Synthesis of Cyclooctenones Using Intramolecular Hydroacylation

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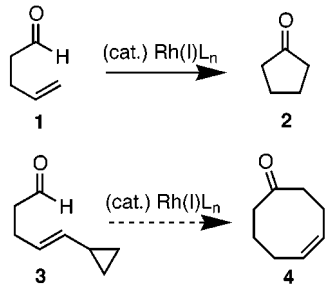
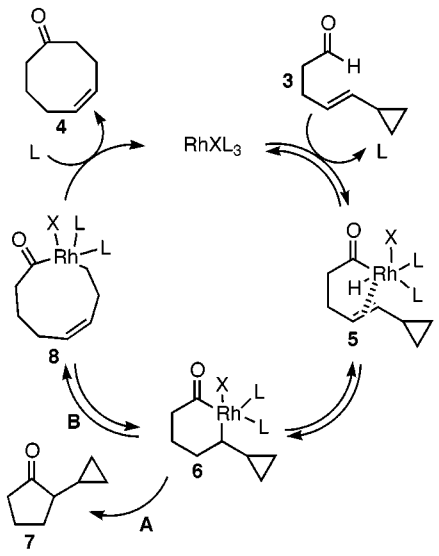
Reactions that involve insertion of transition metal-based catalysts into C−H bonds and the subsequent creation of ring structures represent an underdeveloped area of organic synthesis. The Rh(I)-catalyzed cyclization of 4-pentenals to cyclopentanones (Scheme 1, **1** → **2**), an intramolecular hydroacylation, is an example of such a reaction.[1] First reported 28 years ago by Sakai using $RhCl(Ph_3P)_3$,[1a] this reaction has remained largely limited to the synthesis of five-membered rings[2] due to competitive decarbonylation as ring size increases and rates of cyclization decrease. Application of this reaction to the synthesis of medium rings such as cyclooctenones would be a useful transformation;[3] however, it is inefficient due to the prohibitively slow cyclization rates of eight-membered rings. We hypothesized that the intramolecular hydroacylation reaction could be extended to the synthesis of cyclooctenones by strategic placement, in the starting material, of a cyclopropane ring capable of fragmentation (Scheme 1, **3** → **4**). Recently, a similar strategy was used by Wender[4] and Trost[5] in transition metal-catalyzed [5+2] cycloadditions, affording seven-membered rings. This contribution describes the extension of intramolecular hydroacylation to the synthesis of eight-membered rings using the strategy outlined in Scheme 1.

Scheme 1



The thoroughly investigated mechanism of the intramolecular hydroacylation reaction provides a basis for the conversion of **3** → **4**.[1b,c,e] A proposed catalytic cycle is depicted in Scheme 2. Initially, the Rh(I) catalyst oxidatively inserts into the aldehyde C−H bond of **3**, affording acyl-Rh(III) intermediate **5**. Intramolecular hydrometalation of **5** affords the six-membered Rh-metallacycle **6**. Two pathways are accessible to **6**. Reductive elimination (pathway A) is usually observed with intermediates related to **6**, delivering cyclopentanones (e.g. **7**). The presence of a cyclopropane ring adjacent to Rh(III) in **6** provides access to pathway B leading to ring fragmentation and isomerization affording nine-membered Rh-metallacycle **8**. Intermediate **8** would be expected to undergo reductive elimination to generate 4-cycloocten-1-one **4**. Although there is precedent for ring opening of cyclopropanes adjacent to Rh(III),[4,6,7] questions remained regarding the extrapolation to intermediate **6**, the relative rates of pathway A versus pathway B, and the influence of the catalyst structure on these relative rates. An additional concern was the potential for Rh(I)-catalyzed ring opening of the vinyl cyclopropane prior to C−H insertion.[8]

