

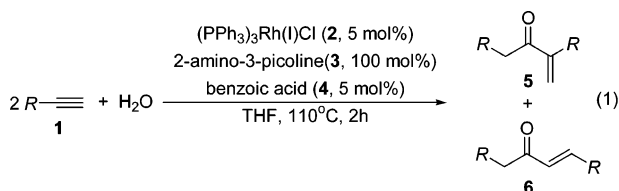
## Chelation-Assisted Hydrative Dimerization of 1-Alkyne Forming $\alpha,\beta$ -Enones by an Rh(I) Catalyst

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Alkyne is one of the interesting substrates in the transition-metal-catalyzed reaction since it can be transformed into a wide range of synthetically important intermediates.<sup>1</sup> In the course of our ongoing studies of hydroacylation of alkyne with aldehyde using a catalytic system of Rh(I) and 2-aminopicoline, as well as the related reaction,<sup>2</sup> we found that  $\alpha,\beta$ -enones could be directly formed from two 1-alkyne molecules and H<sub>2</sub>O using the same catalysts (eq 1). Some of the very few examples of the transition-metal-catalyzed alkyne dimerization utilizing H<sub>2</sub>O include the following: the Ru-catalyzed hydrative diyne cyclization,<sup>3</sup> the propargyl alcohol dimerization,<sup>4</sup> and the stoichiometric reaction forming Rh-bound enones.<sup>5</sup> In this communication, we wish to report a novel catalytic intermolecular hydrative dimerization of 1-alkyne and a preliminary investigation into the roles of catalysts.



When the reaction experiment of 1-octyne (**1a**) and H<sub>2</sub>O was carried out using the catalytic system of **2**, **3**, and **4** in THF at 110 °C for 2 h, a mixture of branched  $\alpha,\beta$ -enone **5a** and linear enone **6a** was obtained in an 82% isolated yield with approximately a 4:1 ratio (Table 1, entry 1).<sup>6</sup> Other 1-alkynes were also applied in this experiment, and it was found that secondary, as well as primary, aliphatic 1-alkynes underwent the same reaction to produce  $\alpha,\beta$ -enones that favor the branched isomer **5** over the linear isomer **6** in good to moderate yields (entries 1–5).<sup>7</sup> However, with a tertiary 1-alkyne, such as 2,2'-dimethylpropyne (**1f**), the linear  $\alpha,\beta$ -enone (**6f**) was isolated exclusively without producing the branched isomer **5f** (entry 6). These results imply that a branch:linear ratio seems to be controlled by the alkyl substituent of 1-alkyne.

It is interesting to note that the three components of **2**, **3**, and H<sub>2</sub>O are all essential to the production of the hydrative dimerization compounds of 1-alkyne (Table 2). Without any one of these, no desired  $\alpha,\beta$ -enones were obtained (entries 2–4). 2-Amino-3-picoline (**3**) played an important role in this hydrative dimerization of 1-alkyne since without **3**, only enynes,<sup>8</sup> the direct dimerization products of 1-alkyne, were isolated, and it was also noteworthy that the resulting enynes were not involved in this transformation (entry 3).<sup>9</sup>

The position and existence of the methyl group in **3** are not critical for yielding  $\alpha,\beta$ -enones, except for the 6-position on the pyridine ring (Table 3, entries 1–5). However, the 2-position of the primary amino group on the pyridine ring is essential for performing the reaction (Table 3, entries 6–8).

**Table 1.** Hydrative Dimerization of Various 1-Alkynes<sup>a</sup>

Entry	Alkyne ( <b>1</b> )	Yield(%) <sup>b</sup>	( <b>5/6</b> ) <sup>c</sup>
1	<i>n</i> -C <sub>6</sub> H <sub>13</sub> —C≡C—R ( <b>1a</b> )	82	( <b>5a/6a</b> : 78/22)
2	<i>n</i> -C <sub>4</sub> H <sub>9</sub> —C≡C—R ( <b>1b</b> )	63	( <b>5b/6b</b> : 84/16)
3	<i>n</i> -C <sub>7</sub> H <sub>15</sub> —C≡C—R ( <b>1c</b> )	67	( <b>5c/6c</b> : 78/22)
4	<i>n</i> -C <sub>8</sub> H <sub>17</sub> —C≡C—R ( <b>1d</b> )	72	( <b>5d/6d</b> : 75/25)
5	Cy—C≡C—R ( <b>1e</b> )	66	( <b>5e/6e</b> : 75/25)
6	<i>t</i> -Bu—C≡C—R ( <b>1f</b> )	59 <sup>d</sup>	( <b>5f/6f</b> : 0/100)

