Cycloaddition

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

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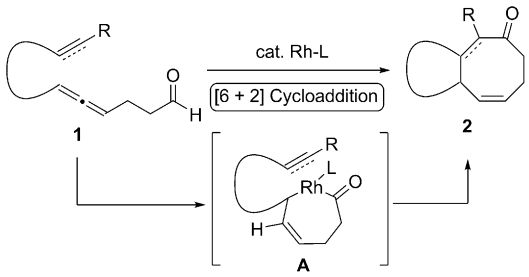
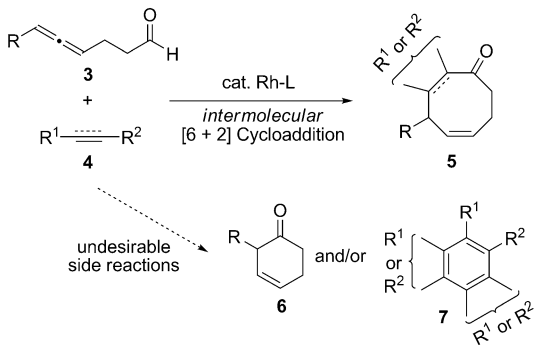
Eight-membered carbocyclic compounds are widely found in natural products that have unique medical and biological activities.[1] Transition-metal-catalyzed [*m*+*n*] and/or [*m*+*n*+*o*] cycloadditions (e.g., [4+4], [6+2], and [4+2+2]) are the most promising strategies for the construction of polycyclic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

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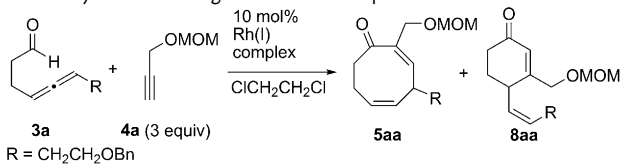
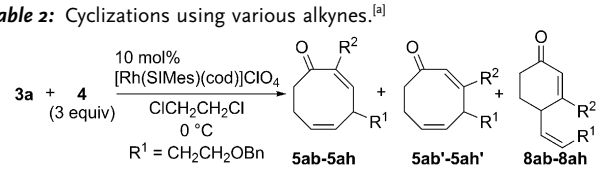
Table 1: Cyclization using various Rh^{I} complexes.



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]



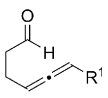
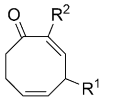
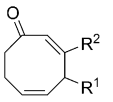
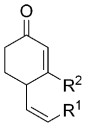
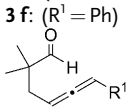
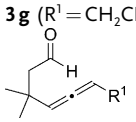
Entry	Alkyne **4**	*t* [h]	Yield [%]		
			5	**5′**	**8**
	BnO(CH2)n (**4b** (*n* = 1), **4c** (*n* = 2))				
1		17	82	–	–
2		39	74	–	–
3[b]	*p*-$BrC_6H_4CO_2$ (**4d**)	24	75	–	–
4[b]	TsN (**4e**)	15	61	–	–
5[b]	HO (**4f**)	15	64	10	–
6[c]	*n*Bu (**4g**)	46	68	5	11
7[b]	MeO_2C (**4h**)	4	56	22	–

[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).

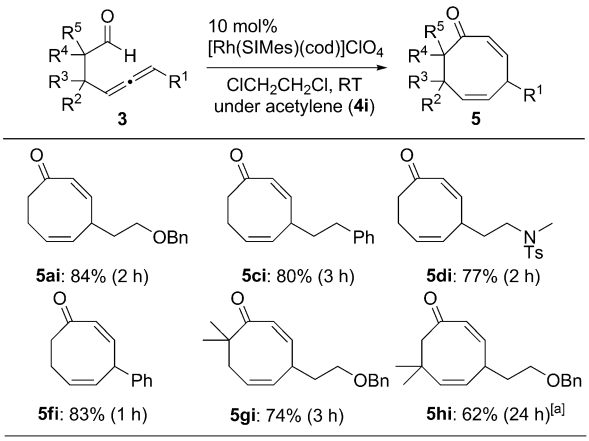
Next, we investigated the cyclization of various 4-allenals **3** with terminal alkyne **4a** (Table 3). Cyclizations of **3b**–**3d** with **4a** proceeded in a stereoselective manner to afforded eight-membered rings **5ba**–**5da** in good to high yields (entries 1–3). 4-Allenal **3e**, having a TMS 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