Scheme 2



Compound **9** was constructed to test our hypothesis (Scheme 3).[9] Treatment of **9** with $RhCl(Ph_3P)_3$ did not result in any intramolecular hydroacylation products (entry 1). Addition of 2-amino-3-picoline, an additive known to facilitate hydroacylation by the formation of a pyridylimine intermediate,[10] delivered both cyclooctenone **10** and cyclopentanone **11** in a 1:6 ratio (entry 2). Use of $[Rh(dppe)]ClO_4$, a cationic Rh(I) catalyst developed by Bosnich for intramolecular hydroacylation,[1d] switched the selectivity of the reaction to favor eight-membered ring **10** over **11** in a ratio of 9.4:1 (entry 3). However, decarbonylation was observed and the yield of **10** was limited to 47% (entry 3). A catalyst with a more dissociated anion, [Rh(dppe)]OTf, delivered **10** in 50% yield to the exclusion of **11** (entry 4). Attempts to use lower catalyst loadings led to diminished yields due to low conversion, although reactions that were performed with 20 mol % catalyst loading under an atmosphere of ethylene produced less decarbo-

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(2) For the synthesis of a six-membered ring via intramolecular hydroacylation, see: Gable, K. P.; Benz, G. A. *Tetrahedron Lett.* **1991**, *32*, 3473.

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(4) (a) Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720. (b) Wender, P. A.; Husfeld, C. O.; Langkopf, E.; Love, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 1940. (c) Wender, P. A.; Glorius, F.; Husfeld, C. O.; Langkopf, E.; Love, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 5348. (d) Wender, P. A.; Dyckman, A. J.; Husfeld, C. O.; Kadereit, D.; Love, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 10442.

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(7) For the fragmentation of three- and four-membered rings adjacent to acyl-Rh(III) bonds, see: Murakami, M.; Takahashi, K.; Amii, H.; Ito, Y. *J. Am. Chem. Soc.* **1997**, *119*, 9307.

(8) Khusnutdinov, R. I.; Dzhemilev, U. M. *J. Organomet. Chem.* **1994**, *471*, 1 and references therein.

(9) Synthesis and characterization of **9** and all substrates are reported in the Supporting Information.

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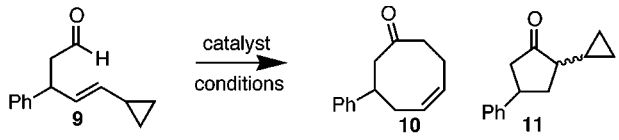
Scheme 3

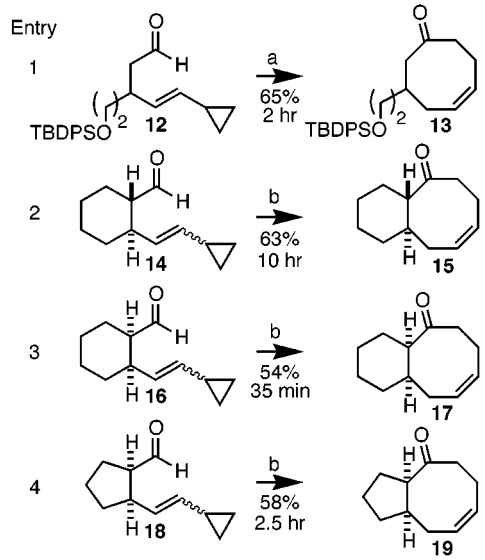


Entry	Catalyst	Conditions	Isolated Yields	
1	$RhCl(Ph_3P)_3$	$PhCH_3$, 165°C	0%	0%
2	$RhCl(Ph_3P)_3$	THF, 100°C 2-amino-3-picoline	7%	44%
3	$[Rh(dppe)]ClO_4$ (40 mol%)	$Cl(CH_2)_2Cl$, 83°C	47%	5%
4	[Rh(dppe)]OTf (20 mol%)	$Cl(CH_2)_2Cl$, 65°C	50%	0%
5	$[Rh(dppe)]ClO_4$ (20 mol%)	$Cl(CH_2)_2Cl$, 65°C	40%	0%
6	$[Rh(dppe)]ClO_4$ (5 mol%)	$Cl(CH_2)_2Cl$, 65°C ethylene	23%	0%
7	$[Rh(dppe)]ClO_4$ (20 mol%)	$Cl(CH_2)_2Cl$, 65°C ethylene	65%	0%

nylation products and improved yields (entries 5−7).[1b] The optimal conditions for cyclooctenone formation involved the use of 20 mol % $[Rh(dppe)]ClO_4$ under an atmosphere of ethylene affording **10** in 65% yield. Use of a moderately coordinating solvent such as THF dramatically inhibited the reaction, presumably due to coordination of the cationic Rh(I) catalyst.