<sup>a</sup> Reaction conditions: 0.432 mmol of 1-alkyne, 5 mol % **2**, 100 mol % **3**, 100 mol % H<sub>2</sub>O, 5 mol % **4**, THF (0.22 mL), 110 °C (bath temp), 2 h. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by GC. <sup>d</sup> A mixture of enone and ketimine (1:9).

**Table 2.** Reaction of **1a** with Various Reaction Conditions<sup>a</sup>

entry	catalytic system	product	yield of $\alpha,\beta$ -enones (%) <sup>b</sup>
1	<b>2/3/H<sub>2</sub>O/4</b>	$\alpha,\beta$ -enones	82 <sup>c</sup>
2	<b>3/H<sub>2</sub>O/4</b>	none	0
3	<b>2/H<sub>2</sub>O/4</b>	enynes	0 <sup>d</sup>
4	<b>2/3/4</b>	$\alpha,\beta$ -enones	<1 <sup>e</sup>

<sup>a</sup> Reaction conditions: 0.432 mmol of **1a**, 5 mol % **2**, 100 mol % **3**, 100 mol % H<sub>2</sub>O, 5 mol % **4**, THF (0.22 mL), 110 °C (bath temp), 2 h. <sup>b</sup> GC yield. <sup>c</sup> Isolated yield. <sup>d</sup> Mixture of 65% 1-octyne and 35% enynes, only. <sup>e</sup> Only 80% 1-octyne remained.

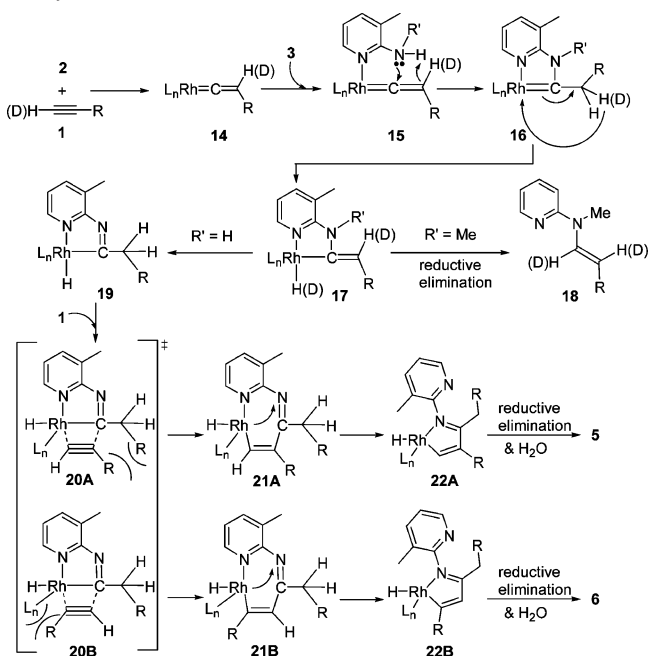
**Table 3.** Reaction of **1a** with Various Amines

Entry	amine	yield(%) <sup>a</sup> ( <b>5a/6a</b> )	Entry	amine	yield(%) <sup>a</sup> ( <b>5a/6a</b> )
1		82 (78/22)	5		51 (75/25)
2		65 (83/17)	6		0 <sup>c</sup>
3		50 (74/26)	7		0 <sup>c</sup>
4		<5 <sup>b</sup>	8		0 <sup>c</sup>

<sup>a</sup> Isolated yield. <sup>b</sup> GC yield. <sup>c</sup> Enynes only.

