ORGANIC LETTERS

2002
Vol. 4, No. 6
933−935

Rhodium-Catalyzed Synthesis of Cyclohexenones via a Novel [4 + 2] Annulation

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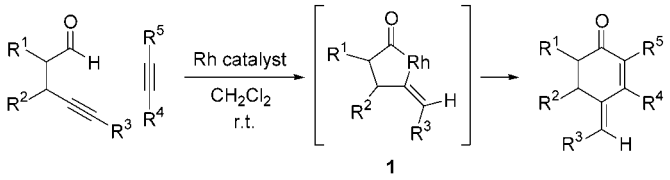
Received December 29, 2001

ABSTRACT



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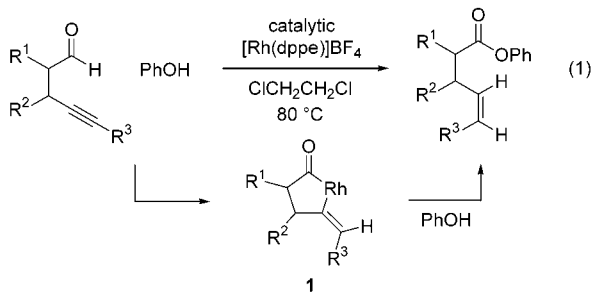
In the presence of a rhodium catalyst, 4-alkynals react with alkynes to furnish cyclohexenones, presumably via metalacycle 1; as far as we are aware, this is the first example of the generation of this class of compounds through such a transformation. In view of the easy accessibility of 4-alkynals (alkynylmetal + α,β-unsaturated aldehyde) and alkynes, this [4 + 2] cyclization constitutes an interesting new approach to functionalized cyclohexenones.

We have recently demonstrated that treatment of a 4-alkynal with phenol in the presence of a rhodium catalyst leads to an interesting reduction−oxidation reaction (eq 1).[1] We believe that rhodium metalacycle **1**, formed via intramolecular hydroacylation of the alkyne, is a key intermediate in this process.



(1)

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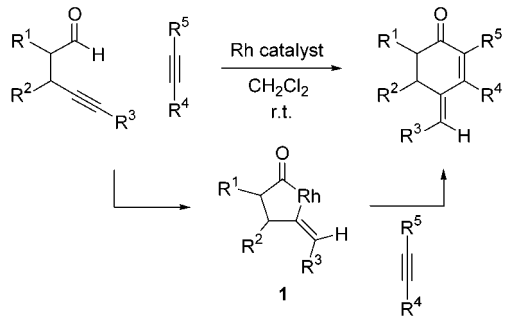
Obviously, one can envision intercepting metalacycle **1** with a number of compounds, in addition to phenol. For example, metalacycles serve as intermediates in a wide range of transition metal-catalyzed cycloadditions, a very powerful family of carbon−carbon bond-forming processes, reacting with species such as alkenes and alkynes.[2,3] We are not aware, however, of any precedent for a metalacycle such as **1** participating in a cycloaddition. In this Letter, we establish that rhodium complexes catalyze a novel [4 + 2] annulation of 4-alkynals with alkynes to generate cyclohexenones, presumably via metalacycle **1** (eq 2).[4]



(2)

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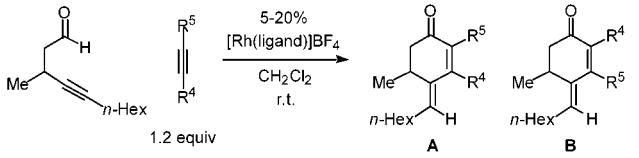
To minimize the likelihood of self-coupling of the 4-alkynal, we initially focused our attention on cycloadditions with terminal alkynes. We were pleased to discover that, with

(1) Tanaka, K.; Fu, G. C. Submitted for publication.

