

Cycloaddition

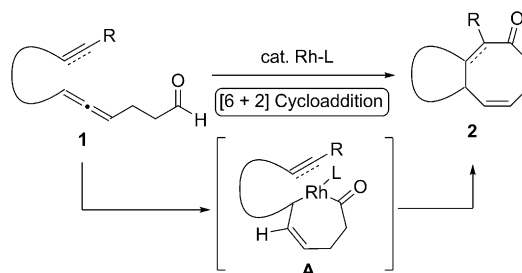
Construction of Monocyclic Eight-Membered Rings: Intermolecular Rhodium(I)-Catalyzed [6+2] Cycloaddition of 4-Allenals with Alkynes**

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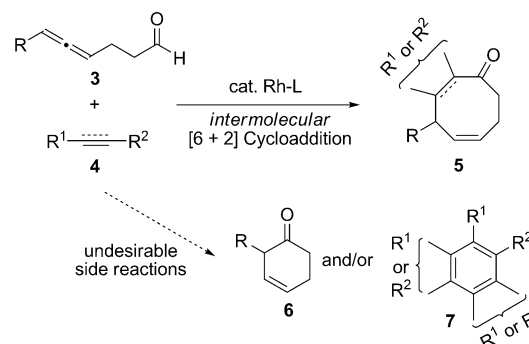
Eight-membered carbocyclic compounds are widely found in natural products that have unique medical and biological activities.^[1] Transition-metal-catalyzed $[m+n]$ and/or $[m+n+o]$ cycloadditions (e.g., $[4+4]$, $[6+2]$, and $[4+2+2]$) are the most promising strategies for the construction of polycyclic eight-membered-ring compounds.^[2,3] However, the construction of a simple but functionalized monocyclic eight-membered carbocyclic system is still difficult even when using transition-metal-catalyzed cycloadditions, and only a few examples have so far been reported.^[4] Herein we report Rh^I-catalyzed intermolecular $[6+2]$ cycloadditions of 4-allenals and alkynes to give functionalized monocyclic eight-membered-ring compounds.^[4f,5-8]

We recently reported a Rh^I-catalyzed intramolecular $[6+2]$ cycloaddition of 4-allenals with tethered alkynes and alkenes (Scheme 1).^[5c] In this reaction, the rhodacycle **A** is initially formed through hydroacylation^[9] of the 4-allenal moiety of **1** followed by insertion into a C–C multiple bond in the tether to afford bicyclic eight-membered-ring compound **2**.

We envisaged that if this intramolecular $[6+2]$ cycloaddition could be expanded to an intermolecular reaction between 4-allenal **3** and alkyne **4**, monocyclic octanone derivative **5** would be obtained (Scheme 2).^[10] However, the application of the intramolecular reaction to an intermolecular version is generally difficult because of unfavorable entropy and the high probability of side reactions (e.g., formation of **6** through hydroacylation of allenal **3**^[5c] and formation of **7** by trimerization of alkyne **4**).



Scheme 1. Rh^I-catalyzed intramolecular $[6+2]$ cycloaddition. L = ligand.



Scheme 2. Plan for intermolecular $[6+2]$ cycloaddition.

To examine the feasibility of the plan, the cyclization of 4-allenal **3a** with terminal alkyne **4a** in the presence of various Rh^I complexes was initially investigated (Table 1). The use of [Rh(IMes)(cod)]ClO₄, which is the most effective for the above-mentioned intramolecular cyclization (Scheme 1), afforded the desired eight-membered ring **5aa** in 61 % yield along with six-membered ring **8aa** in 19 % yield (entry 1).^[11] It was found that [Rh(SIMes)(cod)]ClO₄ was also effective in this intermolecular reaction, and the cyclic compound **5aa** was produced selectively in 68 % yield (entry 2). Lowering the reaction temperature from room temperature to 0 °C improved the yield of the eight-membered-ring compound **5aa** up to 83 % (entry 3). Furthermore, the catalyst loading could be reduced to 2 mol % under similar reaction conditions, thereby giving **5aa** in 84 % yield (entry 4). On the other hand, [RhCl(PPh₃)₃] and [Rh(dppe)]ClO₄ did not promote the desired reaction at all, and the starting material **3a** was recovered in 69 % and 78 % yield, respectively (entries 5 and 6).

