On the Nature of the Catalytic Palladium-Mediated Elimination of Allylic Carbonates and Acetates To Form 1,3-Dienes

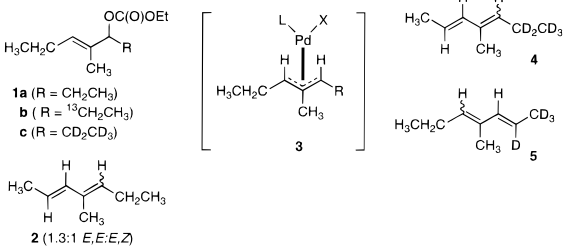
James M. Takacs,* Edward C. Lawson, and Francis Clement

Department of Chemistry, University of Nebraska-Lincoln Lincoln, Nebraska 68588-0304

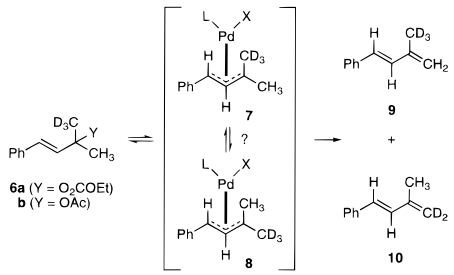
Received July 8, 1996

The palladium-catalyzed elimination of allylic alcohol derivatives to form 1,3-dienes is a well-known synthetic transformation. In conjunction with studies on the telomerization of 1,3-butadiene Smutny reported what may be the earliest preparative procedure, the $(Ph_3P)_4Pd$-catalyzed elimination of an octadienyl phenyl ether to 1,3,7-octatriene.[1] In the late 1970s Tsuji[2] and Trost[3] introduced popular variants of the reaction, employing an allylic acetate as the substrate. More recently, it was reported that allylic carbonates react under yet milder conditions,[4] particularly using the very efficient 1:1 $Pd(OAc)_2$:PBu_3 catalyst system introduced by Tsuji and co-workers.[5] This latter catalyst system shows unusual regioselectivity in the elimination of certain cyclic allylic carbonates[6] and should be considered the current method of choice for the palladium-catalyzed elimination of allylic alcohol derivatives.

We became interested in the details of this reaction as a result of other studies in our labs[7] and prepared allylic carbonate **1a** and two isotopically labeled derivatives (i.e., **1b** and **1c**). Palladium-catalyzed elimination of **1a** under the Tsuji conditions (0.10 equiv of $[Pd(OAc)_2/PBu_3]$, THF, 25 °C, 12 h) affords 4-methyl-2,4-heptadiene (**2**) as a 1.3:1 mixture of isomers about the trisubstituted double bond. The ^{13}C-labeled derivative **1b** affords a similar mixture of heptadienes, wherein the ^{13}C-label is roughly equally distributed between C(2) and C(6). The distribution of the ^{13}C label is consistent with the reaction proceeding via a symmetric intermediate such as **3**. The deuterated derivative **1c** affords dienes **4** and **5** in greater than a 5:1 ratio, indicating a large preference for the loss of hydrogen over deuterium under these conditions.



To confirm the high isotope effect observed for compound **1c**, we prepared the isotopically labeled allylic carbonate **6a**.[8] Palladium-catalyzed elimination of **6a** (0.10 equiv of $[Pd(OAc)_2/PBu_3]$, THF, 25 °C, 8 h) affords a mixture of dienes **9** and **10** in the ratio of 8.6 ± 0.5:1.[9] Again, in the internal competition between loss of hydrogen versus deuterium, loss of hydrogen is strongly preferred. Large isotope effects are also observed in the palladium-catalyzed elimination of allylic acetate **6b** under several reaction conditions, including those commonly employed for the preparative reactions. For example, treatment of **6b** with 0.1 equiv of $[Pd(OAc)_2$, 10 PPh_3, dioxane, 100 °C$]$[2] affords a 5.4 ± 0.6:1 ratio of **9**:**10** and 0.1 equiv of $[Pd(PPh_3)_4$, THF, 65 °C$]$[3] affords a 6.9 ± 0.6:1 mixture.[10,11]



