Evidence for a Cyclic Mechanism in (η³-Allyl)palladium Chemistry. Promotion of β-Hydride Elimination by Unsaturated Organometallics

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The β-hydride elimination is a key step in many fundamental organometallic reactions that involve interconversion of alkyl and olefin ligands.[1] The commonly accepted, 4-electron-4-center mechanism for this reaction[2] is strongly supported by the observation of agostic interactions in many alkylmetal and allylmetal complexes.[3] With (η³-allyl)palladium complexes,[4] the elimination reaction is of special interest because it produces conjugated dienes under mild conditions.[5,6] For example, the Pd(0)-catalyzed conversion of allylic acetates to dienes proceeds in common organic solvents at ambient temperatures. Lack of regiospecificity, however, limits the usefulness of this method in synthesis.[7] Here we report that in the presence of stoichiometric amounts of β,γ-unsaturated organometallic reagents the reaction becomes highly regiospecific. Evidence is provided to support a 6-electron 6-center cyclic mechanism rather than the above mentioned 4-electron-4-center pathway.

The reaction of linalyl acetate (**1**), geranyl acetate (**2**), and neryl acetate (**3**) with catalytic amounts of Pd(PPh₃)₄ produces acetic acid and a mixture of myrcene (**4**), (*E*)-ocimene (**5**), and (*Z*)-ocimene (**6**) in a ratio of 74:13:13 (Scheme 1).[8] Product distribution is independent of substrate's structure (either **1**, **2**, or **3**), solvent (dioxane, toluene, THF, chloroform), catalyst concentration, and reaction time.[9] Only a minor dependence on temperature is observed, with slightly higher proportions of

Scheme 1

R =
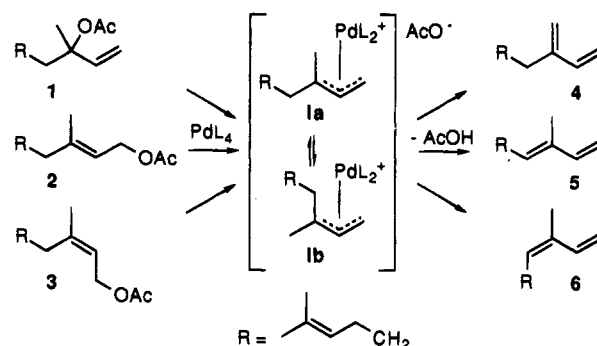
ocimenes appearing at higher temperatures. It has been proposed that a base[10] could promote elimination by abstracting a β-proton from the (allyl)palladium complex, **I**.[11,12] Nevertheless, we found that neither reaction rate nor product distribution is affected by amine bases,[13] and in few cases the reaction is even slightly inhibited. These observations suggest that all three products originate from a unimolecular partitioning of a common intermediate, i.e., an equilibrium mixture of *syn*- and *anti*-(η³-allyl)PdL₂⁺ complexes (**Ia** and **Ib**).

We have long been intrigued by the influence of β,γ-unsaturated organometallics on the elimination reaction.[14] The above described Pd(0)-catalyzed elimination of **1**−**3** was therefore studied in the presence of allyltributylstannane, **7**, allenyltributylstannane, **8**, and propargylzinc bromide, **9** (Table 1). With linalyl acetate, **1** (entries 1−4), the presence of these organometallic reagents causes three significant changes: (a) the elimination reaction is accelerated by 5 times with **7** and by more than 1000-fold with **9**, (b) the proportions of **4** are decreased (now 48%, rather than 75%), and (c) the ratio of **5:6** increases from 1:1 to approximately 1:2.5. Using excess **7** and following the reactions by ¹H NMR, we found that only 1 equiv of the organostannane (with respect to **1**) is consumed with concomitant formation of 1 equiv of propene. Moreover, when a pentadeuteriated linalyl acetate, **1a**,[15] is employed, 1 equiv of 3-deuteriopropene is produced along with acetoxytributylstannane and a mixture of tetradeuteriated **4**, **5**, and **6** (eq 1). The kinetic isotope effect (k_H/k_D = 2.6 in the absence of **7**; 2.2 in its presence) indicates that cleavage of an allylic C−H bond occurs in the rate-limiting step of both reactions.[16]

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(1) Cross, R. J. In *The Chemistry of the Metal-carbon Bond*; Hartley, F. R., Patai, S., Eds.; New York, 1985; Vol. 2, Chapter 8.

