J. Am. Chem. Soc. **1994,** *116,* 2183–2184

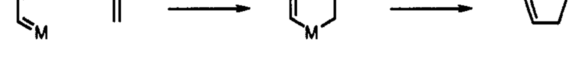
A Cycloaddition Approach to Cyclopentenes via Metalladienes as 4π Partners

Barry M. Trost* and A. Stephen K. Hashmi

Department of Chemistry, Stanford University
Stanford, California 94305-5080

Received November 12, 1993

Cycloaddition reactions represent almost the ideal in terms of synthetic efficiency: they are highly atom economical and frequently are selective. Among such reactions, the Diels–Alder reaction stands out. One of the strengths of this process has been the ability to replace carbon by other elements, notably heteroatoms like nitrogen and oxygen, in both reaction partners, opening opportunities for synthesizing heterocycles.[1] We wondered whether a transition metal might function in such a role since the resultant "heterocycle" could undergo further reactions, such as reductive elimination, to generate ring systems not available by direct Diels–Alder reactions as illustrated in eq 1.

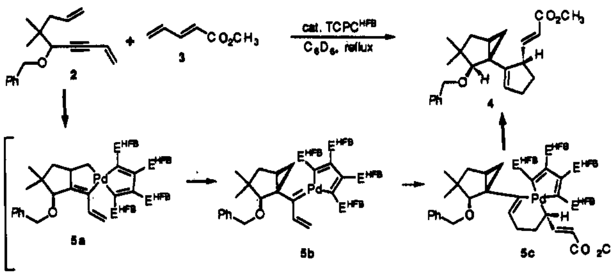


(1)

1

Although vinylalkylidene complexes like **1** are known, their participation in a process like that illustrated in eq 1 is not.[2,3] We report that such a process may be a general approach for the construction of unusual cyclopentenoids.

The indication that such a process may occur came as a result of our probing the mechanism of the enyne metathesis with tetrakis(methoxycarbonyl)palladacyclopentadiene (TCPC)[4] and its related trifluoroethyl and heptafluorobutyl esters ($\mathrm{TCPC}^{\mathrm{TFE}}$ and $\mathrm{TCPC}^{\mathrm{HFB}}$).[5,6] Heating a 2.5:1 mixture of ynediene **2** and methyl pentadienoate (**3**) with 2.5 mol % of $\mathrm{TCPC}^{\mathrm{HFB}}$ in C_6D_6 at reflux gave a 90% yield of a single cycloadduct **4**[7] as a 5:1 mixture diastereomeric at the carbon bearing oxygen (eq 2, major adduct depicted). The assignment of the relative stereochemistry of the acrylate and the cyclopropane arises by analogy to the stereochemistry of a cycloadduct whose stereochemistry was established by X-ray crystallography.[8] The stereochemistry at the carbon bearing oxygen derives from the absence of an NOE to the cyclopropyl methylene protons in the major adduct but its presence in the minor one. The reaction is best envisioned as involving interception of the vinylalkylidene complex **5b** formed via a presumed metallavinylcyclopentene to metallavinylcyclopropane rearrangement of the initial adduct **5a** by the pentadienoate to give **5c** followed by reductive elimination to product as shown in eq 2.[6]



(2)

Simple olefins, even those "activated" by conjugation to either an aryl ring or a carbonyl group, fail to intercept the intermediate. On the other hand, a wide variety of conjugated systems illustrated in Scheme 1 successfully serve as a trap. Several points are to be noted. $\mathrm{TCPC}^{\mathrm{TFE}}$ generally appears to be a more effective catalyst than $\mathrm{TCPC}^{\mathrm{HFB}}$. For example, the yield of **8** (X = H)[7] is 61% with $\mathrm{TCPC}^{\mathrm{HFB}}$ compared to 71% with $\mathrm{TCPC}^{\mathrm{TFE}}$. Electron-withdrawing groups enhance the effectiveness of the trap (cf. formation of **6** to **9**[7]). A dramatic illustration is the comparison between 1-ethynylcyclohexene and 1-((methoxycarbonyl)ethynyl)cyclohexene wherein the former fails to react but the latter gives cycloadduct **12**,[7] albeit in modest yield. In all cases, the *sterically more hindered* unsaturation preferentially reacts. For acceptors bearing electron-withdrawing groups, the unsaturation distal to that group preferentially reacts. Nevertheless, steric hindrance on the reactive unsaturation does impede reaction. Thus, whereas adducts **7**[7], **8**,[7] and **9**[7] form with high efficiency, methyl 5-methylhexadienoate fails to intercept the reactive intermediate: only self-trapping product of the enyne was observed.[6] The chemoselectivity of the reaction is quite high, as illustrated by the compatibility of free hydroxyl groups, aldehydes, esters, acetylenes, etc.