10.1021/ol017308v CCC: $22.00
Published on Web 02/16/2002

[Rh(dppe)]BF_4 as the catalyst, 4-alkynals do indeed react with phenylacetylene to produce the desired cyclohexenone (Table 1, entry 1). With respect to regiochemistry, the phenyl

Table 1. Rhodium-Catalyzed Synthesis of Cyclohexenones via [4 + 2] Annulation of 4-Alkynals and Alkynes: Variation of the Alkyne



entry	R^4	R^5	ligand	% yield[a] (**A**:**B**)
1	H	Ph	dppe	48 (3:1)
2	H	Ph	dppf	53 (1:7)
3	H	*n*-Dec	dppe	52 (4:1)
4	H	*n*-Dec	dppf	42 (1:6)
5	CO_2Et	Ph	dppe	79 (6:1)
6	COMe	Ph	dppe	80 (2:1)

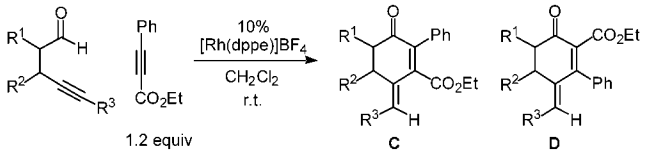
[a] All yields are isolated yields (average of two runs).

group of the alkyne is preferentially incorporated α to the carbonyl when [Rh(dppe)]BF_4 is the catalyst. Interestingly, simply by changing the phosphine ligand from dppe to dppf, we can generate the opposite regioisomer with good selectivity (entry 1 vs entry 2). This complementarity also holds for alkyl-substituted terminal alkynes (entry 3 vs entry 4).

Clearly, being able to react 4-alkynals not only with terminal but also with internal alkynes would significantly broaden the scope of this annulation method. We have determined that, in the presence of electron-poor disubstituted alkynes, [Rh(dppe)]BF_4-catalyzed [4 + 2] cycloaddition cleanly affords the desired cyclohexenones (Table 1, entries 5 and 6). For all of these annulations, a single olefin isomer (*E*) is produced.[5−8]

We have also explored the scope of this process with respect to the 4-alkynal (Table 2). The reaction tolerates a

Table 2. Rhodium-Catalyzed Synthesis of Cyclohexenones via [4 + 2] Annulation of 4-Alkynals and Alkynes: Variation of the 4-Alkynal



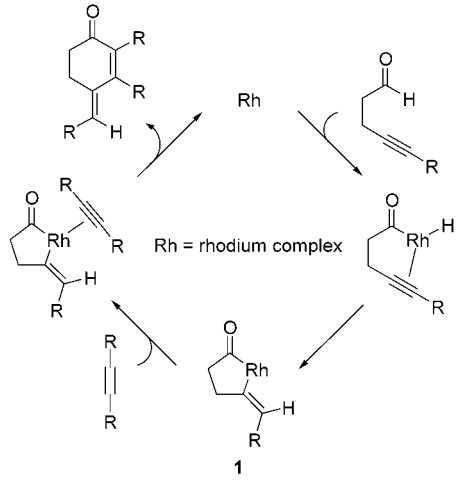
entry	R^1	R^2	R^3	% yield[a] (**C**:**D**)
1	H	Me	*n*-Hex	79 (6:1)
2	Me	H	*n*-Hex	76 (7:1)
3[b]	H	H	*n*-Dec	65 (6:1)
4	H	Me	1-cyclohexenyl	64 (5:1)
5	H	Ph	$SiMe_3$	99 (7:1)

[a] All yields are isolated yields (average of two runs). [b] 20% catalyst was used.

range of substitution patterns at the 2 and 3 positions (R^1 and R^2), as well as alkyl (entries 1−3), alkenyl (entry 4), and silyl (entry 5) substituents at the remote position of the alkyne (R^3).

Our working hypothesis for the mechanism of this novel annulation is illustrated in Scheme 1.[9,10] We believe that the

Scheme 1. Possible Mechanism for the Rhodium-Catalyzed Synthesis of Cyclohexenones via [4 + 2] Annulation of 4-Alkynals and Alkynes



rhodium catalyst oxidatively inserts into the aldehyde C−H bond, affording a rhodium acyl hydride. Cis addition of the

(2) (a) For a review of transition metal-catalyzed carbocyclizations, see: Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635−662. (b) For a review of transition metal-mediated cycloaddition reactions, see: Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49−92. (c) For a review of transition metal-mediated cycloaddition reactions of alkynes, see: Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081−1119.