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(4) (a) Trost, B. M. *Acc. Chem. Res.* **1980,** *13,* 385. (b) Tsuji, J. *Organic Synthesis with Palladium Compounds*; Springer: Berlin, 1980. (c) Trost, B. M.; Verhoeven, T. R. *Comprehensive Organometallic Chemistry*; Pergamon: New York, 1982; Vol. 8, p 779.

(5) (a) Tsuji, J.; Yamakawa, T.; Kaito, M.; Mandai, T. *Tetrahedron Lett.* **1978,** 2075. (b) Trost, B. M.; Verhoeven, T. R.; Fortunak, J. M. *Tetrahedron Lett.* **1979,** 2301. (c) Carpita, A.; Bonnacorsi, F.; Rossi, R. *Tetrahedron Lett.* **1984,** *25,* 5193. (d) Trost, B. M.; Mignani, S. *J. Org. Chem.* **1986,** *51,* 3435. (e) Otera, J.; Niibo, Y.; Okuda, K. *Chem. Lett.* **1986,** 1829.

(6) Conjugated dienes are undesired side products in reactions involving (η³-allyl)palladium(II) intermediates. We have reported on useful approaches to suppress this elimination process by stabilizing these intermediates. See: Keinan, E.; Roth, Z. *Israel J. Chem.* **1990,** *30,* 305.

(7) For example, in the Pd(0)-catalyzed elimination of acetic acid from sclareyl diacetate, a key step in the synthesis of Ambrox from sclareol, out of the three isomeric diene products, the main isomer (60%) is essentially useless for the synthesis of Ambrox. See: Coste-Maniére, I. C.; Zahra, J. P.; Waegell, B. *Tetrahedron Lett.* **1988,** *29,* 1017.

(8) All reactions were carried out in dry THF under N₂ with 5 mol % of Pd(PPh₃)₄. Product distribution was determined by GC using hexadecane as an internal standard (see footnote 13). Very similar results were obtained with reactions carried out in CDCl₃ and monitored by ¹H NMR using the following signals: **4,** 6.36 (ddd, *J* = 18.2, 11.4, 0.6 Hz); **5,** 6.34 (ddd, *J* = 17.3, 10.8, 0.7 Hz); **6,** 6.78 (ddd, *J* = 17.3, 10.8, 0.9 Hz).

(9) The three isomeric products do not interconvert easily under the reaction conditions. Similar observations were reported earlier.[5a,7]

(10) In most cases where this reaction has been applied in synthesis, a base (usually a tertiary amine) was employed.[5] See also: Åkermark, B.; Nyström, J.-E.; Rein, T.; Bäckvall, J.-E.; Helquist, P.; Aslanian, R. *Tetrahedron Lett.* **1984,** *25,* 5719.

(11) (a) Hayashi, T.; Kishi, K.; Uozumi, Y. *Tetrahedron: Asymmetry* **1991,** *2,* 195. (b) Åkermark, B.; Vitagliano, A. *Organometallics* **1985,** *4,* 1275.

(12) As hydride transfer to allylic ligands occurs via intramolecular transfer from the metal (Keinan, E.; Greenspoon, N. *Tetrahedron Lett.* **1982,** *23,* 241), the principle of microscopic reversibility suggests that palladium hydride elimination would also be unimolecular.

(13) Linalyl acetate, **1** (1 mmol), was mixed with Pd(PPh₃)₄ (4 mol %) and hexadecane (0.12 mmol, a GC internal standard) in dry THF (1.2 mL) under N₂, 25 °C, together with one of the following bases (1 mmol): diisopropylamine, pyridine, 1,4-diazabicyclo[2.2.2]octane (DABCO), 2,2,6,6-tetramethylpiperidine, 1,8-bis(dimethylamino)naphthalene (Proton Sponge), 4-(dimethylamino)pyridine. In all cases, including a mixture without base, reaction was complete with 1-2 h with constant distribution of products (**4:5:6** in a ratio of 74:13:13 ± 3%).

(14) For example, attempts to cross-couple allylic acetates with allylstannanes (Trost, B. M.; Keinan, E. *Tetrahedron Lett.* **1980,** *21,* 2595) and allenylstannanes (Keinan, E.; Peretz, M. *J. Org. Chem.* **1983,** *48,* 5302) under Pd(0) catalysis led to facile elimination to dienes. Similar observations were reported by Negishi for the reaction of geranyl and neryl acetates with propargylzinc bromide: Matsushita, H.; Negishi, E.-I. *J. Org. Chem.* **1982,** *47,* 4161.