With a reactive trap like methyl pentadienoate, a 1:1 ratio of substrate to acceptor suffices to completely suppress dimerization of the enyne. The reaction has been performed with as little as 0.1 mol % of catalyst, but a lower limit has not yet been established. The reaction directly scales up; thus, adduct **7** was obtained in 75% yield on a 10-mmol scale using a 1:1 ratio of reactants and 1 M concentration.

Substituents on the allyl fragment of the ynediene are well tolerated. Thus the silyl (**14**) and methyl (**15**) substrates form the cycloadducts **16**[7] and **17**[7] in high yields (eq 3). Particularly interesting are the cases of the cyclic substrates **18** (*n* = 1 and *n* = 2) (eq 4). Substituents on the olefin of the enyne unit are also well tolerated. A particularly interesting example is substrate **21** since it derives from a simple palladium-catalyzed cross-coupling of the enyne **20** and methyl 2-butynoate (eq 5). Cycloaddition with methyl pentadienoate under the standard conditions with $\mathrm{TCPC}^{\mathrm{TFE}}$ at 43 °C gave a 52% yield of a major adduct[7] in addition to two minor stereoisomers. The presence of a highly acidic proton in **22** adjacent to the ester may account for the isomers since the substrate **23** undergoes cycloaddition to a single cycloadduct in 90% yield (eq 6). An NOE combined with DEPT, COSY, and HETCOR spectra allows assignment

---

(1) For reviews, see: Needleman, S. B.; Kuo, M. C. C. *Chem. Rev.* **1962**, *62*, 405. Hamer, J. *1,4-Cycloaddition Reactions, the Diels–Alder Reaction in Heterocyclic Syntheses*; Academic Press: New York, 1967. Rasmussen, J. K.; Hassner, A. *Chem. Rev.* **1976**, *76*, 389. Weinreb, S. M.; Levin, J. I. *Heterocycles* **1979**, *12*, 949. Petrzilka, M.; Grayson, J. I. *Synthesis* **1981**, 753. Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087. Boger, D. L. *Chem. Rev.* **1986**, *86*, 781. Boger, D. L; Weinreb, S. M. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987. Katritzky, A. R.; Denis, N. *Chem. Rev.* **1989**, *89*, 827. Weinreb, S. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, Chapter 4.2, pp 401–450. Boger, D. L. *Ibid.* Chapter 4.3, pp 451–512.

(2) Parlier, A.; Rudler, H.; Yefsak, R.; Alvarez, C. *J. Organomet. Chem.* **1985**, *328*, C21. Parlier, A.; Rudler, H.; Platzner, N.; Fontanille, M.; Somu, A. *J. Chem. Soc., Dalton Trans.* **1987**, 1041. Hoye, T. R.; Rehberg, G. M. *Organometallics* **1989**, *8*, 2070. Hoye, T. R.; Rehberg, G. M. *Organometallics* **1990**, *9*, 3014. Padwa, A.; Krumpe, K. E.; Gareau, Y.; Chiaccio, V. *J. Org. Chem.* **1991**, *56*, 2523. Hoye, T. R.; Dinsmore, C. J. *J. Am. Chem. Soc.* **1991**, *113*, 4343. Katz, T. J.; Yang, G. X.-Q. *Tetrahedron Lett.* **1991**, *32*, 5895. Harvey, D. F.; Lund, K. P.; Neil, D. A. *Tetrahedron Lett.* **1991**, *32*, 6311. Harvey, D. F.; Lund, K. P. *J. Am. Chem. Soc.* **1991**, *113*, 5066. Hoye, T. R.; Suriano, J. A. *Organometallics* **1992**, *11*, 2044. Mori, M.; Watanuki, S. *J. Chem. Soc., Chem. Commun.* **1992**, 1082. Ogawa, A.; Takami, N.; Sekiguchi, M.; Ryn, I.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1992**, *114*, 8729. Padwa, A.; Austin, D. J.; Gareau, Y.; Kassir, J. M.; Xu, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 2637.