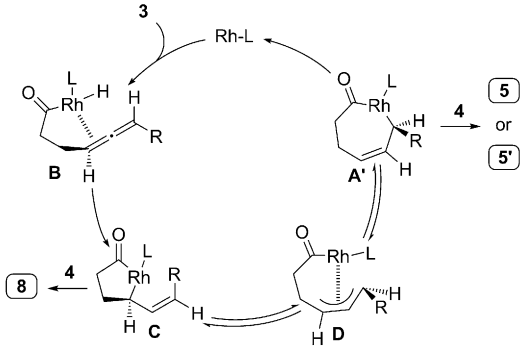
[a] All reactions were carried out in the presence of [Rh(SIMes)(cod)]ClO_4 (10 mol%) in $ClCH_2CH_2Cl$ (0.1 M solution with respect to **3**) at 0 °C. R^2 = CH_2OMOM. [b] Carried out at RT. [c] Hydroacylation product **6g** was obtained in 8% yield. TMS = trimethylsilyl.

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.



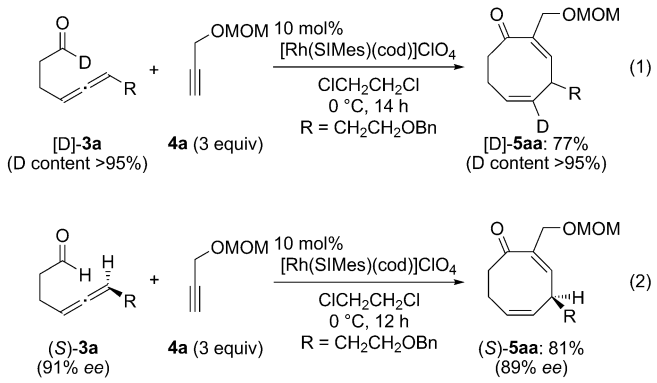
Scheme 3. Cyclization under acetylene. All reactions were carried out in $ClCH_2CH_2Cl$ (0.1 M solution with respect to **3**). [a] **8hi** was obtained in 12% yield.

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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[1] T. Oishi, Y. Ohtsuka in *Studies in Natural Products Synthesis*, *Vol. 3* (Ed.: Atta-ur-Rahman, Elsevier, Amsterdam, **1989**, p. 73.
[2] For reviews, see a) M. Lautens, W. Klute, W. Tam, *Chem. Rev.* **1996**, *96*, 49; b) L. Yet, *Chem. Rev.* **2000**, *100*, 2963; c) M. Murakami, *Angew. Chem.* **2003**, *115*, 742; *Angew. Chem. Int. Ed.* **2003**, *42*, 718; d) I. Nakamura, Y. Yamamoto, *Chem. Rev.* **2004**, *104*, 2127; e) H. Butenschön, *Angew. Chem.* **2008**, *120*, 5367; *Angew. Chem. Int. Ed.* **2008**, *47*, 5287; f) Z.-X. Yu, Y. Wang, Y. Wang, *Chem. Asian J.* **2010**, *5*, 1072; g) P. A. Inglesby, P. A. Evans, *Chem. Soc. Rev.* **2010**, *39*, 2791.
[3] For selected examples of synthesis of natural product containing an eight-membered ring by transition-metal-catalyzed cycloaddition, see a) P. A. Wender, N. C. Ihle, C. R. D. Correia, *J. Am. Chem. Soc.* **1988**, *110*, 5904; b) P. A. Wender, M. P. Croatt, B. Witulski, *Tetrahedron* **2006**, *62*, 7505; c) X. Fan, L.-G. Zhuo, Y. Q. Tu, Z.-X. Yu, *Tetrahedron* **2009**, *65*, 4709; d) Y. Liang, X. Jiang, Z.-X. Yu, *Chem. Commun.* **2011**, *47*, 6659; e) Y. Liang, X. Jiang, X.-F. Fu, S. Ye, T. Wang, J. Yuan, Y. Wang, Z.-X. Yu, *Chem. Asian J.* **2012**, *7*, 593.
[4] For Ni^0-catalyzed [4+4] cycloadditions, see a) A. Tenaglia, P. Brun, B. Waegell, *J. Organomet. Chem.* **1985**, *285*, 343; b) P.

Brun, A. Tenaglia, B. Waegell, *Tetrahedron Lett.* **1983**, *24*, 385; for Pd^0-catalyzed [4+4] cycloadditions, see c) M. Murakami, K. Itami, Y. Ito, *Synlett* **1999**, 951; d) P. H. Lee, K. Lee, Y. Kang, *J. Am. Chem. Soc.* **2006**, *128*, 1139; for Co^0-catalyzed [4+2+2] cycloadditions, see e) G. Hilt, J. Janikowski, *Angew. Chem.* **2008**, *120*, 5321; *Angew. Chem. Int. Ed.* **2008**, *47*, 5243; for Rh^I-catalyzed [7+1] cycloadditions, see f) Z.-K. Yao, J. Li, Z.-X. Yu, *Org. Lett.* **2011**, *13*, 134, and also see Ref. [2f].

