Cycloaddition

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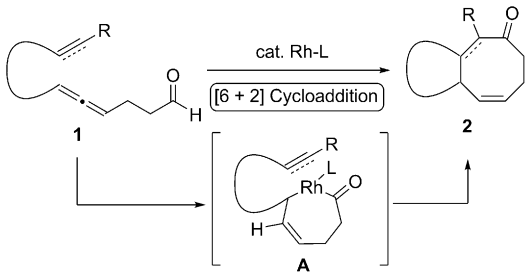
Construction of Monocyclic Eight-Membered Rings: Intermolecular Rhodium(I)-Catalyzed [6+2] Cycloaddition of 4-Allenals with Alkynes**

Yoshihiro Oonishi, Akihito Hosotani, and Yoshihiro Sato**

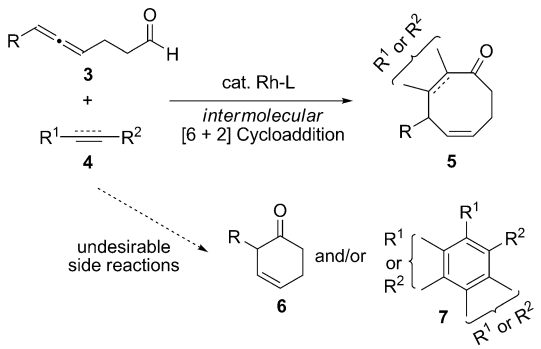
Eight-membered carbocyclic compounds are widely found in natural products that have unique medical and biological activities.[1] Transition-metal-catalyzed [*m*+*n*] and/or [*m*+*n*+*o*] cycloadditions (e.g., [4+4], [6+2], and [4+2+2]) are the most promising strategies for the construction of polycyclic 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 mutiple 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 $[Rh(IMes)(cod)]ClO_4$, 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 $[Rh(SIMes)(cod)]ClO_4$ 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, $[RhCl(PPh_3)_3]$ and $[Rh(dppe)]ClO_4$ 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

[*] Dr. Y. Oonishi, A. Hosotani, Prof. Dr. Y. Sato
Faculty of Pharmaceutical Sciences, Hokkaido University
Nishi 6, Kita 12, Kita-ku Sapporo 060-0812 (Japan)
.
E-mail: biyo@pharm.hokudai.ac.jp
Homepage: http://gouka.pharm.hokudai.ac.jp/FSC/jpn/page/top_page.htm

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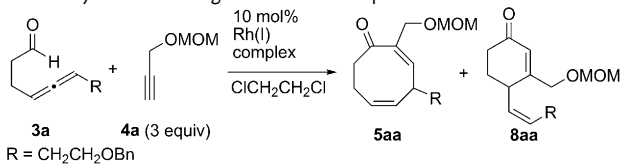
Table 1: Cyclization using various Rh^{I} complexes.

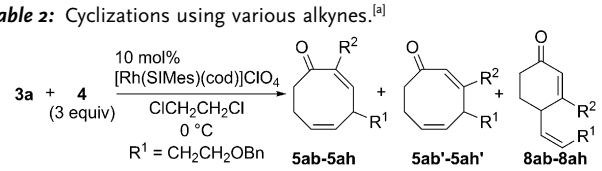


3a **4a** (3 equiv) **5aa** **8aa**

Entry	Rh^{I} complex	Conditions	Yields [%][a]	
			5aa	**8aa**
1	$[Rh(IMes)(cod)]ClO_4$[b]	RT, 9 h	61 (57)	19 (17)
2	$[Rh(SIMes)(cod)]ClO_4$[b]	RT, 2 h	68	–
3	$[Rh(SIMes)(cod)]ClO_4$[b]	0 °C, 12 h	83 (81)	–
4	$[Rh(SIMes)(cod)]ClO_4$[c]	0 °C, 24 h	84	–
5[d]	$[RhCl(PPh_3)_3]$	RT, 24 h	–	–
6[d]	$[Rh(dppe)]ClO_4$[e]	RT, 24 h	–	–