(15) 6-Methylhept-5-en-2-one was treated two times with a mixture of THF, D₂O, and NaOH for 20 h at room temperature. ¹H NMR indicated 96% incorporation of five deuterium atoms in the recovered ketone. The latter was reacted with excess vinylmagnesium bromide in THF at 0 °C, affording linalool-*d₅*, which was then acetylated to give **1a**.

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Table 1

entry	substrate	organometallic	products (4:5:6)
1	1		74:13:13
2	1	(allyl)SnBu₃ (7)	49:15:36
3	1	(propargyl)ZnBr (8)	48:14:38
4	1	(allenyl)SnBu₃ (9)	48:15:37
5	2		74:11:15
6	2	(allyl)SnBu₃	25:20:55
7	2	(propargyl)ZnBr	0:27:73
8	2	(allenyl)SnBu₃	0:25:75
9	3		74:16:10
10	3	(allyl)SnBu₃	63:13:24
11	3	(propargyl)ZnBr	100:0:0
12	3	(allenyl)SnBu₃	100:0:0

ᵃ All reactions were carried out in THF, with initial product distribution being determined by GC after 30 min.[8,13] Each experiment was repeated at least three times. Reactions with 7 and 8 were repeated in CDCl₃, confirming the GC results by ¹H NMR.

$$\text{(4-6)-}d_4 \quad (1)$$
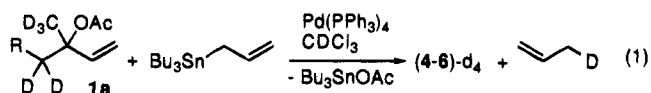
A more pronounced effect is observed with substrates 2 and 3. In the presence of either 8 or 9 the elimination is very fast and becomes highly regiospecific, with 2 producing only ocimene (entries 7 and 8), while 3 affords exclusively myrcene (entries 11 and 12). The same trends are also observed in the presence of 7, but regiospecificity is incomplete, with 2 producing ocimene-enriched mixtures (entry 6) and 3 affording myrcene-enriched mixtures (entry 10). Again, significant rate enhancements are observed. For example, the reaction of 3 in THF is 6 times faster with 7 and 1600 times faster with 9.

At least three alternative mechanistic pathways could be considered on the basis of the above described results (Scheme 2): (a) a unimolecular β-hydride elimination that occurs without direct involvement of the organotin reagent, producing acetic acid, which may later participate in a Pd-catalyzed protonolysis of allylstannane; (b) transmetalation of an allylic or propargylic unit to palladium[17] followed by an intramolecular deprotonation of the β-hydrogen via a cyclic, 6-electron 6-center transition state; and (c) similar transmetalation followed by a regular 4-electron 4-center β-hydride elimination and subsequent reductive elimination to produce propene.

Although 7 is stable in a mixture of chloroform−acetic acid, it undergoes rapid protonolysis to produce propene and acetoxytributylstannane upon addition of catalytic amounts of Pd(PPh₃)₄. However, this Pd-catalyzed protonolysis is completely inhibited by excess Proton Sponge.[13] Since the latter has no effect on the Pd-catalyzed elimination of 1 we can rule out mechanism a. Moreover, the Pd-catalyzed elimination of 1 is promoted by allyl- and allenylstannane, 7 and 8; but not with phenyl-, benzyl-, and methylstannane. In fact, benzyltributylstannane is an effective inhibitor of the elimination reaction; thus ruling out mechanism c and supporting mechanism b, which involves a cyclic transition state, II.[18]

Mechanism b may also account for the unique regiospecificity. The observed constant distribution of products in the unpromoted reaction, independent of the substrate's structure (Table 1, entries 1, 5, and 9), implies that elimination is slower than the equilibration of *syn* and *anti* complexes, Ia and Ib (Scheme 1). Conversely, the very high regiospecificity observed with 2 and 3 in the presence of 8 and 9 suggests that elimination is now faster than the *syn−anti* equilibration. Moreover, product distribution reflects changes in the reaction mechanism. Formation of 5 and 6 from 2 and formation of 4 from 3 implies that

(16) Kinetic isotope effects were determined by ¹H NMR, measuring the elimination rates of 1 and 1a in CDCl₃ with or without 7.[8]

(17) (a) Sheffy, F. K.; Godschalx, J. P.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4833. (b) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033.

