A Versatile New Method for the Synthesis of Cyclopentenones via an Unusual Rhodium-Catalyzed Intramolecular Trans Hydroacylation of an Alkyne

Ken Tanaka and Gregory C. Fu*

Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

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Because cyclopentenones serve both as key intermediates in the synthesis of a wide array of significant bioactive compounds (e.g., prostaglandins[1]) and as interesting natural products in their own right (e.g., jasmone[2] and pentenomycins[3]), the development of efficient methods for their construction constitutes an important ongoing challenge. Of the existing approaches to the synthesis of cyclopentenones, the Pauson−Khand reaction is perhaps the most well-known.[4] This powerful method does, however, suffer from certain deficiencies, including poor regioselectivity in the incorporation of the olefin and modest yield in reactions of unstrained or hindered olefins, as well as internal alkynes. As a consequence of these considerations, the intramolecular Pauson−Khand reaction, which furnishes bicyclic compounds, has been more widely applied than the intermolecular process.

The transition metal-catalyzed intramolecular hydroacylation of 4-alkenals has become a well-established method for producing cyclopentanones (eq 1).[5−9] In contrast, the corresponding reaction of 4-alkynals, which are readily available through 1,4-addition of alkynylmetals to α,β-unsaturated aldehydes, to generate cyclopentenones has not been described; in fact, Larock has noted that, under conditions in which 4-alkenals undergo $Rh(PAr_3)_3$-Cl-catalyzed cyclization, a 4-alkynal furnishes no product.[6b] One potential difficulty in achieving intramolecular hydroacylations

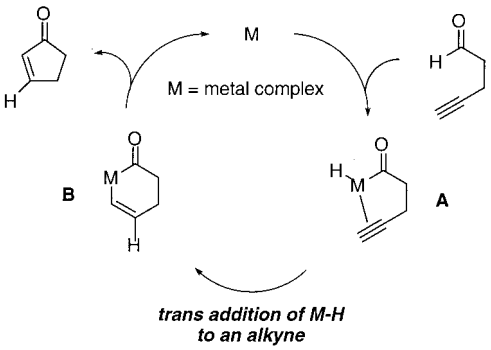
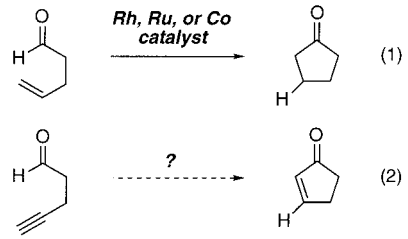
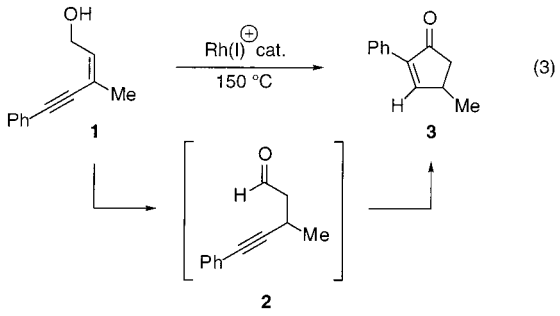


Figure 1. A possible pathway for metal-catalyzed intramolecular hydroacylations of 4-alkynals.

of 4-alkynals is the need, if the process follows a pathway analogous to the reactions of 4-alkenals, for a trans addition of a metal hydride to an alkyne (Figure 1).[10]



During a recent investigation of rhodium-catalyzed isomerizations of allylic alcohols to aldehydes,[11] while attempting to convert allylic alcohol **1** to 4-alkynal **2**, we obtained a small amount of cyclopentenone **3**, presumably via **2** (eq 3). In view of the lack of precedent for such an intramolecular hydroacylation, we decided to pursue the development of this unanticipated side reaction into a versatile new route to cyclopentenones.



Among the phosphines (e.g., binap, dppf, and dcpe) and solvents (e.g., CH_2Cl_2, THF, benzene, and CH_3NO_2) that we have examined, the combination of Rh/dppe and acetone has proved to be the most effective. Under these conditions, we can achieve the intramolecular hydroacylation of a broad range of 4-alkynals to produce cyclopentenones in good yield (eq 4).

