

134. Catalytic Intramolecular Palladium-Ene Reactions

Preliminary Communication¹⁾

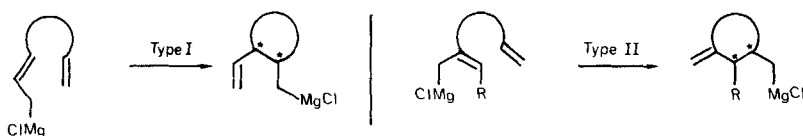
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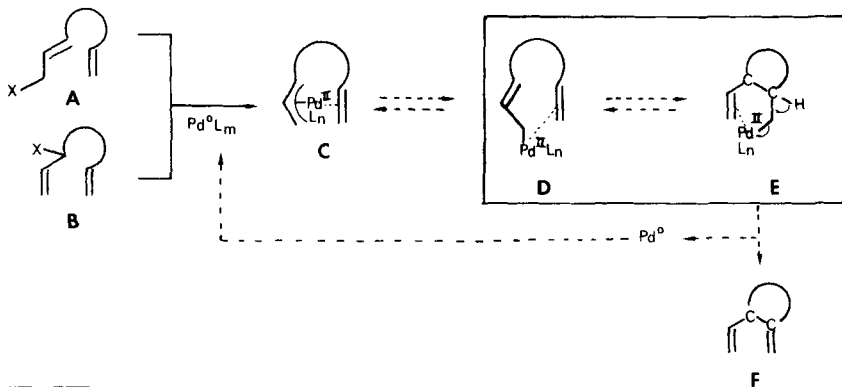
$\text{Pd}(\text{dba})_2[\text{dba} = \text{dibenzylideneacetone}]/\text{PPh}_3$ - or $\text{Pd}(\text{PPh}_3)_4$ -catalyzed cyclizations of acetoxy-dienes **2** $\rightarrow$ **3** and **10** $\rightarrow$ **11** gave 1-vinyl-2-methylidene-substituted cyclopentanes and cyclohexanes in high yield, consistent with a palladium-ene/ β -elimination mechanism (**D** $\rightarrow$ **E** $\rightarrow$ **F**, Scheme 2). The efficient and highly stereoselective cyclizations **4** $\rightarrow$ **7** and **8** $\rightarrow$ **9** illustrate intramolecular allylpalladium insertions into 1,2-dialkyl-, trialkyl-, and cyclic alkenes followed by elimination of the exocyclic β -H giving 1,2-divinylcyclopentanes. These new olefin insertions proceed faster in AcOH (compared to THF) and occur preferentially *cis* relative to the Pd (**13** $\rightarrow$ **14** $\rightarrow$ **15**).

Scheme 1



In conjunction with our previous studies of the magnesium-ene cyclization [1] (Scheme 1), we envisaged the extension of this concept to catalytic intramolecular palladium-ene reactions²⁾ (Scheme 2).

Scheme 2

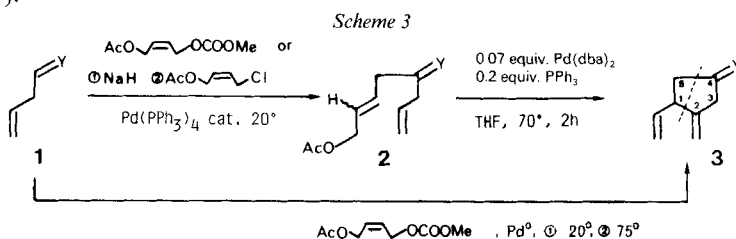


¹⁾ Presented at the '4th IUPAC-Symposium on Organometallic Chemistry Directed towards Organic Synthesis' (OMCOS IV), July 28, 1987, Vancouver, Canada.

²⁾ Review articles on Pd-mediated reactions: [2]. For Pd^{II} -catalyzed cyclizations of enynes, see [3].

Whereas norbornadiene [4], norbornene [4], and 1,3-dienes [5] were reported to insert into stoichiometric amounts of allylpalladium complexes, simple olefins (*e.g.* styrene, cyclohexene, 1,4-cyclohexadiene, and 1,5-cyclooctadiene) did not undergo this reaction under similar conditions [4a]. Nevertheless, we assumed the intramolecular ene process **D** → **E** to be entropically facilitated and a subsequent irreversible β -elimination **E** → **F** to withdraw the ene product **E** from the equilibrium **D** $\rightleftharpoons$ **E**.

In-situ preparation of the olefinic allylpalladium intermediates **C** could be accomplished by oxidative addition of Pd^0 complexes to allyl-acetates (**A**, **B**) [2]. The required 1-acetoxy-2,7(8)-dienes **A** were readily obtained in 68 to 95% yield, predominantly as their (*E*)-isomers, *via* $\text{Pd}(\text{PPh}_3)_4$ -catalyzed alkylation of 1-acetoxy-4-chloro-2-butene [6] or, preferably, (4-acetoxy-2-butenyl)methyl carbonate³⁾ with a 3(4)-alkenyl-1,1-disulfone³⁾, or with 3-alkenyl-malonates as exemplified by the transformation **1a**⁴⁾ → **2**⁴⁾ (Scheme 3).



