derivatives **7** in good to excellent yields. It was also found that cyclization of enantiomerically enriched (*S*)-**6a** (94% ee) gave cyclic ketone derivative (*S*)-**7a** in high yield with reasonable chirality transfer (86% ee). This result indicates that this cyclization proceeds through stereoselective formation of rhodacycle **H′** followed by insertion of a multiple bond.

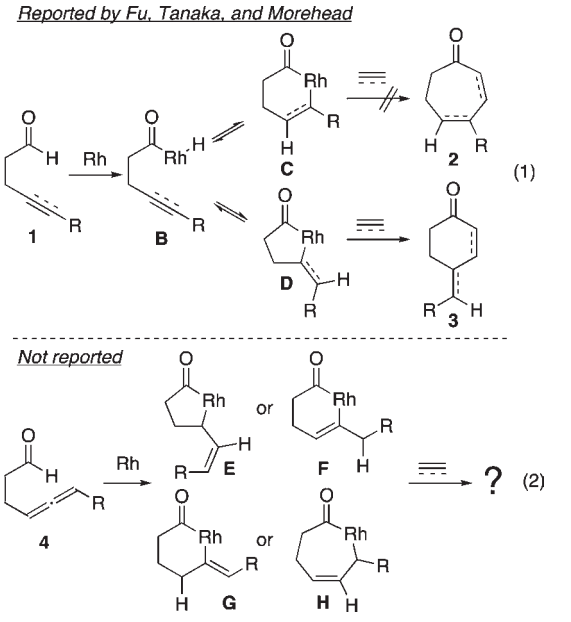
Transition-metal-catalyzed [*m* + *n*] and/or [*m* + *n* + *o*] cycloadditions represent an important class of reactions because of their ability to construct complex polycyclic skeletons in one reaction in a highly stereoselective[1] and step-economical fashion.[2] Various types of cycloaddition (e.g., [4 + 1], [4 + 2], [2 + 2 + 1], [2 + 2 + 2], etc.) using rhodium catalysts have been extensively studied, and highly enantioselective variants have also been developed.[3] The trigger of most of the reactions is stereoselective formation of rhodacycle intermediate **A** via *oxidative cycloaddition* of two C−C multiple bonds to a low-valent rhodium complex, and cyclized products are produced through insertion of a multiple bond (e.g., alkene, alkyne, carbon monoxide, etc.) into intermediate **A** followed by reductive elimination (Scheme 1).

Recently, another type of Rh(I)-catalyzed [*m* + *n*] cycloaddition has been reported by Fu,[4] Tanaka,[5] and Morehead,[6] in which oxo-rhodacycle intermediate **C** or **D** would be formed from 4-alkenals or 4-alkynals **1** through *hydroacylation* (eq 1 in Scheme 2). In these reactions, **C** and **D** are in equilibrium via intemediate **B**, and insertion of a C−C multiple bond into **D** would be more favorable than that into **C**, affording cyclic compound **3** selectively. In contrast to extensive studies of rhodium-catalyzed hydroacylation[7] of 4-alkenals[8] and 4-alkynals,[9] including the reactivity of oxo-rhodacycle intermediates such as **C** and **D**[4,6] and asymmetric variants,[5] there has been no report on intramolecular hydroacylation between allene and aldehyde or the reactivity of oxo-rhodacycle intermediates derived from allenals toward C−C multiple bonds (eq 2 in Scheme 2).[10] In the reaction of 4-allenal **4** with a rhodium complex, it is possible to produce four oxo-rhodacycle intermediates (**E**−**H**). If the stereoselective formation of **E**− **H** and the reaction of the intermediate with C−C multiple bonds were established, a novel [*m* + *n*] cycloaddition producing a polycyclic skeleton containing a medium-sized ring would be realized. We herein report a Rh(I)-catalyzed formal [6 + 2] cycloaddition [11] of 4-allenals with C−C multiple bonds.

**Scheme 1. Rh(I)-Catalyzed Cycloadditions**




**Scheme 2. Rh(I)-Catalyzed Cycloaddition through Hydroacylation**




In order to obtain preliminary information on oxo-rhodacycle intermediates derived from allene−aldehydes, hydroacylation of allenal **4a** using various rhodium complexes was examined (Scheme 3). It was found that the use of [Rh(IMes)(cod)]$ClO_4$,

