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Application of Rh(I)-Catalyzed C–H Bond Activation to the Ring Opening of 2-Cycloalkenones in the Presence of Amines

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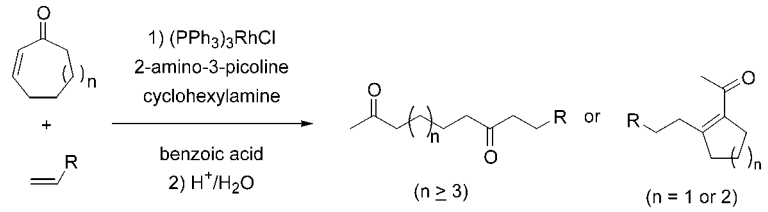
ABSTRACT



Herein described is the application of the Rh(I)-catalyzed C–H bond activation to the ring-opening of 2-cycloalkenones in the presence of cyclohexylamine. This reaction includes the C–C double bond cleavage of 2-cycloalkenones through the conjugate addition of cyclohexylamine followed by the retro-Mannich-type fragmentation. The resulting ring-opened intermediates subsequently underwent either chelation-assisted hydroacylation to afford a ring-opened dicarbonyl compound or *β*-alkylation via a ring contraction.

The activation of C−H bonds by transition metal catalysts is considered to be one of the most efficient tools for a new C−C bond coupling in organic synthesis.[1] By utilizing a chelation-assistance strategy, we had successfully developed a series of catalytic C−H bond activation reactions such as hydroacylation of olefins[2] and *ortho*-alkylation of aromatic ketones.[3] In our efforts toward C−H bond activation, we reported the Rh(I)-catalyzed hydroiminoacylation of alkynes with allylamines, which included the C−C double bond cleavage of a reaction intermediate, α,*β*-unsaturated ketimine, by primary amines.[4] Therefore, our Rh(I)-catalyzed C−H bond activation was applied to 2-cycloalkenones to explore the scope of the reaction for conjugated carbonyl compounds and provide new multifunctionalized compounds. Herein, we present the amine-assisted C−C double bond cleavage of 2-cycloalkenones followed by the Rh(I)-catalyzed C−H bond activation or hydroiminoacylation.

In our experiment, 2-cycloalkenone (**1**)[5] reacts with 1-alkene (**2**) at 130 °C for 1 h in toluene under the cocatalyst system consisting of $(PPh_3)_3RhCl$ (**3**, 3 mol %), 2-amino-3-picoline (**4**, 20 mol %), cyclohexylamine (**5**, 100 mol %), and benzoic acid (**6**, 5 mol %) to afford a mixture of ketones **7** and **8** in a high yield (Table 1). For example, the reaction of 2-cyclononenone (**1a**) and 1-hexene (**2a**) under the above

(1) For reviews, see: (a) Ryabov, D. *Chem. Rev.* **1990**, *90*, 403−424. (b) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879−2932. (c) Dyker, G. *Angew. Chem.* **1999**, *111*, 1808−1822; *Angew. Chem., Int. Ed.* **1999**, *38*, 1698−1712. (d) Guari, Y.; Sabo-Etienne, S.; Chaudret, B. *Eur. J. Inorg. Chem.* **1999**, 1047−1055.

(2) (a) Jun, C.-H.; Chung, K.-W.; Hong, J.-B. *Org. Lett.* **2001**, *3*, 785−787. (b) Jun, C.-H.; Lee, D.-Y.; Lee, H.; Hong, J.-B. *Angew. Chem., Int. Ed.* **2000**, *39*, 3070−3072. (c) Jun, C.-H.; Lee, H.; Park, J.-B.; Lee, D.-Y. *Org. Lett.* **1999**, *1*, 2161−2164. (d) Jun, C.-H.; Hong, J.-B. *Org. Lett.* **1999**, *1*, 887−889. (e) Jun, C.-H.; Huh, C.-W.; Na, S.-J. *Angew. Chem., Int. Ed.* **1998**, *37*, 145−147. (f) Jun, C.-H.; Lee, H.; Hong, J.-B. *J. Org. Chem.* **1997**, *62*, 1200−1201. (g) Jun, C.-H.; Lee, D.-Y.; Hong, J.-B. *Tetrahedron Lett.* **1997**, *38*, 6673−6676.

(3) (a) Jun, C.-H.; Hong, J.-B.; Kim, Y.-H.; Chung, K.-W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3440−3442. (b) Jun, C.-H.; Moon, C. W.; Hong, J.-B.; Lim, S.-G.; Chung, K.-W.; Kim, Y.-H. *Chem. Eur. J.* **2002**, *8*, 485−492.