A study of the scope of the reaction is presented in Scheme 4. Conversion of **12** to **13** (entry 1) demonstrated the compatibility of the catalyst and *tert*-butyldiphenylsilyl-protected alcohols. In comparison, *tert*-butyldimethylsilyl protecting groups were cleaved under the reaction conditions. For the synthesis of fused 5−8 and 6−8 ring systems it was determined that [Rh(dppe)]OTf was superior to $[Rh(dppe)]ClO_4$ as depicted in entries 2−4. Both trans (entry 2) and cis (entry 3) fused 6−8 ring systems were cyclized in 63% and 54% yields, respectively. The 5−8 fused ring system

Scheme 4[a]

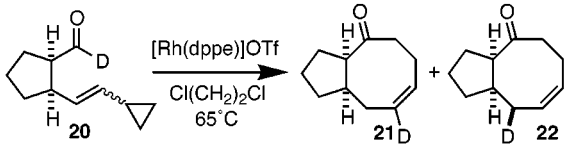


[a] Reagents: (a) 20 mol % $[Rh(dppe)]ClO_4$, ethylene, $Cl(CH_2)_2Cl$, 65 °C. (b) 20 mol % [Rh(dppe)]OTf, $Cl(CH_2)_2Cl$, 65 °C.

19 (entry 4) was formed upon exposure of **18** to [Rh(dppe)]OTf in 58% yield.

To probe the mechanism of our intramolecular hydroacylation reaction, deuterium-labeled substrate **20** was constructed and exposed to [Rh(dppe)]OTf (Scheme 5). Due to the difficulty in obtaining **20** as a pure *E* isomer, cyclizations were performed on 78:22 and 95:5 (*Z*/*E*) mixtures to exclude the possibility of a coincidental product ratio complicating the analysis. Both experiments (entries 1 and 2) led to the generation of deuterium-labeled products **21** and **22** in a ratio that directly corresponded to the *Z*/*E* ratio of **20**.

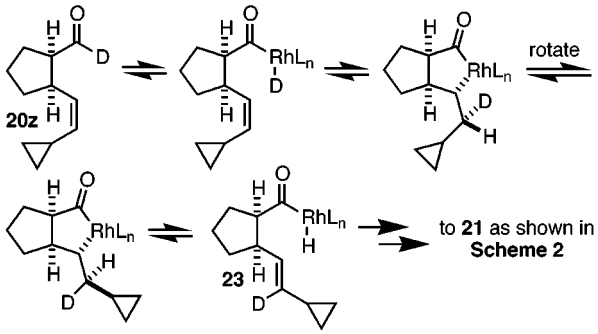
Scheme 5



entry	olefin ratio (*Z* : *E*)	product ratio (**21**:**22**)
1	78 : 22	78 : 22
2	95 : 5	94 : 6

One explanation of these results is that the *E* isomer of **20** proceeds directly to **22** through the mechanism depicted in Scheme 2. Meanwhile, **20z** initially proceeds through the olefin isomerization mechanism in Scheme 6 involving formation of a five-membered Rh-metallacycle, bond rotation, and β-hydrogen abstraction resulting in formation of deuterium-labeled intermediate **23**. This *E* olefin then proceeds to **21** through the mechanism in Scheme 2.

Scheme 6



In summary, intramolecular hydroacylation has been extended to the synthesis of eight-membered rings. Key elements of this approach were the maintenance of a rapid hydrometalation step (Scheme 2, **5** → **6**) and the strategic placement of a cyclopropane ring that rapidly fragments prior to reductive elimination, leading to the generation of 4-cycloocten-1-ones. Cationic Rh(I) catalysts were found to be superior to neutral Rh(I) catalysts for facilitating cyclopropane ring fragmentation. The success of this reaction provides a foundation to further extend the scope of intramolecular hydroacylation and other related reactions.

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Supporting Information Available: Details of experimental procedures and analytical data are included (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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