[a] Yields were determined by NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. Yields of isolated products are given in parenthesis. [b] Reactions were carried out using 10 mol% $[Rh(NHC)(cod)]ClO_4$ generated in situ from [Rh(NHC)(cod)]Cl (10 mol%) and $AgClO_4$ (10 mol%) in $ClCH_2CH_2Cl$ (0.1 M solution with respect to **3a**). [c] The reaction was carried out using 2 mol% $[Rh(NHC)(cod)]ClO_4$ generated in situ from [Rh(NHC)(cod)]Cl (2 mol%) and $AgClO_4$ (2 mol%) in $ClCH_2CH_2Cl$ (1.0 M solution with respect to **3a**). [d] The starting material **3a** was recovered in yields of 69% (entry 4) and 78% (entry 5). [e] The reaction was carried out using 10 mol% $[Rh(dppe)]ClO_4$ generated in situ from $[Rh(dppe)(nbd)]ClO_4$ (10 mol%) under an atmosphere of hydrogen in $ClCH_2CH_2Cl$ (0.1 M solution with respect to **3a**). Bn = benzyl, MOM = methoxymethyl, IMes = 1,3-dimesitylimidazol-2-ylidene, cod = cycloocta-1,5-diene, dppe = ethane-1,2-diylbis(diphenylphosphane).

Table 2: Cyclizations using various alkynes.[a]



5ab-5ah **5ab'-5ah'** **8ab-8ah**

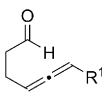
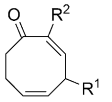
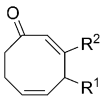
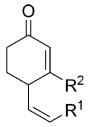
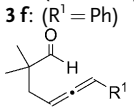
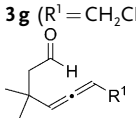
Entry	Alkyne **4**	*t* [h]	Yield [%]		
			5	**5′**	**8**
	BnO(CH2)n — **4b** (*n* = 1), **4c** (*n* = 2)				
1		17	82	–	–
2		39	74	–	–
3[b]	*p*-$BrC_6H_4CO_2$ — **4d**	24	75	–	–
4[b]	TsN — **4e**	15	61	–	–
5[b]	HO — **4f**	15	64	10	–
6[c]	*n*Bu — **4g**	46	68	5	11
7[b]	MeO_2C — **4h**	4	56	22	–

[a] All reactions were carried out in $ClCH_2CH_2Cl$ (0.1 M solution with respect to **3a**). [b] Carried out at RT. [c] Carried out in 0.5 M solution with respect to **3a**. Ts = toluene-4-sulfonyl.

a benzyloxy or benzoate moiety, proceeded in a steroselective manner to give cyclic compounds **5ab**–**5ad** in high yields (entries 1–3). The cyclization of **3a** with **4e**, having a tethered sulfonamide moiety, afforded **5ae** in 61% yield as the sole product (entry 4). On the other hand, the use of propargyl alcohol (**4f**) afforded **5af** along with its regioisomer **5af′** in yields of 64% and 10%, respectively (entry 5). When 1-hexyne (**4g**) was used in this cyclization, the eight-membered rings **5ag** and **5ag′** were obtained in yields of 68% and 5%, respectively, along with the six-membered ring **8ag** in 11% yield (entry 6). In the case of **4h**, having an electron-withdrawing group, **5ah** and **5ah′** were obtained in yields of 56% and 22%, respectively (entry 7).

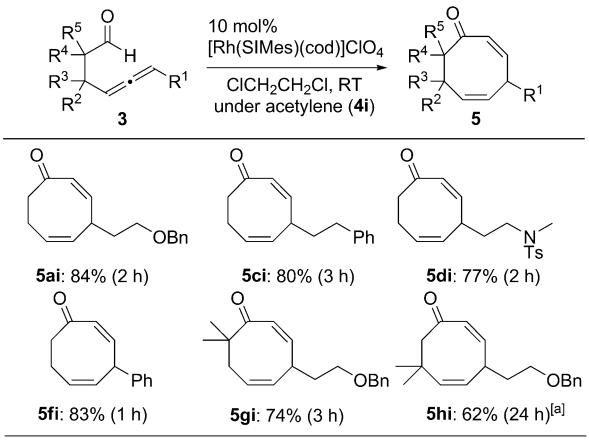
Next, we investigated the cyclization of various 4-allenals **3** with terminal alkyne **4a** (Table 3). Cyclizations of **3b**–**3d** with **4a** proceeded in a stereoselective manner to afforded eight-membered rings **5ba**–**5da** in good to high yields (entries 1–3). 4-Allenal **3e**, having a TMS moiety on the allene unit, gave the desired cyclic compound **5ea** in 82% yield as the sole product (entry 4). On the other hand, when **3f**, having a phenyl group on the allene part, was employed in this cyclization, **5fa** and its regioisomer **5fa′** were obtained in yields of 51% and 23%, respectively (entry 5). The reaction of **3g** or **3h**, having groups between the aldehyde and allene, gave **5ga** or **5ha** in yields of 37% or 44%, respectively (entries 6 and 7).[12]