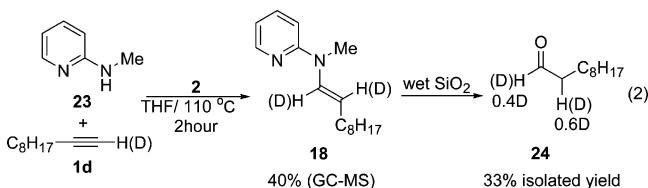
On the basis of the above observations, we speculate that the following mechanism for the hydrative dimerization of 1-alkyne is taking place, though other reaction routes cannot be excluded (Scheme 1).

Initially, a Rh(I)–vinylidene complex (**14**), a common intermediate for the transition-metal-mediated reaction of 1-alkynes, might be generated from 1-alkyne **1** and complex **2**.<sup>10</sup> A direct attack of **3** to **14** in **15** leads to the iminoacylrhodium(III)–hydride complex

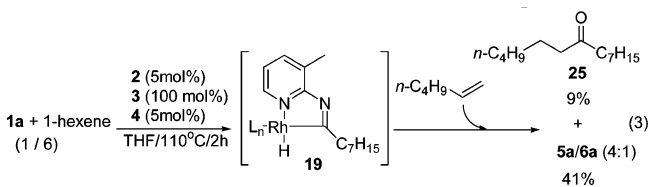
**Scheme 1.** Proposed Mechanism of the Hydrative Dimerization of 1-Alkyne

**19** through intermediates **16** and **17**.<sup>11</sup> Carbometalation of 1-alkynes **1** with **19** followed by the coordination-site slippage in **20A** and **20B** to **21A** and **21B**, respectively, gives the five-membered metallacycles, **22A** and **22B**, respectively.<sup>5</sup> Reductive elimination and subsequent hydrolysis of **22A** and **22B** furnishes  $\alpha,\beta$ -enones **5** and **6**, respectively.

The proposed elementary steps, such as **15**, **16**, and **17**, were supported by the reaction of 1-decyne (**1d**) with 2-*N*-methylaminopyridine (**23**) instead of **3**, giving enamine **18** and its hydrolysis product **24** (eq 2).<sup>12</sup> Furthermore, the deuterium experiment using D-substituted 1-decyne clearly exhibited the expected deuterium incorporation (the distribution ratio of the aldehyde proton and the  $\alpha$  proton was 0.4:0.6) in **24** via one  $\beta$ -hydrogen (or deuterium) migration in **16** to the rhodium center, giving **17** (see the Supporting Information for the <sup>2</sup>H NMR spectrum of **24**).<sup>13</sup>



Intermediate **19** was trapped with the excessive use of 1-hexene by employing a 1:6 ratio of **1a**/1-hexene to give 7-tetradecanone (**25**) in a 9% yield along with a 41% yield of **5a/6a** (4:1), which was determined by GC-MS, inferring that 1-alkyne is much more reactive than 1-alkene in this reaction (eq 3).



The carbometalation of 1-alkyne into **19** may explain the major formation of the branched  $\alpha,\beta$ -enone **5** over the linear enone **6** since

the observed ratio seems to be determined by the delicate balance between the steric interaction in **20A** and **20B** (Scheme 1). Thus, in the case of a tertiary 1-alkyne, such as **1f**, which would exert a maximum steric hindrance as in **20A**, the formation of the single isomer of the linear  $\alpha,\beta$ -enone **6f** could be explained.

In summary, the chelation-assisted catalytic system with Rh(I)/2-amino-3-picoline underwent an intermolecular hydrative dimerization reaction of 1-alkyne to give  $\alpha,\beta$ -enones. This transformation represents a new reaction pathway for the synthesis of  $\alpha,\beta$ -enones directly from 1-alkynes. More detailed mechanistic studies are underway.

**Acknowledgment.** This work was supported by the National Research Laboratory (NRL) (2000-N-NL-01-C-271) Program administered by the Ministry of Science and Technology and CBMH.

