

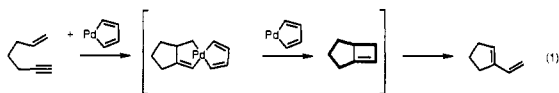
A Pd-Catalyzed [2 + 2] Cycloaddition. Mechanism of a Pd-Catalyzed Enyne Metathesis

Barry M. Trost,^{*,†} Makoto Yanai,[†] and Karst Hoogsteen[‡]

Department of Chemistry, Stanford University
Stanford, California 94305-5080
Merck Research Laboratories, P.O. Box 2000
Rahway, New Jersey 07065-0900

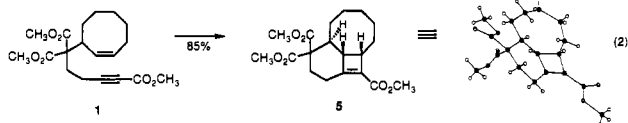
Received January 4, 1993

While the suggestion that the transition-metal-catalyzed olefin metathesis might proceed by a [2 + 2] cycloaddition followed by cycloreversion was proven incorrect,¹ the intriguing prospect for transition-metal-catalyzed [2 + 2] cycloadditions remains.² Our report of a Pd-catalyzed metathesis of 1,6-enynes³ led us to suggest that such a cycloaddition indeed occurred but that the intermediate cyclobutene was highly strained because it was the equivalent of a *trans*-cycloheptene (see emboldened structure, eq 1), a species



not known to exist at ambient temperature.⁴ On the other hand, the stability of *trans*-cyclooctene at ambient temperature⁵ suggests that increasing the tether length of the enyne could lead to an isolable cyclobutene if the pathway of eq 1 is correct. In this communication, we report the success of this goal.

The cyclooctene substrate **1**,⁶ available in straightforward fashion from 3-bromocyclooctene and dimethyl 4-(trimethylsilyl)-3-butynylmalonate in three steps, was explored as our test substrate. Heating a mixture of 4% TCPCH^{FB} (**2**), 4% tri-*o*-tolylphosphite (**3**), bis(heptafluorobutyl) acetylenedicarboxylate (**4**), and enyne **1** in dichloroethane at 80 °C gave an 85% yield of a crystalline (mp 98.5–99.5 °C) isomer (**MS** and combustion analysis) lacking vinylic protons but bearing two sp² carbons (δ 162.3, 129.0) (eq 2). X-ray crystallography of **5**⁶ confirmed the



[†] Stanford University.

[‡] Merck Research Laboratories.

(1) For general references on metathesis, see: (a) Dragutan, V.; Balaban, H. T.; Dimonic, M. *Olefin Metathesis and Ring-opening Polymerization of Cyclo-Olefins*; Wiley: New York, 1985. (b) Ivin, K. J. *Olefin Metathesis*; Academic Press: London, 1983. (c) Nugent, W. A.; Mayer, J. M. *Metal-Ligand Multiple Bonds*; Wiley: New York, 1988; Chapter 7.

(2) For a leading reference on metal-catalyzed dimerization of acetylenes to cyclobutadienes, see: Ville, G. A.; Vollhardt, K. P. C.; Winter, M. J. *Organometallics* **1984**, *3*, 1177. For reaction with strained olefins and activated acetylenes, see: Mitsudo, T.; Hori, Y.; Watanabe, Y. *J. Organomet. Chem.* **1987**, *334*, 157. Mitsudo, T.; Kokuryo, K.; Shinsugi, T.; Nakagawa, Y.; Watanabe, Y.; Takegami, Y. *J. Org. Chem.* **1979**, *44*, 4492 and references cited therein. Also see: Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987; p 816.

(3) (a) Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 1636. (b) Trost, B. M.; Trost, M. K. *J. Am. Chem. Soc.* **1991**, *113*, 1850.

(4) Corey, E. J.; Carey, F. A.; Winter, R. A. E. *J. Am. Chem. Soc.* **1965**, *87*, 934. For a review, see: Liebman, J. F.; Greenberg, A. *Chem. Rev.* **1976**, *76*, 311.

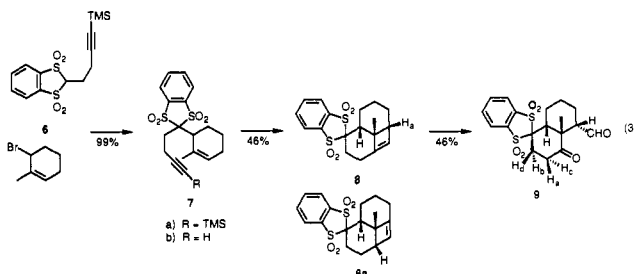
(5) Cope, A. C.; Pike, R. A.; Spencer, C. R. *J. Am. Chem. Soc.* **1953**, *75*, 3212.

(6) This compound has been fully characterized spectroscopically, and its elemental composition has been established by high-resolution mass spectroscopy and/or combustion analysis.

(7) TCPCH^{FB} = tetrakis((heptafluorobutoxy)carbonyl)palladacyclopentadiene.

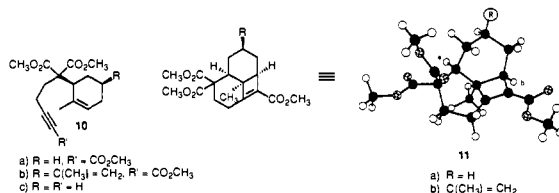
cyclobutene structure and indicated an unexpected stereochemical result—a *trans*-8,6 ring fusion!