(1) For reviews, see: (a) Noyori, R.; Suzuki, M. *Science* **1993**, *259*, 44−45. (b) Straus, D. S.; Glass, C. K. *Med. Res. Rev.* **2001**, *21*, 185−210. (c) Corey, E. J. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 455−465.

(2) For leading references to jasmone and its derivatives, see: (a) Dobbs, D. A.; Vanhessche, K. P. M.; Brazi, E.; Rautenstrauch, V.; Lenoir, J.-Y.; Genêt, J.-P.; Wiles, J.; Bergens, S. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1992−1995. (b) Fràter, G.; Bajgrowicz, J. A.; Kraft, P. *Tetrahedron* **1998**, *54*, 7633−7703.

(3) For leading references, see: Seepersaud, M.; Al-Abed, Y. *Tetrahedron Lett.* **2000**, *41*, 4291−4293.

(4) For reviews, see: (a) Schore, N. E. *Org. React.* **1991**, *40*, 1−90. (b) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263−3283. (c) Chung, Y. K. *Coord. Chem. Rev.* **1999**, *188*, 297−341.

(5) For examples of intramolecular hydroacylations of 4-alkenals in the presence of stoichiometric $Rh(PPh_3)_3Cl$, see: Sakai, K.; Ide, J.; Oda, O.; Nakamura, N. *Tetrahedron Lett.* **1972**, 1287−1290.

(6) For examples of intramolecular hydroacylations of 4-alkenals in the presence of catalytic amounts of rhodium complexes, see: (a) Lochow, C. F.; Miller, R. G. *J. Am. Chem. Soc.* **1976**, *98*, 1281−1283. (b) Larock, R. C.; Oertle, K.; Potter, G. F. *J. Am. Chem. Soc.* **1980**, *102*, 190−197. (c) Sakai, K.; Ishiguro, Y.; Funakoshi, K.; Ueno, K.; Suemune, H. *Tetrahedron Lett.* **1984**, *25*, 961−964. (d) Fairlie, D. P.; Bosnich, B. *Organometallics* **1988**, *7*, 936−945.

(7) For examples of catalytic enantioselective intramolecular hydroacylations of 4-alkenals, see: (a) James, B. R.; Young, C. G. *J. Chem. Soc., Chem. Commun.* **1983**, 1215−1216. James, B. R.; Young, C. G. *J. Organomet. Chem.* **1985**, *285*, 321−332. (b) Taura, Y.; Tanaka, M.; Funakoshi, K.; Sakai, K. *Tetrahedron Lett.* **1989**, *30*, 6349−6352. Tanaka, M.; Imai, M.; Fujio, M.; Sakamoto, E.; Takahashi, M.; Eto-Kato, Y.; Wu, X. M.; Funakoshi, K.; Sakai, K.; Suemune, H. *J. Org. Chem.* **2000**, *65*, 5806−5816. (c) Barnhart R. W.; Wang, X.; Noheda, P.; Bergens, S. H.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1994**, *116*, 1821−1830. Bosnich, B. *Acc. Chem. Res.* **1998**, *31*, 667−674 and references therein.

(8) For examples of intramolecular hydroacylations of 4-alkenals in the presence of catalytic amounts of ruthenium complexes, see: Eilbracht, P.; Gersmeier, A.; Lennartz, D.; Huber, T. *Synthesis* **1995**, 330−334.

(9) For examples of intramolecular hydroacylations of 4-alkenals in the presence of catalytic amounts of cobalt complexes, see: (a) Vinogradov, M. G.; Tuzikov, A. B.; Nikishin, G. I.; Shelimov, B. N.; Kazansky, V. B. *J. Organomet. Chem.* **1988**, *348*, 123−134. (b) Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **1997**, *119*, 3165−3166.

(10) While attempting to decarbonylate an aldehyde with $RhCl(PPh_3)_3$, Nicolaou observed a novel intramolecular hydroacylation of a 5-alkynal to generate a cyclohexenone (78% yield based on 50% conversion). To the best of our knowledge, this single example (a stoichiometric process: 2.5 equiv of $RhCl(PPh_3)_3$ were used, relative to isolated cyclohexenone) is the only report to date of an intramolecular hydroacylation of an acetylenic aldehyde. See: Nicolaou, K. C.; Gross, J. L.; Kerr, M. A. *J. Heterocycl. Chem.* **1996**, *33*, 735−746.

