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Rhodium(I)-Catalyzed Intramolecular Carbocyclic Ring Fusion: A New Approach to Medium-Sized-Ring Ketones

Mark A. Huffman and Lanny S. Liebeskind*

Department of Chemistry
Emory University
Atlanta, Georgia 30322

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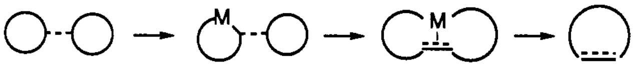
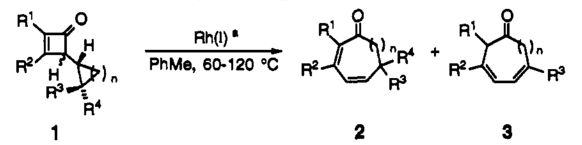
Intramolecular carbocyclic ring enlargement reactions in organic synthesis consist of three primary types: (1) incorporation of a side chain into the ring, (2) bridge cleavage in bicyclic compounds, and (3) ring cleavage with simultaneous bond formation between two side chains (pericyclic reactions).[1] A novel synthetic method would be the fusion of two small rings into a single larger one. This transformation might be accomplished in either an intermolecular or an intramolecular manner through the ability of transition metal complexes to insert into strained rings (eq 1).[2-4] Described here is the successful development of the intramolecular variant of the strategy for the synthesis of seven- and eight-membered-ring dienones.[5,6]



(1)

Previous work has shown that cyclobutenones react with certain transition metal reagents and catalysts to give reactive η^2- and η^4-vinylketene complexes.[7,8] Building on this knowledge, the search for a ring fusion catalyst was begun with the 4-cyclopropyl-2-cyclobutenone **1a**. Thermolysis of **1a** in C_6D_6 led to slow decomposition without formation of any detectable cycloheptadienone, a result consistent with the findings of Herndon using a related system.[9] However, in the presence of catalytic quantities of rhodium(I) complexes, cycloheptadienone **2a** was formed in a few hours at 60 °C. Of the catalysts investigated, $RhCl(PPh_3)_3$ gave the highest yield (Table I, entry 1). The other 4-cyclopropyl-2-cyclobutenones (**1b–e**) showed better reactivity with $[Rh(\mu\text{-}Cl)(1,5\text{-cyclooctadiene})]_2$ (entries 2–5), and most required reaction temperatures of 90–120 °C.[10] At these elevated temperatures, partial isomerization of the initially formed 2,4-dienones **2** to the 3,5-dienones **3** occurred. This 1,5-hydrogen shift is a known thermal reaction,[11] and heating **2a** to 90 °C for 16 h in the absence of catalyst gave a greater than 3:1 ratio of **3a** to **2a** (93% mass recovery). No catalysis of the 1,5-hydrogen shift by rhodium was observed at lower temperatures.

Table I. Rhodium-Catalyzed Ring Fusion

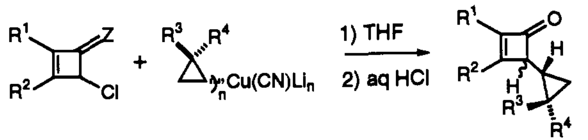


1 **2** **3**

entry	products	*n*	R^1	R^2	R^3	R^4	yield, % 2	yield, % 3
1	**2a**	1	H	Ph	H	H	84	–
2	**2b,3b**	1	*n*-Bu	*n*-Bu	H	H	30	40
3	**2c,3c**	1	Me	*i*-PrO	H	H	40	13
4	**3d**	1	Et	Et	Ph	H	–	32
5	**2e**	1	H	Ph	Me	Me	36	–
6	**2f**	2	H	Ph	H	H	90	–
7	**2g,3g**	2	*n*-Bu	*n*-Bu	H	H	47	14

[a] Rh(I) catalyst = 5 mol % $RhCl(PPh_3)_3$, entries, 1, 6, 7; 2.5 mol % $[Rh(\mu\text{-}Cl)(cod)]_2$, entries 2–5.

Scheme I[a]



1a-e

1a, 67 %; Z = OCH_2CH_2O, n = 1
1b, 82 %; Z = OCH_2CH_2O, n = 2
1c, 44 %; Z = O, n = 1
1d, 55 %; Z = OCH_2CH_2O, n = 2
1e, 56 %; Z = OCH_2CH_2O, n = 1

[a] See Table I for substituents.

Substitution on the cyclopropyl group led only to products from cleavage of the less substituted cyclopropane ring bond (entries 4, 5), although yields were lower in these cases. Similar results were obtained starting from pure diastereomers or from mixtures. Furthermore, in reactions monitored by ^1H NMR, each isolated diastereomer of **1d** equilibrated to a 1.4:1 mixture of diastereomers by the time 50% reaction had occurred.

4-Cyclobutyl-2-cyclobutenones also undergo ring fusion to give cyclooctadienones (entries 6, 7). $[Rh(\mu\text{-}Cl)(cod)]_2$ is a poor catalyst for these reactions, indicating that donor ligands such as PPh_3 may be required in order to open the cyclobutane ring. The cyclooctadienone products also undergo double-bond migration at elevated temperatures (entry 7).

4-Cyclopropyl-2-cyclobutenones **1a–e** were made by the coupling of cyclopropyl copper reagents with 4-chlorocyclobutenones, protected in most cases as the ethylene acetal (Scheme I).