In conjunction with a program directed toward the synthesis of taxanes, we were particularly interested in cyclohexene substrates. Alkylation of the phenylsulfonyl analog of **6** did not proceed, whereas the sterically less bulky 1,3-benzodithiole tetraoxide **6**,⁸ gave a nearly quantitative yield of the substrate **7b** (NaH, DMF) after desilylation (K₂CO₃, CH₃OH, CHCl₃, eq 3). Under the above conditions, cyclization gave a crystalline

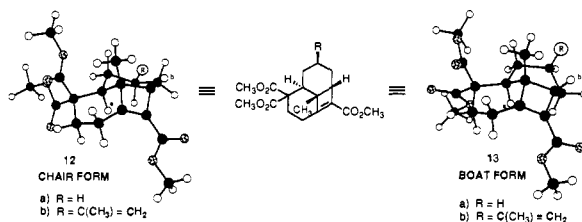


(mp 225 °C) cyclobutene isomer (**8**)⁶ for which the position of the double bond was confirmed by ozonolysis to the keto aldehyde **9**. COSY NMR experiments revealed a closed coupled system for H_a–H_d in **9** at δ 3.36 (ddd, $J = 15.8, 13.5, 7.1$ Hz, H_a), 2.93 (ddd, $J = 15.4, 13.6, 6.1$ Hz, H_b), 2.44 (ddd, $J = 15.9, 5.9, 2.1$ Hz, H_c), and 2.27 (ddt, $J = 15.7, 7.1, 2.1$ Hz, H_d) with additional long-range coupling of the latter proton to the bridgehead proton—a feature that establishes the double bond of the precursor **8** as depicted rather than the isomeric cyclobutene **8a** which involves olefin isomerization.⁹ The allylic cyclobutene proton H_a of **8** (δ 3.08) shows coupling to the adjacent methylene group of $J = 12.1, 4.4$ Hz indicative of this proton being pseudoaxial, consistent with *cis*–*cis* ring fusions, in contrast to the stereochemistry observed in the cyclooctenyl case (vide infra).

Surprisingly, replacement of the *gem* sulfonyl substituents with *gem* diester groups as in **10c**⁶ led to only very low conversion under standard conditions. However, introduction of an electron-



withdrawing group on the terminal acetylenic carbon of **10c** (LDA, ClCO₂CH₃, quantitative) gave a substrate (**10a**) which reacted under the standard conditions to provide a 52% yield of the cycloisomer **11** or **12** (or low-energy boat conformer **13**) corresponding to a *cis*- or *trans*-fused 6,6 ring fusion, respectively.



Molecular modeling reveals that H_a has dihedral angles of 56° and 175° in **11**, 75° and 165° in **12**, and 53° and 170° in **13** with the hydrogens of the adjacent methylene group and that H_b has dihedral angles of 2° and 120° in **11**, of 34° and 80° in **12**, and

(8) Cf.: Kundig, E. P.; Cunningham, A. F. Jr. *Tetrahedron* **1988**, *44*, 6855.

(9) Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc.* **1987**, *109*, 4753.

32° and 149° in **13** with the hydrogens of its adjacent methylene group. Using the normal Karplus relationships, the observed coupling constants for H_a (δ 2.65) of 4.6 and 10.2 Hz and for H_b (δ 2.84) of 11.5 and 5.4 Hz correspond more closely to those expected for the dihedral angles of **11** than of either **12** or **13**, in support of the assignment of the *cis*-6,6 ring fusion as depicted in **11a**.⁶ COSY and hetero-COSY nmr experiments provided additional support for the structural assignment.

While the cyclization of **10a** may proceed through a chair conformation possessing the acetylenic side chain in either an equatorial or an axial orientation, the stereochemical assignment of the product **11a** suggested that cyclization may have proceeded from the conformer possessing an equatorial side chain. To verify this conclusion, we examined the conformationally more rigid substrate **10b**.⁶ Cyclization proceeded under the same conditions as above, requiring 8 days to give a 75% yield of **11b**,⁶ whose COSY ¹H NMR spectrum revealed the same proton relationships as for **11a**.

The isolation of the cyclobutenes in the reactions of 1,7-enynes clearly supports their intervention in the metathesis of 1,6-enynes. While we lack direct evidence for the palladacyclopentene intermediate at this juncture,⁹ its involvement provides the most logical pathway for the formation of the cyclobutenes. Both conformational and electronic effects contribute to the success

of the reaction, and it appears as if one of these effects may compensate for inadequacies in the other. A most interesting contrast occurs in the stereochemical course of this reaction in comparing the cyclooctene and cyclohexene substrates. In the former, the acetylene approaches the olefin on the face opposite that to which the tether is attached; whereas, in the latter, the approach is on the same face as the tether—results that parallel our observations with the intramolecular Pd-catalyzed TMM cycloadditions to cyclooctenyl versus cyclohexenyl acceptors.¹⁰ Conformational analyses analogous to those presented for the cycloaddition reactions nicely account for this dichotomy.

Acknowledgment. We thank the National Science Foundation and the General Medical Sciences Institute of the National Institutes of Health for their generous support of our programs and the Nisshin Flour Milling Co., Ltd. for their support of M.Y. Mass spectra were provided by the Mass Spectrometry Facility, University of California—San Francisco, supported by the NIH Division of Research Resources.

Supplementary Material Available: Characterization data for **1**, **5**, **7b**, **8**, **9**, **10a**, **10b**, **11a**, and **11b** (3 pages). Ordering information is given on any current masthead.

(10) Trost, B. M.; Grese, T. A. *J. Am. Chem. Soc.* **1991**, *113*, 7363.