[5] For Rh^I-catalyzed intramolecular [6+2] cycloadditions, see a) P. A. Wender, A. G. Correa, Y. Sato, R. Sun, *J. Am. Chem. Soc.* **2000**, *122*, 7815; b) F. Inagaki, K. Sugikubo, Y. Oura, C. Mukai, *Chem. Eur. J.* **2011**, *17*, 9062; c) Y. Oonishi, A. Hosotani, Y. Sato, *J. Am. Chem. Soc.* **2011**, *133*, 10386.

[6] For Rh^I-catalyzed [5+2+1] cycloadditions, see a) P. A. Wender, G. G. Gamber, R. D. Hubbard, L. Zhang, *J. Am. Chem. Soc.* **2002**, *124*, 2876; b) H. A. Wegner, A. de Meijere, P. A. Wender, *J. Am. Chem. Soc.* **2005**, *127*, 6530; c) Y. Wang, J. Wang, J. Su, F. Huang, L. Jiao, Y. Liang, D. Yang, S. Zhang, P. A. Wender, Z.-X. Yu, *J. Am. Chem. Soc.* **2007**, *129*, 10060; d) F. Huang, Z.-K. Yao, Y. Wang, Y. Wang, J. Zhang, Z.-X. Yu, *Chem. Asian J.* **2010**, *5*, 1555.

[7] For Rh^I-catalyzed [4+2+2] cycloadditions, see a) P. A. Evans, J. E. Robinson, E. W. Baum, A. N. Fazal, *J. Am. Chem. Soc.* **2002**, *124*, 8782; b) S. R. Gilbertson, B. J. DeBoef, *J. Am. Chem. Soc.* **2002**, *124*, 8784; c) P. A. Evans, E. W. Baum, *J. Am. Chem. Soc.* **2004**, *126*, 11150; d) P. A. Evans, E. W. Baum, A. N. Fazal, M. Pink, *Chem. Commun.* **2005**, 63; e) P. A. Wender, J. P. Christy, *J. Am. Chem. Soc.* **2006**, *128*, 5354; f) B. DeBoef, W. R. Counts, S. R. Gilbertson, *J. Org. Chem.* **2007**, *72*, 799.

[8] For the synthesis of a monocyclic eight-membered ring by Rh^I-catalyzed hydroacylation, see a) A. D. Aloise, M. E. Layton, M. D. Shair, *J. Am. Chem. Soc.* **2000**, *122*, 12610; b) D. Crépin, J. Dawick, C. Aïssa, *Angew. Chem.* **2010**, *122*, 630; *Angew. Chem. Int. Ed.* **2010**, *49*, 620.

[9] For a review of hydroacylation, see M. C. Willis, *Chem. Rev.* **2010**, *110*, 725, and references therein.

[10] For Rh^I-catalyzed [4+2] cycloadditions of 4-alkynals or 4-alkenals with C–C multiple bonds, see a) K. Tanaka, G. C. Fu, *Org. Lett.* **2002**, *4*, 933; b) K. Tanaka, Y. Hagiwara, K. Noguchi, *Angew. Chem.* **2005**, *117*, 7426; *Angew. Chem. Int. Ed.* **2005**, *44*, 7260; c) K. Tanaka, Y. Hagiwara, M. Hirano, *Eur. J. Org. Chem.* **2006**, 3582; d) K. Tanaka, Y. Hagiwara, M. Hirano, *Angew. Chem.* **2006**, *118*, 2800; *Angew. Chem. Int. Ed.* **2006**, *45*, 2734; e) K. Tanaka, D. Hojo, T. Shoji, Y. Hagiwara, M. Hirano, *Org. Lett.* **2007**, *9*, 2059; f) D. Hojo, K. Noguchi, M. Hirano, K. Tanaka, *Angew. Chem.* **2008**, *120*, 5904; *Angew. Chem. Int. Ed.* **2008**, *47*, 5820; g) D. Hojo, K. Tanaka, *Org. Lett.* **2012**, *14*, 1492; h) K. Kundu, J. V. McCullagh, A. T. Morehead, Jr., *J. Am. Chem. Soc.* **2005**, *127*, 16042.

[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).