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(2) Ohta, T.; Takaya, H. In *Comprehensive Organic Synthesis, Metal-catalyzed Cycloaddition of Small Ring Compounds*; Trost, B. M., Fleming, I. F., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 1185.

(3) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245.

(4) Bishop, K. C., III. *Chem. Rev.* **1976**, *76*, 461.

(5) A previous example of intramolecular ring fusion exists in the thermal and Ag^+-catalyzed rearrangement of bicyclopropenyls to benzene derivatives, although this unique transformation is almost certainly mechanistically unrelated to the present work. (a) Breslow, R.; Gal, P.; Chang, H. W.; Altman, L. J. *J. Am. Chem. Soc.* **1965**, *87*, 5139. (b) deWolf, W. H.; v. Straten, J. W.; Bickelhaupt, F. *Tetrahedron Lett.* **1972**, 3509. (c) Weiss, R.; Andrae, S. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 150.

(6) A synthesis of cycloheptadienones from alkynes and cyclopropylcarbene complexes of tungsten has been reported which may involve some intermediates similar to those in the present work. Herndon, J. W.; Chatterjee, G.; Patel, P. P.; Matasi, J. J.; Tumer, S. U.; Harp, J. J.; Reid, M. D. *J. Am. Chem. Soc.* **1991**, *113*, 7808.

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(8) Huffman, M. A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1991**, *113*, 2771.

(9) Tumer, S. U.; Herndon, J. W.; McMullen, L. A. *J. Am. Chem. Soc.* **1992**, *114*, 8394.

(10) All new compounds were spectroscopically characterized and furnished adequate analytical or high-resolution mass-spectral data. In a representative experiment, **1b** (299 mg, 1.36 mmol) was dissolved in dry toluene (14 mL) under argon. $[Rh(\mu\text{-}Cl)(cod)]_2$ (17 mg, 0.034 mmol) was added against an argon flow, and the mixture was heated to reflux for 24 h. Radial chromatography on silica with hexanes/ethyl acetate (40:1) eluted two product bands. The first gave **3b** as a colorless oil (119 mg, 0.54 mmol, 40%): ^1H NMR (360 MHz, $CDCl_3$) δ 6.16 (dd, J = 10.6, 5.0 Hz, 1 H), 5.90 (d, J = 5.0 Hz, 1 H), 5.61 (dt, J = 10.6, 5.3 Hz, 1 H), 3.10 (m, 3 H), 2.10 (q, J = 6.7 Hz, 2 H), 1.85 (m, 1 H), 1.64 (m, 1 H), 1.41–1.15 (m, 8 H), 0.87 (t, J = 7.0 Hz, 3 H), 0.86 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.7, 141.3, 128.6, 123.0, 122.9, 58.0, 44.9, 36.6, 30.4, 30.1, 27.3, 22.7, 22.4, 13.9, 13.8; IR (CH_2Cl_2) 2961 (s), 2933 (s), 2875, 2863, 1703 (s), 1607, 1468, 1380 cm^{-1}. Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.52; H, 10.93. The second band gave **2b** as a colorless oil (90 mg, 0.41 mmol, 30%): ^1H NMR (360 MHz, $CDCl_3$) δ 6.21 (dt, J = 11.2, 6.1 Hz, 1 H), 5.88 (d, J = 11.2 Hz, 1 H), 2.67 (m, 2 H), 2.38 (m, 2 H), 2.22 (m, 4 H), 1.36 (m, 8 H), 0.90 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.1, 145.1, 139.4, 134.7, 132.0, 45.9, 35.6, 32.3, 31.1, 29.2, 23.0, 22.8, 22.7, 13.9 (2 coincident C); IR (CH_2Cl_2) 2962 (s), 2933 (s), 2875, 2863, 1644 (s), 1466 cm^{-1}. Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.84; H, 10.94.

(11) ter Borg, A. P.; Kloosterziel, H. *Recl. Trav. Chim. Pays-Bas* **1963**, *82*, 1189.

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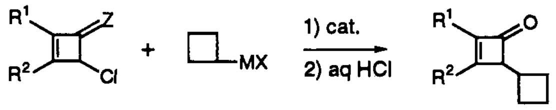
Scheme II[a]



1f,g

1f, 68 %; Z = OCH_2CH_2O, M = Mg, cat. = CuCN (6 %)
1g, 77 %; Z = O, M = Zn, cat. = $Cl_2Ni(PMe_2Ph)_2$ (5 %)

[a] See Table I for substituents.

Cyclobutylcyclobutenones were made by copper-catalyzed coupling of cyclobutylmagnesium chloride with an acetal-protected 4-chlorocyclobutenone, or by nickel-catalyzed coupling of the unprotected chlorocyclobutenone with a cyclobutylzinc reagent (Scheme II). These synthetically interesting secondary aliphatic–secondary allylic cross couplings will be dealt with in more detail in the future.

Together the coupling and fusion reactions represent a fundamentally new strategy for medium-sized-ring synthesis. The full scope of catalyzed ring fusion and the mechanistic questions that it presents remain to be explored.

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Supplementary Material Available: Experimental details for the syntheses of **1a–g**, **2a–c**, **e–g**, and **3a–d**,**g** (13 pages). Ordering information is given on any current masthead page.