**Supporting Information Available:** Experimental details and characterization data for compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (6) (a) A typical procedure includes a screw-capped pressure vial (1 mL) charged with 0.432 mmol of **1a**, 5 mol % **2**, 100 mol % **3**, 5 mol % **4**, 100 mol % H<sub>2</sub>O, and 0.22 mL of THF as a solvent. The mixture was stirred for 2 h in an oil bath that was preheated to 110 °C. After purification by column chromatography, an 82% isolated yield (based on **1a**) of **5a** and **6a** was obtained in a 4:1 ratio (determined by GC). (b) Among various solvents (toluene, DMF, acetone, etc.), temperatures (80–150 °C), and quantities of reagents (**3**, **4**, and H<sub>2</sub>O) that were examined, the above reaction conditions gave the best results. (c) Without benzoic acid, the yield and the conversion rate were halved (36% GC yield).
- (7) (a) In all of the cases, the conversion rate of 1-alkyne was >98% (GC). Along with major  $\alpha,\beta$ -enones, small amounts of side products were also observed. For examples, such as enynes (<2%), vinylic ester of benzoic acid (<2%), and the (*Z*) form of  $\alpha,\beta$ -enone (<4%), which may originate from the isomerization reaction by the Rh-H species, see: Jun, C.-H.; Crabtree, R. H. *J. Organomet. Chem.* **1993**, *447*, 177–187. (b) For the Rh(I)-catalyzed vinyl ester formation of terminal alkynes, see: Bianchini, C.; Meli, A.; Peruzzini, M.; Zanobini, F.; Bruneau, C.; Dixneuf, P. H. *Organometallics* **1990**, *9*, 1155–1160. (c) The reaction with internal alkynes or functionalized alkynes, such as phenylacetylene, 6-hydroxyhexyne, and 5-cyanopentyne, was unsuccessful. (d) When the reaction of 1-alkyne with an internal alkyne, such as 1-hexyne with 4-octyne, was performed, a mixture of homocoupled products of 1-alkyne and cross-coupled products were obtained.
- (8) For examples of the Rh(I)-catalyzed dimerization of terminal alkynes, see: (a) Ohshita, J.; Furumori, K.; Matsuguchi, A.; Ishikawa, M. *J. Org. Chem.* **1990**, *55*, 3277–3280. (b) Schmit, H. J.; Singer, H. *J. Organomet. Chem.* **1978**, *153*, 165–179. (c) Boese, W. T.; Goldman, A. S. *Organometallics* **1991**, *10*, 782–786. (d) Schaefer, M.; Mahr, N.; Wolf, J.; Werner, H. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1315–1318. (e) Tanaka, K.; Shirasaka, K. *Org. Lett.* **2003**, *5*, 4697–4699.
- (9) When the further reaction experiment was performed with the addition of **3** to the reaction mixture in entry 3 (Table 2), a mixture of **5a** and **6a** was formed from the remaining **1a** without consuming preformed enynes.
- (10) (a) Bruneau, C.; Dixneuf, P. H. *Acc. Chem. Res.* **1999**, *32*, 311–323. (b) Bruce, M. I. *Chem. Rev.* **1991**, *91*, 197–257. (c) Weyerhausen, B.; Dötz, K. H. *Eur. J. Inorg. Chem.* **1999**, 1057–1066. (d) Menéndez, C.; Morales, D.; Pérez, J.; Riera, V.; Miguel, D. *Organometallics* **2001**, *20*, 2775–2781.
- (11) Rüba, E.; Hummel, A.; Mereiter, K.; Schmid, R.; Kirchner, K. *Organometallics* **2002**, *21*, 4955–4959.
- (12) In this case, the pyridine ring was also essential to obtain **18** and the anti-Markovnikov's hydration product of 1-decyne, **24**. For transition-metal-catalyzed anti-Markovnikov's hydration of 1-alkyne, see: (a) Grotjahn, D. B.; Incarvito, C. D.; Rheingold, A. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3884–3887. (b) Tokunaga, M.; Wakatsuki, Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 2867–2869. (c) Suzuki, T.; Tokunaga, M.; Wakatsuki, Y. *Org. Lett.* **2001**, *3*, 735–737. (d) Tokunaga, M.; Suzuki, T.; Koga, N.; Fukushima, T.; Horiuchi, A.; Wakatsuki, Y. *J. Am. Chem. Soc.* **2001**, *123*, 11917–11924 and references therein.
- (13) Because of the fast H/D exchange between water and 1-alkyne under typical reaction conditions, the hydrative dimerization using 1D-alkyne or D<sub>2</sub>O was not informative.

JA045789I