The reaction of **6** presumably proceeds via the formation of η^3-allylpalladium intermediates **7** and **8**, which may interconvert under the reaction conditions. Figure 1 illustrates three possible pathways (A−C) for the formation of dienes **9** and **10** from **7** and **8**. The generally accepted mechanism (pathway A) involves isomerization to an η^1-allylpalladium complex (e.g., **11**) followed by β-hydride elimination. However, kinetic isotope effects for a number of β-hydride eliminations have been reported, and the values are generally small, for example, in *trans*-$[(CD_3CH_2)_2Pd(PMePh_2)_2]$ (1.4 ± 0.1),[12] *trans*-$[CD_3CH_2$-Pt $(PEt_3)_2Cl]$ (2.5 ± 0.2),[13,14] and *n*-$C_6H_{13}C(H)DCH_2Ir(PPh_3)_2$-CO (2.3 ± 0.2).[15] The relatively large isotope effects that we observe in the reactions of **1c** and **6** argue against pathway A[16] but would be consistent with a pathway that proceeds via a more nearly linear C-H(D) bond cleavage transition state. Specific base promoted elimination (pathway B) and the general base promoted elimination (pathway C) could accommodate such a transition state. It should be noted that Keinan[11] proposed a cyclic elimination mechanism (i.e., a specific base promoted elimination analogous to pathway B) for the palladium-catalyzed elimination of allyl acetates promoted by unsaturated organometallic reagents. Furthermore, Andersson[17] recently reported

(1) Smutny, E. *J. Am. Chem. Soc.* **1967**, *89*, 6793.
(2) Tsuji, J.; Yamakawa, T.; Kaito, M.; Mandai, T. *Tetrahedron Lett.* **1978**, 2075−8.
(3) Trost, B. M.; Verhoeven, T. R.; Fortunak, J. M. *Tetrahedron Lett.* **1979**, 2301−4.
(4) Takahashi, T.; Nakagawa, N.; Minoshima, T.; Yamada, H.; Tsuji, J. *Tetrahedron Lett.* **1990**, *31*, 4333−6.
(5) Mandai, T.; Matsumoto, T.; Tsuji, J.; Saito, S. *Tetrahedron Lett.* **1993**, *34*, 2513−16.
(6) Mandai, T.; Matsumoto, T.; Nakao, Y.; Teramoto, H.; Kawada, M.; Tsuji, J. *Tetrahedron Lett.* **1992**, *33*, 2549−52.
(7) Takacs, J. M.; Clement, F.; Zhu, J.; Chandramouli, S.; Gong, X. *J. Am. Chem. Soc.* In press.

(8) Allylic carbonate **6a** was prepared in high isotopic purity via addition of methyl-d_3-magnesium iodide (Aldrich Chemicals. 99+ atom % D) to *trans*-4-phenyl-3-butene-2-one (THF, −78 to 0 °C, 85%), followed by low temperature acylation ($EtOCO_2Cl$, THF, −78 to 25 °C, 12 h, 70%) of the lithium alkoxide derived from the tertiary alcohol. **6a** is relatively labile and used without further purification.
(9) The ratio of **9**:**10** is determined by integration of the deuterium NMR spectrum, and the result (8.6 ± 0.5:1) is the average of three independent experiments. It should be noted that the CH_3 and CD_3 moieties occupy chemically different environments in the postulated η^3-allylpalladium intermediates **7** and **8**; one being exo with respect to the palladium complex and the other being endo. Consequently, the ratio of **9**:**10** may be influenced by an inherent preference for elimination from the exo (endo) position unless **7** and **8** interconvert fast relative to elimination. However, this factor alone cannot account for the strong preference for the formation of **9** and does not affect the arguments that follow.
(10) In the course of a related study, Keinan and co-workers (following reference) reported a much lower isotope effect (k_H/k_D = 2.8) for an intermolecular competition between perhydro- and perdeutero linalyl acetates. The competition was carried out using $Pd(PPh_3)_4$ in $CDCl_3$, which are not typical conditions for the palladium-catalyzed elimination. We also observe a relatively low isotope effect for the reaction of **6b** under these conditions (0.1 equiv of $Pd(PPh_3)_4$, $CDCl_3$, 65 °C, **9**:**10** = 2.8 ± 0.2:1).
(11) Keinan, E.; Kumar, S.; Dangur, V.; Vaya, J. *J. Am. Chem. Soc.* **1994**, *116*, 11151−2.
(12) Ozawa, F.; Ito, T.; Yamamoto, A. *J. Am. Chem. Soc.* **1980**, *102*, 6457−63.
(13) Brainard, R. L.; Whitesides, G. M. *Organometallics* **1985**, *4*, 1550−7.
(14) Romeo, R.; Alibrandi, G.; Scolaro, L. M. *Inorg. Chem.* **1993**, *32*, 4688−94.
(15) Evans, J.; Schwartz, J.; Urquhart, P. W. *J. Organomet. Chem.* **1974**, *81*, C37−9.
(16) For similar arguments in a related palladium-catalyzed reaction, see: Chrisope, D. R.; Beak, P.; Saunders, W. H. *J. Am. Chem. Soc.* **1988**, *110*, 230−8.
(17) Andersson, P. G.; Schab, S. *Organometallics* **1995**, *14*, 1−2.