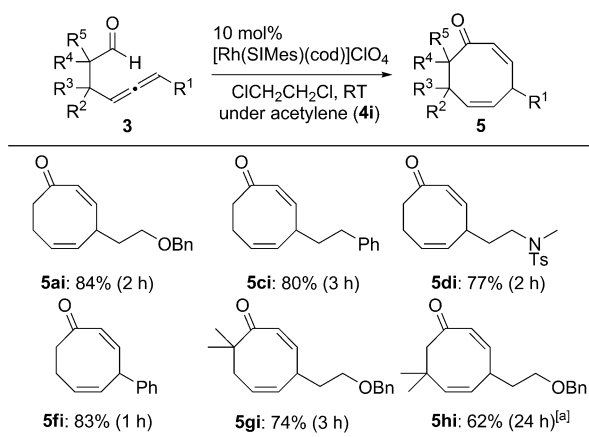
Encouraged by these results, the cyclization of 4-allenal **3a** with various terminal alkynes **4** was examined (Table 2). Cyclization of **3a** with terminal alkynes **4b**, **4c**, and **4d**, having

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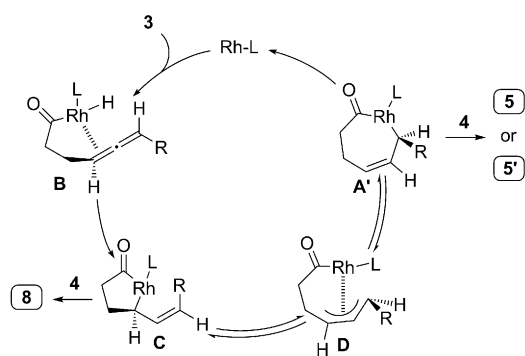
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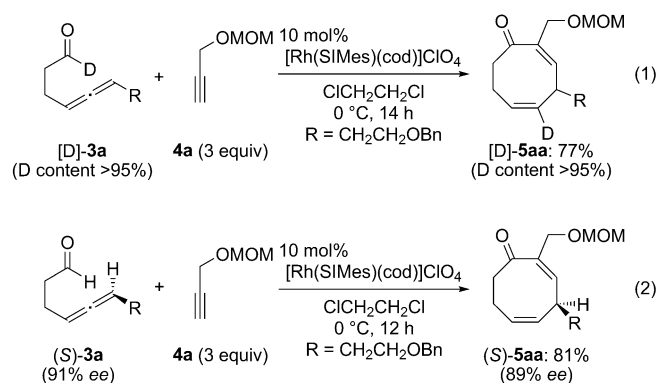
Scheme 3. Cyclization under acetylene. All reactions were carried out in $\text{ClCH}_2\text{CH}_2\text{Cl}$ (0.1 M solution with respect to **3**). [a] **8hi** was obtained in 12% yield.

A possible reaction mechanism for the formation of **5** and **8** is depicted in Scheme 4. Initially, a C–H bond of the aldehyde moiety oxidatively adds to the Rh^{I} complex, and this is followed by insertion of the C=C bond of the allene moiety to give the rhodacycle intermediate **C**. The rhodacycle intermediate **C** would be in equilibrium with the rhodacycle intermediate **A'** through the π -allylrhodium intermediate **D**. Eight-membered ring **5** would be produced through insertion of terminal alkyne **4** into seven-membered rhodacycle intermediate **A'**, while six-membered ring **8** would be formed through insertion of terminal alkyne **4** into five-membered rhodacycle intermediate **C**.^[10] The cyclization of **3** afforded eight-membered ring **5** in preference to six-membered ring **8**.^[13] These results suggest that the equilibrium between **A'** and **C** lies towards **A'** or that the rate of the reaction between **A'** and **4** is faster than that between **C** and **4**.



Scheme 4. Possible reaction mechanism. L = ligand.

Some additional experiments were performed to gain mechanistic insights into the present reaction (Scheme 5). First, the reaction of [D]-**3a**, which was deuterated at the formyl C–H bond, with **4a** gave the corresponding product [D]-**5aa**, having a deuterium on the alkene moiety, in a high yield with a high deuterium content [Eq. (1)], which is completely consistent with the mechanism shown in Scheme 4. Second, when the substrate (*S*)-**3a** (91% ee) was



Scheme 5. Mechanistic studies.

subjected to the above optimal conditions (10 mol% $[\text{Rh}(\text{SiMes})(\text{cod})]\text{ClO}_4$, $\text{ClCH}_2\text{CH}_2\text{Cl}$, 0°C), the product **7a** was obtained in a high yield with a high chirality transfer (89% ee). The absolute configuration of **7a** was assigned to be *S* [Eq. (2)],^[14] which indicates that this reaction proceeds through the enantioselective formation of **C** from the chiral starting material, followed by a stereospecific π -allyl rearrangement to **A'**.

In conclusion, we have succeeded in developing a Rh^{I} -catalyzed intermolecular [6+2] cycloaddition between 4-allenals and alkynes to afford various monocyclic eight-membered-ring compounds in high yields. Eight-membered rings are found in a wide variety of natural products, and the present reaction should provide a new way for constructing functionalized monocyclic eight-membered-ring compounds. Further studies to determine the scope, limitations, and the detailed mechanism of this reaction are in progress.

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- [14] The absolute configuration of (*S*)-**5aa** was assigned by a modified Mosher's method after chemical degradation (see the Supporting Information).