Scheme 2
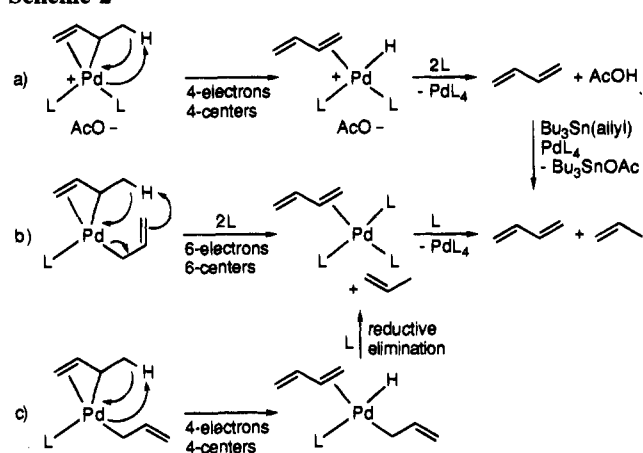


hydrogen is being abstracted selectively from the *syn* carbon. This is exactly the opposite of what one would expect for a normal β-hydride elimination, considering the exclusive agostic interactions of the metal with hydrogens on the *anti* and not on the *syn* carbon.[3] In the case of 2, for example, a rigid, square planar coordination geometry of II could explain the preferential abstraction of hydrogen on the *syn* rather the *anti* carbon producing 5 and 6. Furthermore, the kinetic preference to form 6 rather than 5 is consistent with IIa being sterically less crowded than IIb.

IIa R = H, R' = alkyl
IIb R = alkyl, R' = H
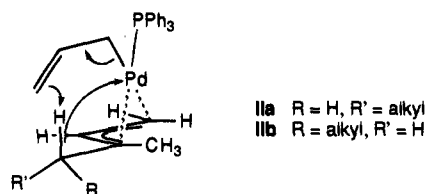
Cyclic, 6-electron 6-center transition states, similar to the one proposed here, are traditionally more widespread in the literature of organic chemistry than of organometallic reactions.[19,20] They should, however, be considered more often in reaction mechanisms across the entire periodical table.[21]

(18) The proposed 6-electron-6-center transition state would formally generate metallacyclopropane which is equivalent to a η²-alkene complex:
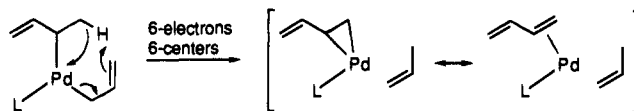
An alternative drawing of four arrows across seven atoms would engender a highly unsaturated palladium species which seems unlikely to occur:
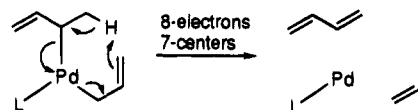
(19) For precedents in palladium chemistry, see: (a) Bäckvall, J.-E.; Nordberg, R. E.; Björkman, E.; Moberg, C. *J. Chem. Soc., Chem. Commun.* **1980**, 943. (b) Bäckvall, J.-E.; Nordberg, R. E.; Wilhelm, D. *J. Am. Chem. Soc.* **1985**, *107*, 6892. (c) Grennberg, H.; Langer, V.; Bäckvall, J.-E. *J. Chem. Soc., Chem. Commun.* **1991**, 1190. (d) Hutchins, R. O.; Learn, K. *J. Org. Chem.* **1982**, *47*, 4380. (e) Mandai, T.; Matsumoto, T.; Kawada, M.; Tsuji, J. *J. Org. Chem.* **1992**, *57*, 6090.

(20) For examples with other metals, see: (a) Chabardes, P.; Kuntz, E.; Varagnat, J. *Tetrahedron* **1977**, *33*, 1775. (b) Pauling, H.; Andrews, D. A.; Hindley, N. C. *Helv. Chim. Acta* **1976**, *59*, 1233. (c) Erman, M. B.; Aul'chenko, I. S.; Kheifits, L. A.; Dulova, V. G.; Novikov, Ju. N.; Vol'pin, M. E. *Tetrahedron Lett.* **1976**, *34*, 2981. (d) Hosogai, T.; Fukita, Y.; Ninagawa, Y.; Nishida, T. *Chem. Lett.* **1982**, 357. (e) Narasaka, K.; Kusama, H.; Hayashi, Y. *Tetrahedron* **1992**, *48*, 2059. (f) Belgacem, J.; Kress, J.; Osborn, J. A. *J. Mol. Catal.* **1994**, *86*, 267. (g) Sunderlin, L. S.; Squires, R. R. *J. Am. Chem. Soc.* **1993**, *115*, 337.

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