(4) Jun, C.-H.; Lee, H.; Moon, C. W.; Hong, H.-S. *J. Am. Chem. Soc.* **2001**, *123*, 8600−8601.

(5) 2-Cycloalkenones larger than 2-cycloheptenone were prepared by the known procedures as described in Supporting Information. See: (a) Ito, Y.; Fujii, S.; Nakatsuka, M.; Kawamoto, F.; Saegusa, T. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, pp 327−333. (b) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596−7597.

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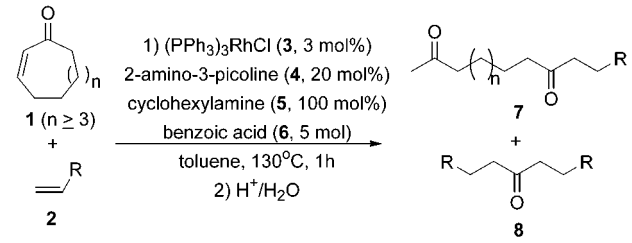
Table 1. Ring Opening/Hydroacylation of 2-Cycloalkenones (**1**)[a]



entry	1	R of 2	product ratio (7/8)	isolated yield (%)
1	**1a** ($n = 3$)	nC_4H_9 (**2a**)	87/13 (**7a**/**8a**)	86
2		nC_6H_{13} (**2b**)	70/30 (**7b**/**8b**)	96
3		tC_4H_9 (**2c**)	74/26 (**7c**/**8c**)	99
4		Me_3Si (**2d**)	88/12 (**7d**/**8d**)	99
5		Cy (**2e**)	72/28 (**7e**/**8e**)	67
6	**1b** ($n = 4$)	nC_4H_9 (**2a**)	87/13 (**7f**/**8a**)	86[b]
7	**1c** ($n = 5$)	**2a**	85/15 (**7g**/**8a**)	68[b]
8	**1d** ($n = 6$)	**2a**	85/15 (**7h**/**8a**)	61[b,c]
9	**1e** ($n = 9$)	**2a**	80/20 (**7i**/**8a**)	89[b,c]

[a] The reaction was carried out with **1** (0.216 mmol) and **2** (0.648 mmol) as starting materials. [b] 5 mol % of **3** was used based upon **1**. [c] 100 mol % of **4** and 1000 mol % of **2** were used.

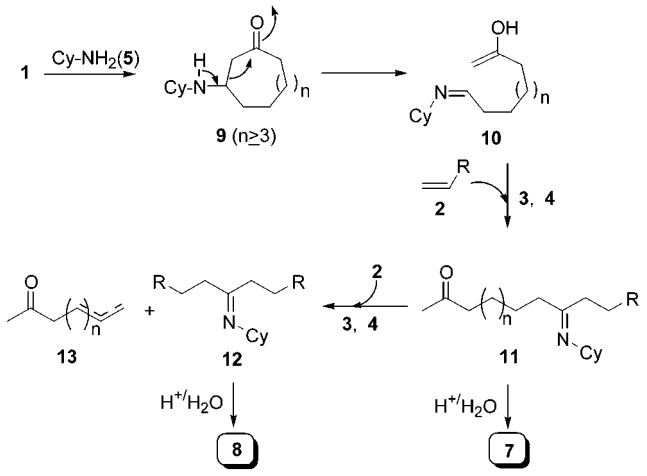
reaction condition gave a 87:13 mixture of pentadecane-2,9-dione (**7a**) and tridecan-7-one (**8a**) in a 86% yield after chromatographic purification (entry 1). Other olefins (**2b**−**e**) were also examined for this reaction, which led to fairly good yields of corresponding 2,9-diones (**7b**−**e**) and symmetric dialkyl ketones (**8b**−**e**) (entries 2−5). 2-Cycloalkenones (**1b**−**e**) with a ring size larger than that of **1a** reacted with **2a** to give the corresponding 2,10-, 2,11-, 2,12-, 2,15-dione (**7f**−**i**), respectively, as well as **8a** in fairly good yields (entries 6−9).