(11) Tanaka, K.; Qiao, S.; Tobisu, M.; Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 9870−9871.

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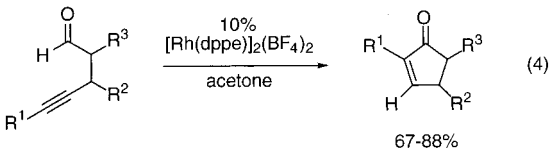
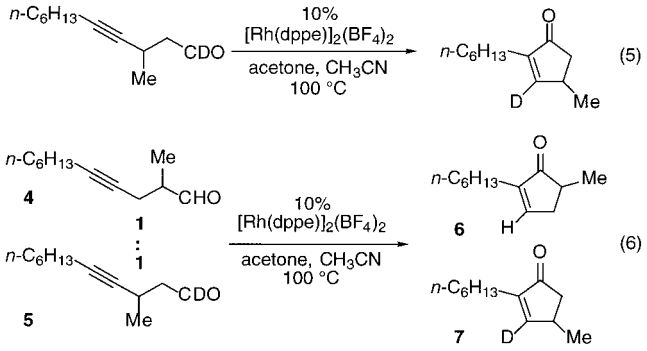


(4)

As illustrated in Table 1, a wide array of 4-alkynals cleanly cyclize upon treatment with catalytic $[Rh(dppe)]_2(BF_4)_2$.[12] 5-Alkyl (entries 1−3)-, 5-aryl (entries 4−5)-, 5-alkenyl (entry 6)-, and 5-alkynyl-substituted (entry 7) aldehydes are suitable substrates for this process.[13] The intramolecular hydroacylation proceeds in the presence of substitution in the β (entries 2, 4, 5, and 6) and the α (entry 3) positions. The effective cyclization of the potentially labile tertiary propargylic ether depicted in entry 5 is worthy of note.

We have begun to explore the mechanism of this intriguing rhodium-catalyzed hydroacylation process. Our working hypothesis is that the reaction follows the pathway outlined in Figure 1.[14] First, in analogy with the well-studied cyclization of 4-alkenals, oxidative addition of the aldehyde C−H bond to Rh(I) furnishes a Rh(III) acyl hydride (**A**).[15] Next, in an unusual step, the rhodium hydride adds in a trans fashion to the coordinated alkyne to generate a six-membered rhodium metalacyclohexene (**A**);[16] in contrast, the intramolecular hydroacylation of *alkenes* proceeds via a conventional cis addition to the carbon−carbon multiple bond.[15,17] Finally, reductive elimination occurs, producing the cyclopentenone and regenerating the Rh(I) catalyst.

Our preliminary mechanistic data are consistent with this pathway. For example, we have demonstrated that the aldehyde hydrogen (deuterium) of the starting material is indeed transferred cleanly to the β position of the cyclopentenone (eq 5). Furthermore, through a crossover experiment, we have established that this transfer proceeds intramolecularly; thus, treatment of a 1:1 mixture of 2-methylundec-4-ynal (**4**) and 1-deuterio-3-methylundec-4-ynal (**5**) with $[Rh(dppe)]_2(BF_4)_2$ furnishes 2-*n*-hexyl-5-methyl-2-cyclopentenone (**6**) and 3-deuterio-2-*n*-hexyl-4-methyl-2-cyclopentenone (**7**) exclusively (eq 6).[18]

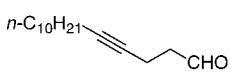
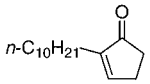
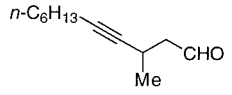
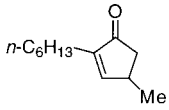
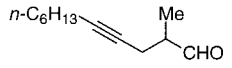
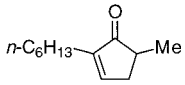
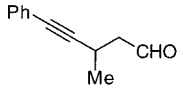
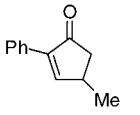
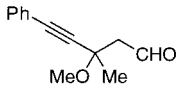
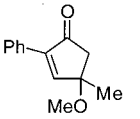
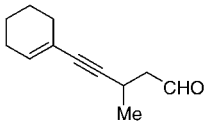
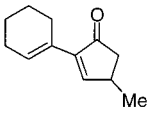
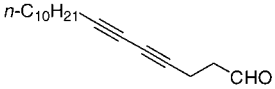
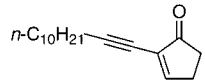


