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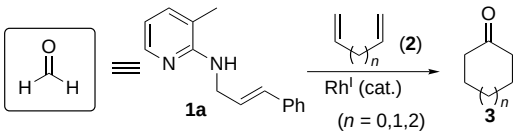
Synthesis of Cycloalkanones from Dienes and Allylamines through C–H and C–C Bond Activation Catalyzed by a Rhodium(I) Complex**

Dae-Yon Lee, In-Jung Kim, and Chul-Ho Jun*

Among numerous examples of transition-metal-mediated cyclization to obtain medium-sized ring compounds,[1] intramolecular hydroacylation provides the most promising way to prepare cyclopentanones from 4-pentenal through the C–H-bond activation of an aldehyde.[2,3] However, its application has been limited to the synthesis of five-membered rings with a few exceptions,[3] because the competing decarbonylation of the acyl metal hydride intermediate prevails during the formation of the larger ring. In the course of our studies into chelation-assisted C–H- and C–C-bond activation,[4] allylic amine **1a**, which bears a coordination site, was devised and used as a masked form of formaldehyde in the hydroacylation of 1-alkenes to synthesize dialkyl ketones.[4d] We envisaged a cyclization of dienes **2**[5–7] with **1a** to furnish cycloalkanones **3** with various sizes, since decarbonylation cannot occur in the reaction of **1a** (Scheme 1). Herein we present a facile synthesis of various cycloalkanones from the reaction of allylic amines with dienes through chelation-assisted C–H- and C–C-bond activation.



Scheme 1. Formation of cycloalkanone **3** from the reaction of allylamine **1a** and diene **2**.

The reactions of **1a** with various dienes (**2**) are summarized in Table 1. For example, when **1a** was allowed to react with 1,4-pentadiene (**2a**) in the presence of $[\{(C_8H_{14})_2RhCl\}_2]$ (**4**, 5 mol %) and PCy_3 (**5**, 15 mol %) at 150 °C for 2 h, cyclohexanone (**3a**) and 2-methylcyclopentanone (**3b**) were obtained in 87 % and 13 % yield, respectively, after hydrolysis (Table 1, entry 1). Furthermore, the reaction with 1,5-hexadiene (**2b**) provided cycloheptanone (**3c**), 2-methylcyclohexanone (**3d**), and 2-ethylcyclopentanone (**3e**) in a ratio of 38:40:22 (Table 1, entry 2).[8]

The mechanism for this reaction is depicted in Scheme 2. Aldimine **6a** is generated by Rh-catalyzed isomerization of **1a**. Subsequent intermolecular hydroiminoacylation[9] of **2b**

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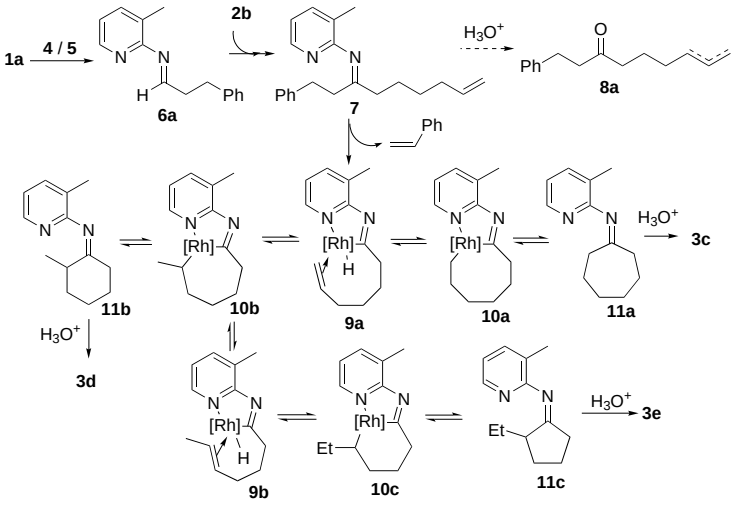
Table 1. The cyclization of dienes **2** with **1a**.[a]

Entry	Dienes **2**	t [h]	Cycloalkanones **3**[b]	Yield
1[c]	**2a**	2	**3a**, **3b**	(100%, 87:13)
2[c,d]	**2b**	2	**3c**, **3d**, **3e**	(82%, 38:40:22)
3[e]	**2c**	0.5	**3f**	(56%)
4[f]	**2d**	2	**3g**	86% (100%)
5	**2e**	4	**3h**	84% (100%)
6	**2f**	5	**3i**	77% (100%)
7[c]	**2g**	3	**3j**	67% (100%)
8[g]	**2h**	18	**3b**	(77%)