(3) Wulff, W. D.; Bauta, W. E.; Kaesler, R. W.; Lankford, P. J.; Miller, R. A.; Murray, C. K.; Yang, D. C. *J. Am. Chem. Soc.* **1990**, *112*, 3642.

(4) Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc.* **1987**, *109*, 4753; **1988**, *110*, 1636.

(5) Trost, B. M.; Trost, M. K. *J. Am. Chem. Soc.* **1991**, *113*, 1850.

(6) Trost, B. M.; Hashmi, A. S. K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1085.

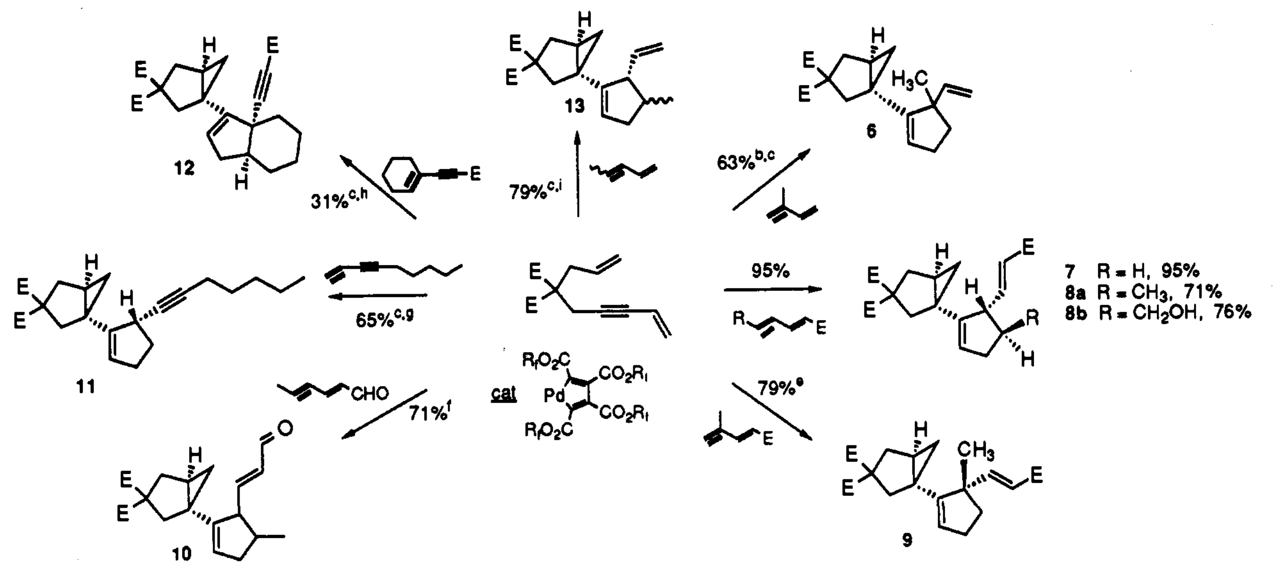
(7) This compound has been fully characterized spectroscopically and its elemental composition established by combustion analysis and/or high-resolution mass spectroscopy.

(8) Performed by Dr. R. G. Ball, Biophysical Chemistry Department, Merck Research Laboratories. To be published.

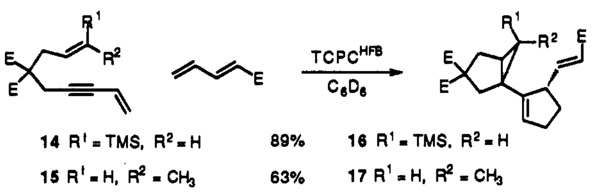
(9) Trost, B. M.; Chan, C.; Rühter, G. *J. Am. Chem. Soc.* **1987**, *109*, 3486.