S0002-7863(96)02313-X CCC: $14.00

that the palladium-catalyzed elimination of allylic acetates was promoted by DBU and that in the presence of DBU a general base promoted elimination (analogous to pathway C) must constitute an important reaction pathway.

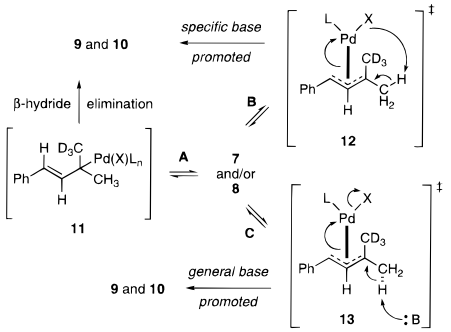
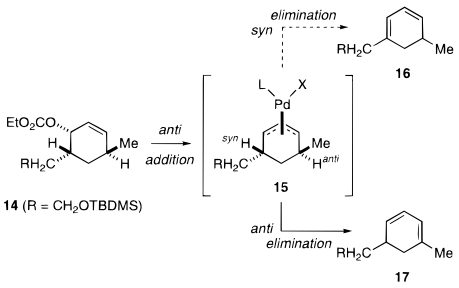


Figure 1. Three possible pathways for the loss of a hydrogen from a η^3-allylpalladium complex, illustrated by the conversion of **7** and/or **8** to dienes **9** and **10**.

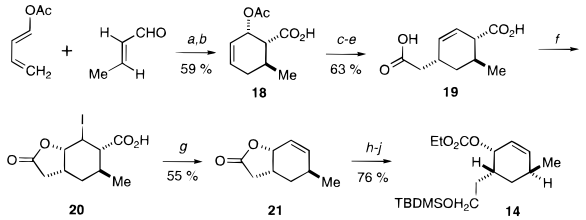
To further distinguish between the potential pathways for the elimination, we synthesized the cyclic allylic carbonate **14** and examined its elimination under the Tsuji conditions. The addition of palladium(0) to the allylic carbonate is expected to be stereospecific and anti; that is, addition to allylic carbonate **14** should afford an intermediate η^3-allyl palladium complex with the relative stereochemistry shown in **15**. Note that the only two hydrogens in **15** can be lost to form diene products. These methine hydrogens are essentially identical except for the remote substitution and their disposition relative to palladium; that is, one will reside syn to palladium, the other anti. Pathways A and B (Figure 1) require syn elimination of the elements $L_nPd(X)$-H, while pathway C is likely to proceed predominantly via an anti elimination of those elements.



The major concern in carrying out such a test of stereospecificity is the potential for palladium to scramble between the diastereomeric faces of the allyl system.[18] If scrambling were to occur, a mixture of **16** and **17** would be obtained regardless of any stereospecificity in the elimination step. Tsuji's observation that regioisomeric dienes are obtained from the reactions of diastereomeric allylic carbonates in certain rigid polycyclic ring systems[6] suggested that such scrambling is slow relative to elimination with the [$Pd(OAc)_2$/PBu_3] catalyst system. Fortunately, this indeed turns out to be the case.

Palladium-catalyzed elimination of **14** (0.10 equiv of [$Pd(OAc)_2$/PBu_3], THF, 25 °C, 12 h, quantitative) affords exclusively cyclohexadiene **17**. We see no evidence for formation of **16** by NMR analysis of the crude reaction mixture. The formation of only cyclohexadiene **17** can be rationalized via stereospecific *anti*-elimination of the elements LnPd(X)-H from an intermediate such as **15**.[19] *syn*-Elimination, as required by

Scheme 1. The Diastereospecific Synthesis of Allylic Carbonate **14**[a]