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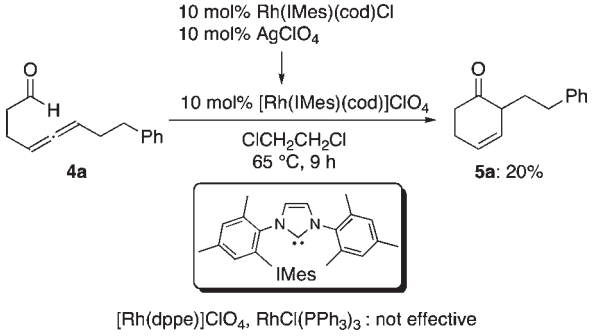
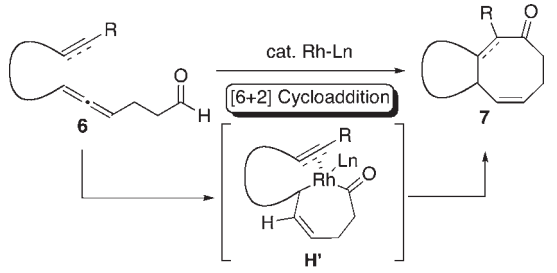
**Scheme 3. Rh(I)-Catalyzed Cyclization of Allenal 4a**




**Scheme 4. Rh(I)-Catalyzed Formal [6 + 2] Cycloaddition**



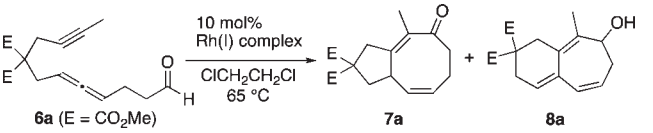

which was generated from Rh(IMes)(cod)Cl and $AgClO_4$, was effective for the hydroacylation process, affording cyclic compound **5a** in 20% yield. This result indicates that oxo-rhodacycle intermediate **H** (eq 2 in Scheme 2) was preferentially produced from **4a** to give **5a** through reductive elimination from intermediate **H**.

Encouraged by this result, we next turned our attention to the reaction of the oxo-rhodacycle intermediate derived from 4-allenals with a C−C multiple bond in a tether (Scheme 4). That is, if insertion of a C−C multiple bond in a tether into the oxo-rhodacycle intermediate **H′** formed from 4-allenal **6** occurs, bicyclic compound **7** containing an eight-membered ring should be produced via a formal [6 + 2] cycloaddition in a one-pot reaction.[1f,11−13]

Surprisingly, in contrast to the above-mentioned simple hydroacylation of **4a**, the cyclization of **6a** with 10 mol % [Rh(IMes)(cod)]$ClO_4$ proceeded smoothly to give a 76% yield of the desired bicyclic compound **7a**,[14] whose structure was unambiguously determined by X-ray analysis (Table 1, run 1).[15] Screening of Rh(I) complexes in the reaction of **6a** was again carried out, and the use of [Rh(I*i*Pr)(cod)]$ClO_4$ and [Rh(IPr)(cod)]$ClO_4$ instead of [Rh(IMes)(cod)]$ClO_4$ decreased the yield of bicyclic ketone **7a** to 23 and 14%, respectively (runs 2 and 3). On the other hand, the reaction using $RhCl(PPh_3)_3$ also gave the bicyclic ketone **7a** in 72% yield, although the reaction needed a longer time to reach completion than that using [Rh(IMes)(cod)]$ClO_4$. The cyclization of **6a** with 10 mol % [Rh(dppe)]$ClO_4$ did not produce **7a** at all but instead gave bicyclic alcohol **8a** in 27% yield.

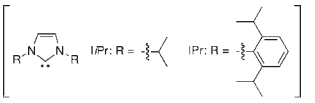
Next, the cyclization of various substrates using [Rh(IMes)(cod)]$ClO_4$ was examined (Table 2). The cyclizations of **6b** and **6c** having phenyl and TMS groups on the alkyne moiety gave **7b** and **7c** in 71 and 90% yield, respectively (runs 1 and 2). Substrate **6d** also afforded cyclized product **7d** in 68% yield (run 3). In the

**Table 1. Reaction Using Various Rh(I) Complexes**




| run | Rh(I) complex | time (h) | yield (%) 7a | yield (%) 8a |
|---|---|---|---|---|
| 1[a] | [Rh(IMes)(cod)]$ClO_4$ | 2 | 76 | – |
| 2[a] | [Rh(I*i*Pr)(cod)]$ClO_4$[c] | 16 | 23 | – |
| 3[a] | [Rh(IPr)(cod)]$ClO_4$[c] | 16 | 14 | – |
| 4 | $RhCl(PPh_3)_3$ | 5 | 72 | – |
| 5[b] | [Rh(dppe)]$ClO_4$ | 1 | – | 27 |

[a] Reactions were carried out using **6a** (0.25 mmol) in $ClCH_2CH_2Cl$ (2.5 mL) and 10 mol % [Rh(NHC)(cod)]$ClO_4$, which was generated in situ from [Rh(NHC)(cod)]Cl (10 mol %) and $AgClO_4$ (10 mol %). [b] The reaction was carried out using 10 mol % [Rh(dppe)]$ClO_4$ generated in situ from [Rh(dppe)(nbd)]$ClO_4$ (10 mol %) under a hydrogen atmosphere. [c] Structures of I*i*Pr and IPr:



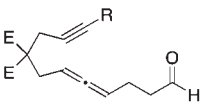
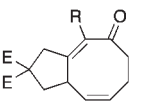
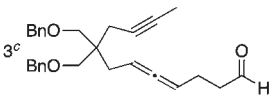
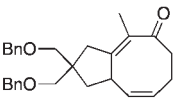
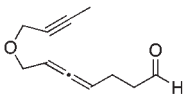
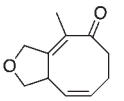
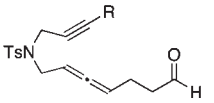
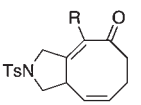
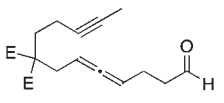
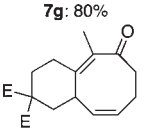
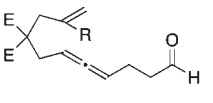
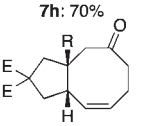

reactions of **6e**, **6f**, and **6g** containing a heteroatom in the chain, the corresponding heterocycles **7e**, **7f**, and **7g** were produced in good to excellent yields (runs 4−6). Elongation of the tether between the alkyne and allene moieties by one carbon was tolerated in the reaction, and 6−8-fused bicyclic ketone derivative **7h** was produced from **6h** in 70% yield (run 7). Notably, the cyclization of substrates **6i** and **6j** having an alkene instead of an alkyne in the tether also proceeded in a stereoselective manner to afford the bicyclic ketones **7i** and **7j** in 86 and 72% yield, respectively.[16]

A possible reaction mechanism for the formation of **7** from **6** is shown in Scheme 5. Initially, a C−H bond of the aldehyde moiety of **6** would be oxidatively added to the Rh(I) complex, after which insertion of the C═C bond of the allene moiety into the Rh−H bond would give oxo-rhodacycle **E′**, which might isomerize to oxo-rhodacycle **H′** via $\pi$-allylrhodium intermediate **K**. Insertion of an alkyne or alkene in the tether into the Rh−C bond in **H′** would occur, producing rhodacycle **L**, from which reductive elimination would lead to bicyclic ketone derivative **7** along with regeneration of the Rh(I) complex.[17]

On the other hand, the formation of bicyclic alcohol **8a** from **6a** using [Rh(dppe)]$ClO_4$ as a catalyst (Table 1, run 5) cannot be explained by the mechanism shown in Scheme 5, and a distinct mechanism is shown in Scheme 6. Here, rhodacycle **N** would be initially formed by oxidative cycloaddition of the alkyne part and the external C═C bond of the allene moiety of **6a** to the Rh(I) complex.[18] Insertion of the aldehyde moiety of **6a** into **N** would then give rhodacycle **P**. $\beta$-Hydride elimination from **P** followed by reductive elimination from the resultant intermediate **Q** would give bicyclic alcohol **8a**.

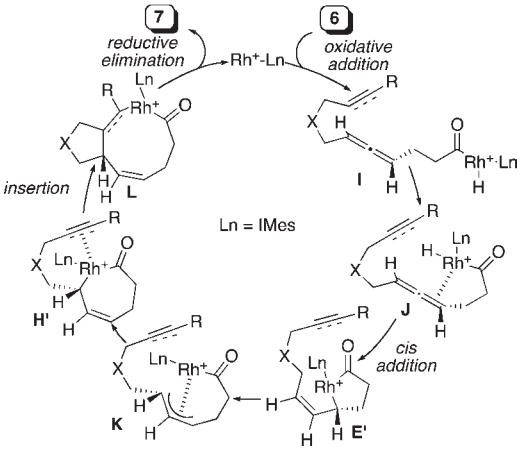
To obtain further insight into the reaction course for the formation of bicyclic ketone **7**, the reaction of deuterized substrate **6a-D** (D content, 97%) with 10 mol % [Rh(IMes)(cod)]$ClO_4$ was carried out at room temperature (Scheme 7). As a result, the cyclic compound **7a-D** having a deuterium on the alkene moiety

**Table 2. Rh(I)-Catalyzed Cyclization of Various Substrates**[a,b]

| run | substrate | time (h) | product |
|---|---|---|---|
| 1<br>2 |  <br>**6b** (R = Ph)<br>**6c** (R = TMS) | 2<br>1 |  <br>**7b**: 71%<br>**7c**: 90% |
| 3[c] |  <br>**6d** | 24 |  <br>**7d**: 68% |
| 4 |  <br>**6e** | 1 |  <br>**7e**: 49% |
| 5<br>6 |  <br>**6f** (R = Me)<br>**6g** (R = TMS) | 1<br>1 |  <br>**7f**: 50%<br>**7g**: 80% |
| 7 |  <br>**6h** | 8.5 |  <br>**7h**: 70% |
| 8[c]<br>9[d] |  <br>**6i** (R = H)<br>**6j** (R = Me) | 48<br>6 |  <br>**7i**: 86%<br>**7j**: 72% |