0002-7863/94/1516-2183$04.50/0

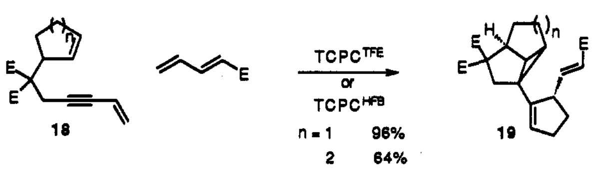
Scheme 1. Acceptors for (Vinylalkylidene)palladium Intermediate[a]



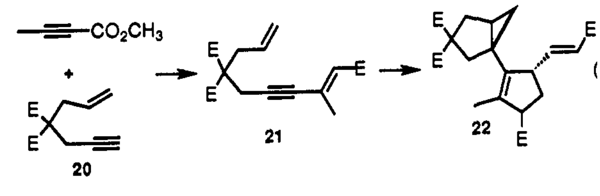
[a] All reactions performed with 5 mol % of TCPC^{TFE} in C_6D_6 at 0.1 M at reflux unless otherwise noted. [b] A 26% yield of the dimer arising by self-trapping was isolated. [c] Yield using TCPC^{HFB}. [d] Yield based upon recovered starting material. [e] An 8:1 ratio of diastereomers. [f] Three isomers in a 2:1:0.3 ratio. [g] A 24% yield of dimer arising by self-trapping was isolated. [h] A 45% yield of dimer arising by self-trapping was isolated. [i] A 2:1 mixture of stereoisomers.



(3)

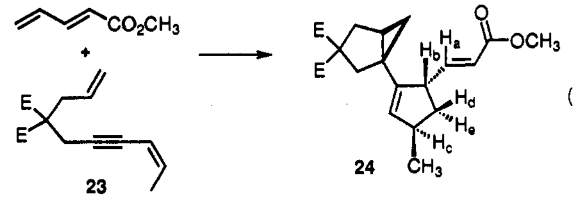


(4)



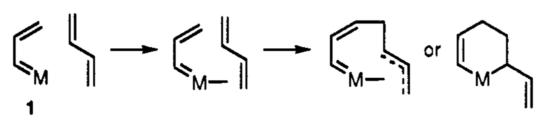
(5)

of the stereochemistry depicted. In particular, the methyl group shows NOEs with H_b and H_d, but not H_e, whereas H_a shows an NOE with H_e, in agreement with the *trans* stereochemistry.



(6)

This cycloisomerization–cycloaddition reaction catalyzed by novel palladium complexes is a general reaction involving two unique processes: formation of a (vinylalkylidene)palladium complex by isomerization and its cycloaddition. The broad scope of the reaction is illustrated by the tolerance of substitution at each site of unsaturation on both reacting partners as well as on the tether of the ynediene substrate. The structural characteristics of the acceptor and the chemoselectivity suggest that cycloadditions of intermediates like **1** may not be straightforward. The results would be consistent with initiation of the cycloaddition by complexation with the unsaturation having the lowest LUMO and/or that which is sterically less hindered (eq 7). The



(7)

unsaturation conjugated to the coordinating site is then delivered to the terminal position of the metalladiene to give either a π or a σ complex as illustrated. While a π-allyl complex is attractive, the ability of vinylacetylenes to be acceptors which cannot form such η^3 complexes suggests that the σ complex may form directly. This picture nicely accommodates why the sterically more hindered double bond of 1,3-dienes or the double bond remote from the electron-withdrawing group preferentially reacts. These observations help to define more generally the characteristics that may be necessary to utilize metalladienes in [4 + 2] type cycloaddition reactions. This process, which increases molecular complexity[10] greatly in a single operation by a simple addition reaction, is both highly selective and highly atom economical; as such it constitutes a synthetically efficient way to construct complex structures.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences, for their generous support of our programs. We are grateful to the Deutsche Forschungsgemeinschaft for fellowship support for A.S.K.H. Mass spectra were generously provided by the University of California—San Francisco Mass Spectrometry Center sponsored by the NIH Division of Research Resources.

Supplementary Material Available: Characterization data for **4**, **7–9**, **11**, **12**, **16**, **17**, **19**, **22**, and **24** (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

---

(10) Bertz, S. H. *J. Am. Chem. Soc.* **1982**, *104*, 5801; *Stud. Phys. Theor. Chem.* **1983**, *28*, 206; *Bull. Math. Biol.* **1983**, *45*, 849. Bertz, S. H.; Sommer, T. J. *Org. Synth. Theory and Applications* **1993**, *2*, 67–92. Wender, P. A.; Miller, B. L. *Org. Synth. Theory Appl.* **1993**, *2*, 27–66.