The mechanism of this reaction was speculated as shown in Scheme 1. The conjugate addition of cyclohexylamine (**5**) to enone **1** and the subsequent retro-Mannich-type fragmentation of **9** in the presence of an acid would generate the ring-opened imine **10**.[6,7] Hydroiminoacylation of 1-alkene (**2**) with aldimine **10** by the cocatalyst system of **3** and **4** might lead to ketimine **11**. This transimination/hydroiminoacylation protocol was well established for the efficient conversion of aldimines to ketimines.[2] Further chelation-assisted C−C bond activation of **11** with **2** in the presence of **3** and **4** could provide a symmetric dialkyl ketimine **12** and **13**. Hydrolysis of ketimine **11** and **12** would produce ketone **7** and **8**. When this reaction was performed with 2-cycloheptenone (**1f**) and 1-hexene (**2a**) under the identical reaction condition, an isomeric mixture of 1-(2-hexyl-cyclopent-1-enyl)-ethanone (**15a**), 1-(2-hexyl-cyclopent-2-

(6) For the C−C double bond cleavage of conjugated enones by amines, see: (a) Eisch, J. J.; Sanchez, R. *J. Org. Chem.* **1986**, *51*, 1848−1852. (b) Yamagami, C.; Weisbuch, F.; Dana, G. *Tetrahedron* **1971**, *27*, 2967−2975.

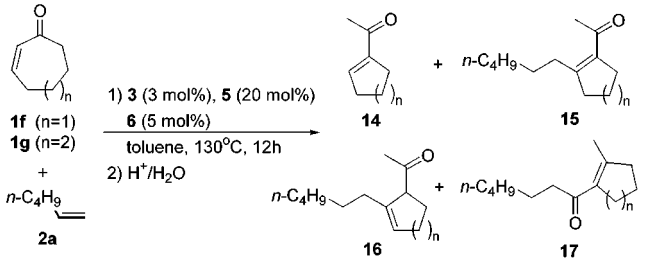
(7) For other examples to cleave the C−C double bond of cyclic enones, see: Kondo, Y.; Kon-I, K.; Iwasaki, A.; Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 414−417.

Scheme 1 Mechanism for Reaction of **1a**−**e** via Hydroacylation



enyl)-ethanone (**16a**), and 1-(2-methyl-cyclopent-1-enyl)-heptan-1-one (**17a**) was obtained in a 27%, 14%, and 43% yield, respectively (entry 1 in Table 2). It is interesting that

Table 2. Ring Cleavage/β-Alkylation of **1f** and **1g**



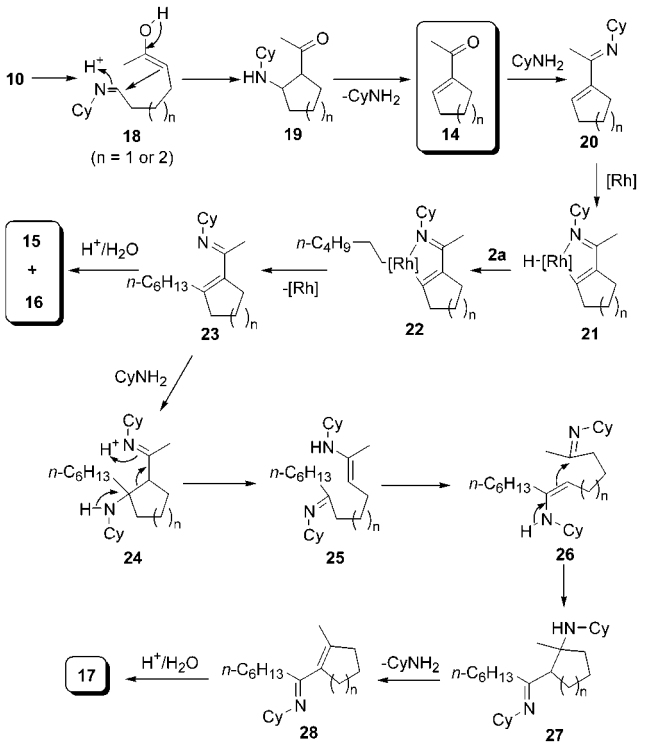
entry	1	2a[a]	4[b]	product (% yield)
1	**1f** ($n = 1$)	5	20	**15a** (27) **16a** (14) **17a** (43)
2		5	0	**15a** (60) **16a** (11) **17a** (8)
3[c]		0	0	**14a** (100)
4[c]	**1g** ($n = 2$)	0	0	**14b** (100)

[a] Equivalents based upon **1**. [b] Mole percent based upon **1**. [c] 200 mol % of **5** was used. The reaction time was 1 h.