[a] **1a** (0.25 mmol), **2** (0.75 mmol), **4** (0.0063 mmol), **5** (0.039 mmol) in toluene (100 mg) at 170°C. The products were identified after hydrolysis. [b] Yields of isolated cyclohexanones (GC yields are given in parentheses). [c] The reaction temperature was 150°C. [d] A mixture of alkenyl ketones **8a** (9%) and **8b** (9%), which were identified as 1-phenyl-3-nonanone and dihexyl ketone, respectively, were also observed (GC) after hydrogenation. [e] A mixture of alkenyl ketones **8c** (23%) and **8d** (21%) was also obtained. [f] The ratio of meso-**2d**/(±)-**2d** (ca. 45:55) was retained in **3g** (determined by ^{1}H NMR spectroscopy). [g] A mixture of alkenyl ketones, identified as a hydrogenated form, 1-phenyl-3-octanone, was obtained (33% yield by GC).

with **6a** gives ketimine **7**, which is hydrolyzed to give acyclic ketone **8a**.[4d] Further C–C-bond activation of **7**, and subsequent β-hydrogen elimination leads to iminoacylrhodium(III) hydride **9a**, and styrene is liberated.[4c,d] The intramolecular hydrometalation of **9a** affords ketimines **11a–c**, which furnish corresponding cycloalkanones **3c–e** after hydrolysis. Among the products, ketimine **11a** is derived from anti-Markovnikov hydrometalation of **9a** via metallacyclic intermediate **10a**, whereas **11b** is formed from Markovnikov reaction of **9a** via **10b**. Further skeletal isomerization of **10b** leads to the formation of **11c** via **9b** and **10c**.

Monitoring the change in the ratio of cycloalkanones in the reaction of **1a** with **2b** revealed that the seven-membered ring



Scheme 2. Postulated mechanism for the cyclization of **2b** with **1a**.

3c was the sole product after 5 min (Figure 1). The ratio of **3c** decreased while those of **3d** and **3e** increased as the reaction progressed.[10] This type of skeletal rearrangement by C–C-

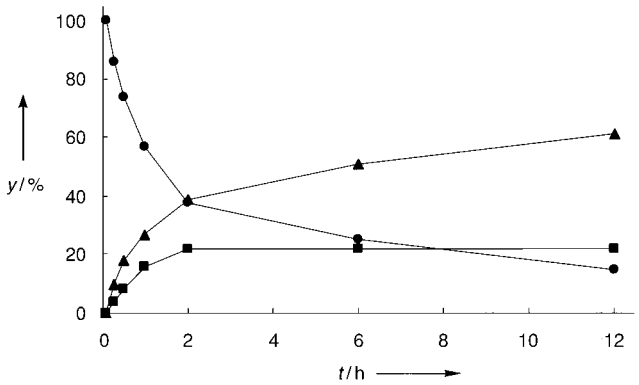


Figure 1. Plot of the ratio of cycloalkanones vs time plot for the reaction of **1a** and **2b** at 150°C. y = Ratio of cycloalkanones determined by GC: ● = **3c**, ▲ = **3d**, ■ = **3e**.

bond activation, which leads to the spontaneous ring contraction of the seven-membered ring to the more stable six- and five-membered rings, has been already studied.[4f,11] However, the initial formation of a seven-membered ring implies that anti-Markovnikiv hydrometalation (Scheme 2, **9a** to **10a**) is favored over Markovnikov hydrometalation (Scheme 2, **9a** to **10b**), maybe as a result of the steric congestion of the (iminoacyl)rhodium system.[4a]

The exclusive formation of a seven-membered ring was observed with substituted dienes. For instance, the reaction of 2-methyl-1,5-hexadiene (**2c**) with **1a** gave 3-methylcycloheptanone (**3f**) as the sole cyclization product in 56% yield, along with alkenyl ketones **8c** and **8d**, which shows that the initial hydroiminoacylation takes place at the less substituted olefin, that is, C5=C6 in **2c** (Table 1, entry 3). The subsequent cyclization occurs at C1=C2 in **2c** to form **3f**, but further ring contraction did not proceed, becuse the formation of the resulting metallacycle intermediate **10d** is disfavored as a result of steric congaestion.