(5)

(6)

In conclusion, we have demonstrated that the rhodium-catalyzed intramolecular hydroacylation of 4-alkynals represents a versatile new catalytic method for the synthesis of cyclopentenones. This method, which appears to proceed via an unusual trans addition of a rhodium hydride to an alkyne, compares favorably with other approaches to the construction of this important family of compounds. Additional synthetic and mechanistic investigations of this ring-forming process are underway.

Table 1. $[Rh(dppe)]_2(BF_4)_2$-Catalyzed Synthesis of Cyclopentenones via the Intramolecular Hydroacylation of 4-Alkynals

Entry	Substrate	Product	Yield (%)[a]
1[b]			67
2[b]			75
3[b]			67
4[c]			88
5[c]			75
6[c]			84
7[d]			76

[a] Isolated yields, average of two runs. [b] CH_3CN (10 equiv) was added; 100 °C. [c] Room temperature. [d] 100 °C.

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Supporting Information Available: Experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Sample experimental (Table 1, entry 4): In the air, $[Rh(dppe)]_2(BF_4)_2$ (34.1 mg, 0.0581 mmol) was placed into a Schlenk tube, which was then filled with argon. Under a positive pressure of argon, 3-methyl-5-phenylpent-4-ynal (100 mg, 0.581 mmol) and acetone (5 mL) were added. The Schlenk tube was closed, and the mixture was stirred at room temperature for 48 h. Then, CH_3CN (1 mL) was added, solvents were removed, and the reaction mixture was purified by flash chromatography (pentane:Et_2O = 3:1), which furnished 4-methyl-2-phenylcyclopent-2-enone (88 mg, 88%) as a colorless oil.

(13) Notes: (a) For the cyclization of 4-alkynals that bear an alkyl group in the 5-position, the addition of CH_3CN (10 equiv) leads to a more effective reaction (entries 1−3). (b) Under the same conditions, cyclization of a 4-alkynal that lacks a 5-substituent does not proceed cleanly.

(14) For the sake of simplicity, the elementary steps are drawn as irreversible.

(15) For mechanistic studies of the rhodium-catalyzed cyclization of 4-alkenals to cyclopentanones, see: (a) Campbell, R. E., Jr.; Miller, R. G. *J. Organomet. Chem.* **1980**, *186*, C27−C31. Campbell, R. E., Jr.; Lochow, C. F.; Vora, K. P.; Miller, R. G. *J. Am. Chem. Soc.* **1980**, *102*, 5824−5830. (b) Fairlie, D. P.; Bosnich, B. *Organometallics* **1988**, *7*, 946−954.

(16) The rhodium-catalyzed *inter*molecular hydroacylation of alkynes with aldehydes proceeds via cis addition of the rhodium hydride to the alkyne. For example, see: (a) Lee, H.; Jun, C.-H. *Bull. Korean Chem. Soc.* **1995**, *16*, 1135−1138. (b) Kokubo, K.; Matsumasa, K.; Miura, M.; Nomura, M. *J. Org. Chem.* **1997**, *62*, 4564−4565. (c) Kokubo, K.; Matsumasa, K.; Nishinaka, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 303−311.

(17) For the isolation of a *cis*-hydridopent-4-enoylrhodium(III) complex, see: Milstein, D. *J. Chem. Soc., Chem. Commun.* **1982**, 1357−1358.

(18) In a preliminary experiment, we have measured $k_H/k_D \approx 1.5$ (100 °C) for the $[Rh(dppe)]_2(BF_4)_2$-catalyzed intramolecular hydroacylation of 3-methylundec-4-ynal (1-*H*- vs 1-*D*-).