this reaction afforded, even in the absence of 2-amino-3-picoline (**4**), the same mixture of products in a fairly good yield with **15a** predominate (entry 2). Without 1-hexene (**2a**) and 2-amino-3-picoline (**4**) in entry 3, the reaction of **1f** gave simply a ring-contracted product, 1-cyclopent-1-enyl-ethanone (**14a**), in a quantitative yield. From these results, it could be inferred that **15a** and **16a** were produced by an initial skeletal rearrangement of **1f** into **14a**, via the amine-assisted ring cleavage and the subsequent β-alkylation of **14a** with **2a** under the Rh(I) catalyst (**3**). When 2-cyclooctenone (**1g**) was examined without **2a**, 1-cyclohex-1-enyl-ethanone (**14b**) was also obtained in 100% yield by GC anaylsis.[8]

The proposed mechanism for the reaction of **1f** and **1g** is depicted in Scheme 2. After the ring opening of **1f** to **10**, the subsequent intramolecular Mannich reaction to **19** seems

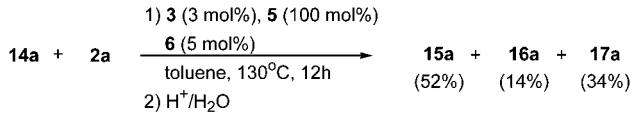
Scheme 2 Proposed Mechanism for Reaction of **1f** and **1g**



to be facilitated by the five- or six-membered ring closure. Deamination of **19** gives α,β-unsaturated ketone product **14**, and the condensation of **14** with cyclohexylamine generates α,β-unsaturated ketimine **20**. Then, the chelation-assisted β-alkylation of **20** with 1-hexene can take place to produce **23** via β C−H bond cleavage by the Rh(I) catalyst. Hydrolysis of **23** furnishes a mixture of **15** and **16**. On the other hand, the other product **17** can be generated from **23** by the following reaction sequence: (i) the conjugate addition of cyclohexylamine (**5**) into **23**; (ii) the retro-Mannich-type fragmentation of the resulting β-amino ketimine **24** to give a ring-opened compound **25**; (iii) the intramolecular Mannich condensation of **26** to produce **28** through intermediate **27**; (iv) the hydrolysis of the resulting ketimine **28**. This proposed

(8) When the reaction was carried out with 5 equiv of **2a**, 1-acetylcyclohexene (**14b**) was obtained as a major product along with a trace amount of β-alkylated compounds that were characterized as 1-(2-hexyl-cyclohexyl)-ethanone, a hydrogenated compound of **15b** and **16b**, by H_2 under Pd/C; see Supporting Information. This result shows that **14b** is not a good substrate for β-alkylation.

Scheme 3. Direct β-Alkylation of **14a** with **2a**



mechanism was supported by the direct β-alkylation of **14a** with **2a** in the presence of catalyst **3** and cyclohexylamine (**5**), which resulted in the identical mixture of products in a good yield (Scheme 3). Direct β-alkylation of **14a** with **2a** is another possibility, which does not need a chelation-assistant auxiliary.[9] However, when the reaction of **14a** with **2a** was carried out in the presence of **3** and **6** without cyclohexylamine (**5**), no β-alkylation proceeded. This result implies that the imine **20**, generated from **14a** and **5**, is a prerequisite intermediate for the β-alkylation. Compound **4** seems to play the same role in part with **5** in this reaction since the ratio of **17a** increased in the presence of both **4** and **5**, whereas low yield of **17a** was obtained with only **5** (entries 1 and 2 in Table 2).

In conclusion, we have demonstrated the application of the Rh(I)-catalyzed C−H bond activation to the ring opening of 2-cycloalkenones in the presence of cyclohexylamine. This reaction includes the C−C double bond cleavage of 2-cycloalkenones through the conjugate addition of cyclohexylamine followed by the retro-Mannich-type fragmentation. Such ring cleavage of 2-cycloalkenones could generate intermediates that would undergo either the chelation-assisted hydroacylation of olefins (e.g., 2-cyclononenone) to afford a ring-opened dicarbonyl compound or β-alkylation (e.g., 2-cycloheptenone) to provide an alkylated ring-contraction product.

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Supporting Information Available: Full experimental details and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL025816E

(9) The Ru-catalyzed direct β-alkylation is only applicable to the vinyl silane or vinyl siloxane. For example, see: (a) Trost, B. M.; Imi, K.; Davies, I. W. *J. Am. Chem. Soc.* **1995**, *117*, 5371−5372. (b) Sato, T.; Kakiuchi, F.; Chatani, N.; Murai, S. *Chem. Lett.* **1998**, 893−894.