Table 3: Cyclizations using various 4-allenals.[a]

Entry	Allenal **3**	*t* [h]	Yield [%]		
					
1	**3b**: (R^1 = CH_2OBn)	21	**5ba**: 69	**5ba′**: –	**8ba**: -
2	**3c**: (R^1 = CH_2CH_2Ph)	18	**5ca**: 81	**5ca′**: –	**8ca**: –
3	**3d**: (R^1 = CH_2CH_2NMeTs)	14	**5da**: 72	**5da′**: –	**8da**: –
4[b]	**3e**: (R^1 = TMS)	1	**5ea**: 82	**5ea′**: –	**8ea**: –
5[b]	**3f**: (R^1 = Ph)	1	**5fa**: 51	**5fa′**: 23	**8fa**: –
6[c]	 **3g** (R^1 = CH_2CH_2OBn)	15	**5ga**: 37	**5ga′**: –	**8ga**: 28
7[b]	 **3h** (R^1 = CH_2CH_2OBn)	21	**5ha**: 44	**5ha′**: –	**8ha**: 17

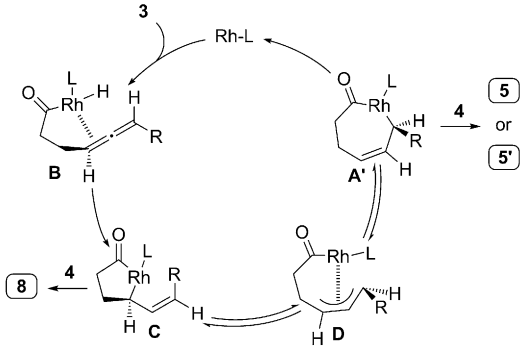
[a] All reactions were carried out in the presence of [Rh(SIMes)(cod)]ClO_4 (10 mol%) in $ClCH_2CH_2Cl$ (0.1 M solution with respect to **3**) at 0 °C. R^2 = CH_2OMOM. [b] Carried out at RT. [c] Hydroacylation product **6g** was obtained in 8% yield. TMS = trimethylsilyl.

It is noteworthy that gaseous acetylene can be utilized as an alkyne in this cyclization. Thus, treatment of **3a** with 10 mol% [Rh(SIMes)(cod)]ClO_4 in an acetylene atmosphere afforded the corresponding compound **5ai** in 84% yield as the sole product (Scheme 3). The reactions of **3c**, **3d**, and **3f** with gaseous acetylene also proceeded smoothly, giving **5ci**, **5di**, and **5fi** in high yields. The reactions of **3g** and **3h** also gave the eight-membered-ring compounds **5gi** and **5hi** in yields of 74% and 62%, respectively.



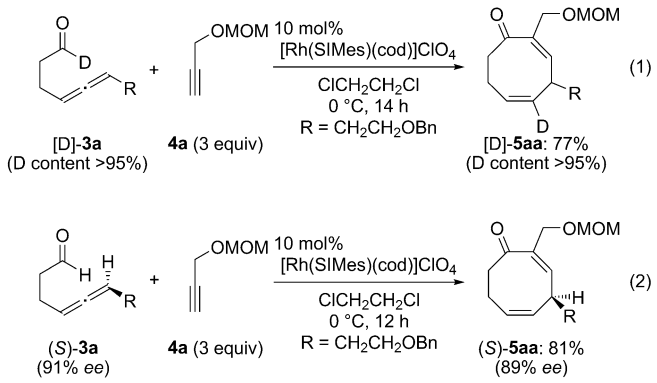
Scheme 3. Cyclization under acetylene. All reactions were carried out in $ClCH_2CH_2Cl$ (0.1 M solution with respect to **3**). [a] **8hi** was obtained in 12% yield.

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 teminal 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% [Rh(SIMes)(cod)]ClO_4, $ClCH_2CH_2Cl$, 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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[11] The structures of **5aa** and **8aa** were determined by 2D NMR spectroscopy (see the Supporting Information).

[12] The six-membered ring **6g** was produced through hydroacylation of **3g**, and see also Ref. [5c].

[13] The same tendency has been observed for Rh^I-catalyzed [4+2+2] cycloaddition reported by Wender and Christy, see Ref. [7e].

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