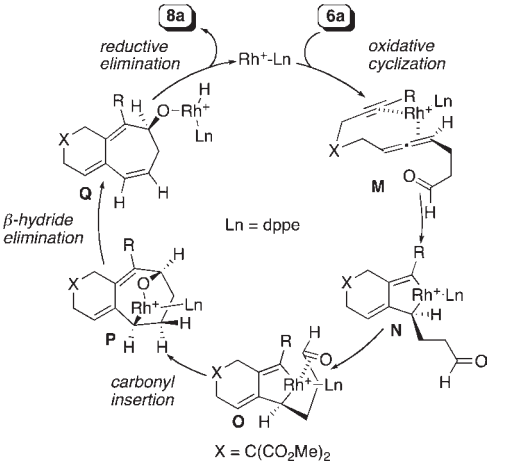
[a] All of the reactions were carried out at 65 °C (except for runs 3, 8, and 9) in a 0.1 M $ClCH_2CH_2Cl$ solution of the substrate using 10 mol % [Rh(IMes)(cod)]$ClO_4$, which was generated in situ from [Rh(IMes)(cod)]Cl (10 mol %) and $AgClO_4$ (10 mol %). [b] E = $CO_2Me$. [c] Run at room temperature. [d] Run at 50 °C.

**Scheme 5. Possible Reaction Mechanism for the Formation of 7**

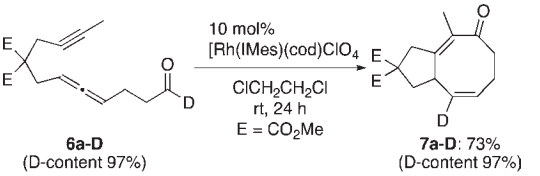



was obtained in high yield and with high D content (97%). This result is completely consistent with the mechanism in Scheme 5.

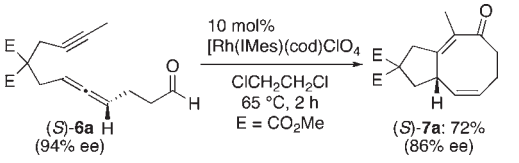
**Scheme 6. Possible Reaction Mechanism for the Formation of 8a**




**Scheme 7. Cyclization of 6a-D Having a Deuterium on the Aldehyde Moiety**




**Scheme 8. Rh(I)-Catalyzed Cyclization of (*S*)-6a**




We conceived that if chiral substrate **6a** were to be employed in this cyclization, cyclic compounds **7a** having the corresponding absolute configuration would be produced via a chirality transfer process. That is, in the reaction of (*S*)-**6a**, the cyclic product (*S*)-**7a** would be produced according to the mechanism in Scheme 5 as a result of enantioselective formation of **E′** followed by stereospecific $\pi$-allyl rearrangement to **H′**. To investigate this hypothesis, substrate (*S*)-**6a** was prepared in an enantiomerically enriched form (94% ee). When (*S*)-**6a** was subjected to the above optimal conditions (10 mol % [Rh(IMes)(cod)]$ClO_4$, $ClCH_2CH_2Cl$, 65 °C), the desired product **7a** was obtained in high yield in an optically active form with a reasonable chirality transfer (86% ee), and its absolute configuration was clearly assigned to be *S* (Scheme 8).[19] The results in Schemes 7 and 8 strongly suggest that the pathway for formation of **7** from **6** is Scheme 5, where the formal [6 + 2] cycloaddition of allenals proceeds via hydroacylation followed by insertion of a C−C multiple bond in the tether into the resultant oxo-rhodacycle.

In summary, we have developed a Rh(I)-catalyzed formal [6 + 2] cycloaddition of 4-allenals with alkynes or alkenes in a

tether, giving 5−8- and 6−8-fused bicyclic ketone derivatives in good to high yields. Furthermore, we have revealed that this cyclization proceeds through the stereoselective formation of oxo-rhodacycle **H′** followed by insertion of a multiple bond. This is the first example of an [*m* + *n*] cycloaddition triggered by the formation of an oxo-rhodacycle from an allene−aldehyde, and further studies along this line, including applications to the synthesis of natural products, are in progress.

## ■ ASSOCIATED CONTENT

**Supporting Information.** Experimental details, characterization data, NMR spectral charts, and X-ray crystal data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

**Corresponding Author**
oonishi@pharm.hokudai.ac.jp; biyo@pharm.hokudai.ac.jp

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(15) See the Supporting Information.

(16) The spectral data of **7i** and **7j** obtained by us were identical to those reported in ref 11.

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