(3) For a recent example of a rhodium-catalyzed intermolecular cycloaddition process that involves an alkyne, see: Wender, P. A.; Barzilay, C. M.; Dyckman, A. J. *J. Am. Chem. Soc.* **2001**, *123*, 179−180.

(4) For the synthesis of quinones via the reaction of maleoylcobalt complexes with alkynes, see: Iyer, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1987**, *109*, 2759−2770, and references therein.

(5) **Typical experimental procedure** (Table 1, entry 5): In the air, [Rh(dppe)]BF_4 (16 mg, 0.027 mmol) was placed into a Schlenk tube, which was then flushed with argon. Under a positive pressure of argon, a solution of ethyl phenylpropiolate (55 μL, 0.33 mmol) and 3-methylundec-4-ynal (50.0 mg, 0.277 mmol) in CH_2Cl_2 (2.0 mL) was added by pipet. The Schlenk tube was closed, and the mixture was stirred at room temperature for 24 h. The solution was then concentrated and purified by preparative TLC (hexanes:EtOAc = 10:1), which furnished (*E*)-6-heptylidene-5-methyl-3-oxo-2-phenylcyclohex-1-enecarboxylic acid ethyl ester (65.2 mg, 0.184 mmol, 66%) and (*E*)-3-heptylidene-4-methyl-6-oxo-2-phenylcyclohex-1-enecarboxylic acid ethyl ester (9.3 mg, 0.026 mmol, 10%).

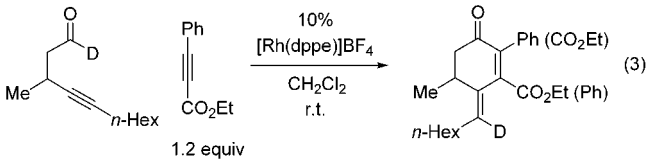
(6) (a) For all of these annulations, the regioisomers have been separated by chromatography. (b) Use of a large excess of the alkyne leads to a very slow reaction.

(7) When pentadec-4-ynal is treated with [Rh(dppe)]BF_4 in the absence of a second alkyne, self-coupling to generate a cyclohexenone proceeds in 80% yield (1.7:1 mixture of regioisomers).

(8) For reactions catalyzed by [Rh(dppf)]BF_4, the predominant side products are cyclopentenones that result from intramolecular hydroacylation of the 4-alkynal (see: Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 11492−11493.). For reactions catalyzed by [Rh(dppe)]BF_4, several side products are generated, including self-coupling products (see ref 7) and compounds formed through cyclotrimerization of the alkyne. For both catalysts, no isomers of **A**/**B** or **C**/**D** could be detected by ^1H NMR.

rhodium hydride to the metal-bound alkyne then provides the five-membered rhodium metalacycle (**1**). Complexation of the second alkyne, followed by β-migratory insertion and reductive elimination, furnishes the cyclohexenone and regenerates the catalyst.

Consistent with this pathway, reaction of a deuterium-labeled aldehyde leads to quantitative, stereospecific incorporation of deuterium in the δ position of the cyclohexenone (eq 3).



(3)

In conclusion, we have developed a novel rhodium(I)-catalyzed intermolecular [4 + 2] cycloaddition of 4-alkynals with alkynes to form cyclohexenones; to the best of our knowledge, this is the first example of the synthesis of this family of compounds through such an annulation process. Given the ready availability of 4-alkynals (1,4-addition of an alkynylmetal to an α,β-unsaturated aldehyde) and of alkynes, we believe that this method represents an attractive new route to highly functionalized cyclohexenones.

Acknowledgment. We thank Dr. Jeffrey H. Simpson for help with NMR experiments and Ivory D. Hills for help with preparation of the manuscript. Support has been provided by Bristol-Myers Squibb, Mitsubishi Chemical (postdoctoral fellowship to K.T.), Novartis, and Pfizer. Funding for the MIT Department of Chemistry Instrumentation Facility has been provided in part by NSF Grants CHE-9808061 and NSF DBI-9729592.

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

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(9) In Scheme 1, for the sake of simplicity, the elementary steps are drawn as irreversible.

(10) 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.