[a] Conditions: (a) 1 equiv of BF_3-OEt_2, CH_2Cl_2, −50 °C, 48 h; (b) excess Jones reagent, acetone, 0 °C, 1 h; (c) 1.2 equiv of TIPSCl, Et_3N, CH_2Cl_2, 0 °C, 3 h; (d) (1) 1.5 equiv of TBDMSCl, 1.1 equiv of KHMDS, THF, −78 to 25 °C, 12 h (2) PhH, reflux, 12 h; (e) 2.2 equiv of Bu_4NF, THF, 25 °C, 15 min; (f) excess I_2, Et_2O, saturated aqueous $NaHCO_3$, 0 °C, 5 h; (g) 3 equiv of $NaHCO_3$, acetone, reflux, 12 h; (h) 2.2 equiv of LAH, Et_2O, 0 °C, 1 h; (i) 1 equiv of TBDMSCl, 0.1 equiv of DMAP, 1 equiv of Et_3N, CH_2Cl_2, 25 °C, 12 h; (j) $EtOCO_2Cl$, 0.1 equiv of DMAP, 4 equiv of C_5H_5N, THF, 0−25 °C.

β-hydride or specific base promoted elimination (Figure 1, pathways A and B), would have led to the isomeric cyclohexadiene **16**.

The diastereoselective synthesis of **14** is worthy of comment. A number of approaches were explored, and the successful route is shown in Scheme 1. BF_3-catalyzed Diels−Alder cycloaddition of 1-acetoxy-1,3-butadiene with crotonaldehyde[20] followed by oxidation with Jones reagent affords **18**. It proved necessary to protect the carboxylic acid as the OTIPS ester in order to carry out the ensuing enolate Claisen rearrangement.[21] After protection, stereospecific [3,3]-rearrangement via an intermediate silyl ketene acetal followed by hydrolysis of the silyl esters affords the diacid **19**. Group selective iodolactonization[22,23] via the more favorable 5-exo mode affords the intermediate *cis*-fused bicyclic lactone **20**. Upon treatment with base **20** undergoes a relatively little used, but facile, decarboxylative elimination[24] to afford the unsaturated bicyclic lactone **21**. LAH reduction of the lactone, followed by selective protection of the primary alcohol with TBDMSCl and acylation of the remaining secondary alcohol, affords the desired allylic carbonate **14**.

In summary, the palladium-catalyzed eliminations of deuterated allylic carbonates **1c** and **6a** proceed with a large preference for loss of hydrogen over deuterium using Tsuji's 1:1 $Pd(OAc)_2$:PBu_3 catalyst. Furthermore, the deuterated allylic acetate **6b** undergoes palladium-catalyzed elimination with a similarly high isotope effect under conditions that are typical for preparative reactions. The palladium-catalyzed elimination of the cyclohexenyl carbonate **14** affords cyclohexadiene **17** resulting from the overall *syn*-elimination of the elements H-O_2COR. These results are not consistent with a commonly accepted mechanism wherein hydrogen is lost via β-hydride elimination; instead, it can be rationalized via stereospecific *anti*-addition of $L_nPd(0)$ to the allylic carbonate followed by stereospecific base promoted *anti*-elimination of the elements $L_nPd(X)$-H (Figure 1, path C).

Acknowledgment. Financial support of this work by the National Institutes of Health (GM34927) is gratefully acknowledged. We thank the NIH (SIG 1-S10-RR06301) for NMR instrumentation funding, the NSF (CHE-93000831) for GC-MS instrumentation funding, and Dr. Richard Shoemaker for technical assistance.

Supporting Information Available: Details of the experimental procedure and characterization data for the synthesis and elimination of allylic carbonate **14** (26 pages). See any current masthead page for ordering and Internet access instructions.

JA962313T

(18) Keinan, E.; Roth, Z. *Isr. J. Chem.* **1990**, *30*, 305−13.

(19) While the reaction is depicted as proceeding via an η^3-allyl palladium intermediate, the conceptually related stereospecific *anti*-elimination of the elements LnPd(X)-H via an η^1-allyl palladium intermediate (*i.e.*, formal E_2 or $E_{2'}$ reaction) cannot be excluded by the present results.

(20) Siegel, C.; Thorton, E. R. *Tetrahedron Lett.* **1988**, *29*, 5225−8.

(21) Ireland, R. E.; Wipf, P.; Armstrong-III, J. D. *J. Org. Chem.* **1991**, *56*, 650−7.

(22) Harding, K. E.; Tiner, T. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 4, pp 363−421.

(23) Chuang, C.-P.; Gallucci, J. C.; Hart, D. J. *J. Org. Chem.* **1988**, *53*, 3210−8.

(24) Cristol, S. J.; Norris, N. P. *J. Am. Chem. Soc.* **1953**, *75*, 2645−6.