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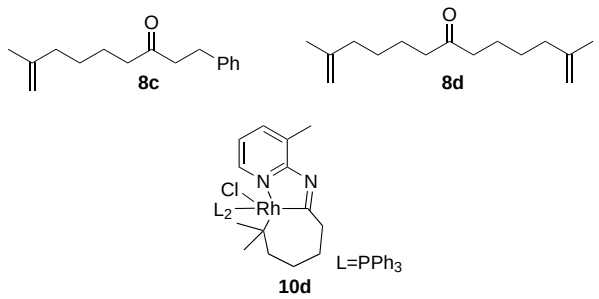
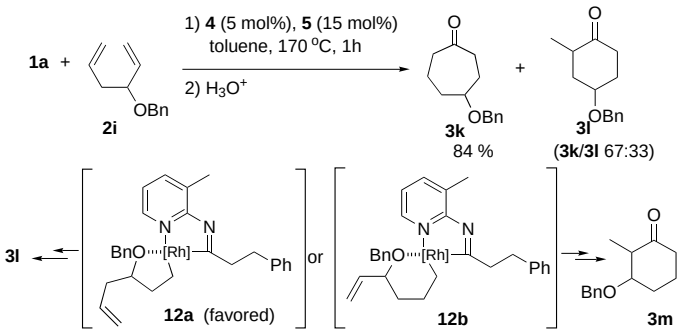


Other 1,5- or 1,4-dienes that bear substituents at C2 or C3 also exclusively yielded seven- or six-membered rings, respectively, without forming ring-contraction products (Table 1, entries 4–7). Notably, even the 1,3-diene piperylene (**2h**) also underwent cyclization to give **3b** in good yield (Table 1, entry 8). So far, the hydroacylation of conjugated dienes has been known to afford β,γ-unsaturated ketone via π-allyl intermediates.[12]

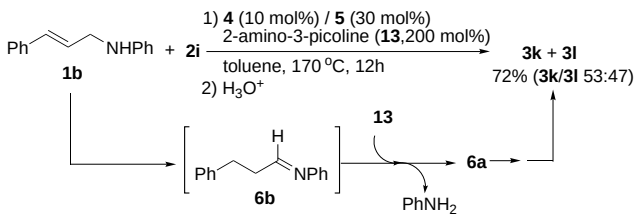
Another interesting substrate is 3-benzyloxy-1,5-hexadiene (**2i**), which reacted with **1a** to give cycloalkanones **3k** and **3l** (67:33; Scheme 3). The formation of **3l** instead of **3m** as a ring-contraction product illustrates that initial hydroiminoacylation occurs exclusively at C1=C2 in **2i** to give intermediate **12a**, which is favored over **12b** as a result of the directing effect of the benzyloxy group, thus forming the stable five-membered metallacycle in **12a**.[13]

Allylic amines that have no coordination site could also be applied to this reaction. For example, *N*-cinnamylamine (**1b**) reacted with **2i** in the presence of 2-amino-3-picoline (**13**) to give **3k** and **3l** in 72% yield after hydrolysis (Scheme 4). This reaction proceeds through the isomerization of **1b** and subsequent transimination[4e,14] of the resulting aldimine **6b** to form **6a**.

In summary, the synthesis of various cycloalkanones by the reaction of allylic amines with dienes was achieved through chelation-assisted C–H- and C–C-bond activation. The use of



Scheme 3. Reaction of **2i** with **1a** in the presence of **4** and **5**.



Scheme 4. Reaction of **1b** and **2i** through transimination.

1a as a masked form of formaldehyde allows the formation of six- and seven-membered cycloalkanones, which has rarely been possible by intramolecular hydroacylation as a result of competing decarbonylation. Furthermore, the reaction with substituted 1,4- or 1,5-dienes exclusively gave cyclohexanones or cycloheptanones, respectively. Even allylic amines that have no coordination site can also be applied to this reaction by utilizing a transimination protocol.

Experimental Section

Reaction of **1b** and **2i**: A screw-capped pressure vial (1 mL) was charged with **1b** (39.2 mg, 0.190 mmol), **2i** (44.9 mg, 0.239 mmol), **13** (43.2 mg, 0.400 mmol), $[\{(C_8H_{14})_2RhCl\}_2]$ (**4**; 7.3 mg, 0.012 mmol), tricyclohexylphosphane (**5**; 10.8 mg, 0.0599 mmol), and the reaction mixture was dissolved in toluene (100 mg). It was stirred in a preheated oil bath (170 °C) for 12 h. Upon completion, the reaction mixture was hydrolyzed (1N HCl) and purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate 5:2) to afford a mixture of **3k** and **3l** in 84% yield (24.8 mg). The ratio of **3k**/**3l** was determined by GC analysis as 53:47.

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