Synthesis of Cyclooctenones Using Intramolecular Hydroacylation

Allen D. Aloise, Mark E. Layton, and Matthew D. Shair*

Department of Chemistry and Chemical Biology
Harvard University, Cambridge, Massachusetts 02138

Received September 8, 2000

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. First reported 28 years ago by Sakai using RhCl(Ph3P)3,1 this reaction has remained largely limited to the synthesis of five-membered rings 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; however, it is inefficient due to the prohibitive 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 Wender2 and Trost3 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

![Scheme 1](Image)

The thoroughly investigated mechanism of the intramolecular hydroacylation reaction provides a basis for the conversion of


$3 \rightarrow 4 \text{,b,c,e}$ 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),4,5,6 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.

![Scheme 2](Image)

Compound 9 was constructed to test our hypothesis (Scheme 3).9 Treatment of 9 with RhCl(Ph3P)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)Cl]2O, a cationic Rh(I) catalyst developed by Bosnich for intramolecular hydroacylation,10 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-


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

nylation products and improved yields (entries 5–7). The optimal conditions for cyclooctenone formation involved the use of 20 mol % [Rh(dppe)]ClO₄ 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)]ClO₄ 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 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.

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.

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.

Acknowledgment. We gratefully acknowledge financial support from the following sources: Bristol-Myers Squibb, Camille and Henry Dreyfus Foundation, Alfred P. Sloan Foundation, Merck & Co., Pharmacia & Upjohn, and SmithKline Beecham. M.E.L. acknowledges an NSF predoctoral fellowship.

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.

JA0055920