Heating diene **2a** with bis(dibenzylideneacetone)palladium [$\text{Pd}(\text{dba})_2$ (= bis[η -1,5-diphenyl-1,4-pentadien-3-one]palladium); 0.07 equiv.] and PPh_3 (0.2 equiv.) in THF at $+70^\circ$ for 2 h gave the expected cyclized 1,4-diene **3a**⁴⁾ in 83% yield (Scheme 3, Table 1). Even more conveniently, product **3a** was obtained in one operation from disulfone **1a** (Entry 2) by treatment with (4-acetoxy-2-butenyl)methyl carbonate (1.0 equiv.), $\text{Pd}(\text{dba})_2$ (0.07 equiv.), and PPh_3 (0.2 equiv.) in THF at $+20^\circ$ (2 h) and then at $+75^\circ$ (2 h). Accordingly, bonds C(4)–C(5) and C(1)–C(2) of cyclopentane **3a** may be efficiently formed by this simple combined alkylation/cyclization procedure.

Table 1. $\text{Pd}(\text{dba})_2/\text{PPh}_3$ -Catalyzed Cyclizations **2** → **3**

Entry	Series	Y	Solvent	mol-equiv. PPh_3	Reaction temp. [$^\circ\text{C}$] (Reaction time)	Yield [%] of 3
1	a	(SO_2 - <i>p</i> -MePh) ₂	THF	0.2	$+70^\circ$ (2 h)	82
2 ^{a)}	a	(SO_2 - <i>p</i> -MePh) ₂	THF	0.2	'1-pot' ^{a)}	76 ^{a)}
3	b	(COOMe) ₂	THF	0.2	$+80^\circ$ (40 h)	20
4	b	(COOMe) ₂	MeOH	0.2	$+80^\circ$ (8 h)	65
5	b	(COOMe) ₂	AcOH	0.2	$+80^\circ$ (1.5 h)	77
6	b	(COOMe) ₂	AcOH	–	$+80^\circ$ (3 h)	–
7	c	(COO) ₂ CMe ₂	AcOH	0.2	$+80^\circ$ (1.5 h)	75

^{a)} $\text{Pd}(\text{dba})_2$ (15 mg) and PPh_3 (20 mg) were added to **1a** (140 mg) in THF (4 ml). Stirring the mixture under Ar at r.t. for 2 h and then at 75° for 2 h, followed by aq. workup and flash chromatography, gave pure **3a** (122 mg, 76% yield from **1a**; m.p. 166 – 167°).

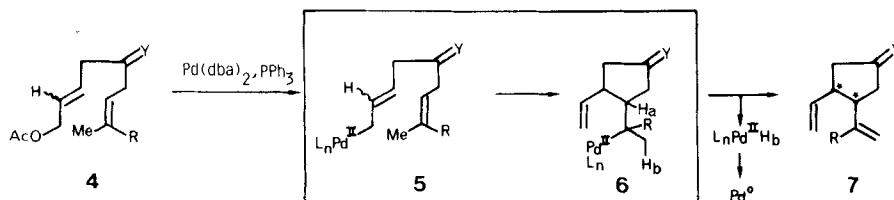
³⁾ Prepared from (*Z*)-1-acetoxy-2-buten-4-ol [7] with ClCOOMe (1.1 mol-equiv.), pyridine (1.5 mol-equiv.), CH_2Cl_2 , $0^\circ \rightarrow +20^\circ$, < 95% yield. **1a** was prepared by mono-alkylation of bis(tolylsulfonyl)methane [8].

⁴⁾ All isolated intermediates and products were characterized by IR, ^1H -NMR (360 MHz), ^{13}C -NMR, and MS.

Solvent effects significantly influence this novel ene process as illustrated by the cyclization of malonate **2b**. Whereas no reaction took place in toluene, CH_2Cl_2 , or DMF, the rate and yield increased on proceeding from THF to MeOH to AcOH (Entries 3–5). Interestingly, the presence of the phosphine turned out to be indispensable (Entry 6).

In striking contrast to 8-alkyl-substituted 2,7-dienylmagnesium halides, which did not cyclize [9], the allylpalladium unit of **5** inserted readily into a terminally mono- and even dimethyl-substituted olefinic bond (**5** $\rightarrow$ **6**; Scheme 4, Table 2).

Scheme 4

Table 2. $\text{Pd}(\text{dba})_2/\text{PPh}_3$ -Catalyzed Cyclizations **4** $\rightarrow$ **7**

Entry	Series	R	Y	Solvent	Reaction temp. [°C] (Reaction time)	Yield [%] of 7
8	a	H	(SO_2 - <i>p</i> -MePh) ₂	THF	+25° (15 h)	80
9 ^{a)}	a	H	(SO_2 - <i>p</i> -MePh) ₂	AcOH	+75° (1.5 h)	91
10	b	Me	(SO_2 - <i>p</i> -MePh) ₂	THF	+85° (40 h)	40
11	b	Me	(SO_2 - <i>p</i> -MePh) ₂	AcOH	+75° (1.5 h)	71

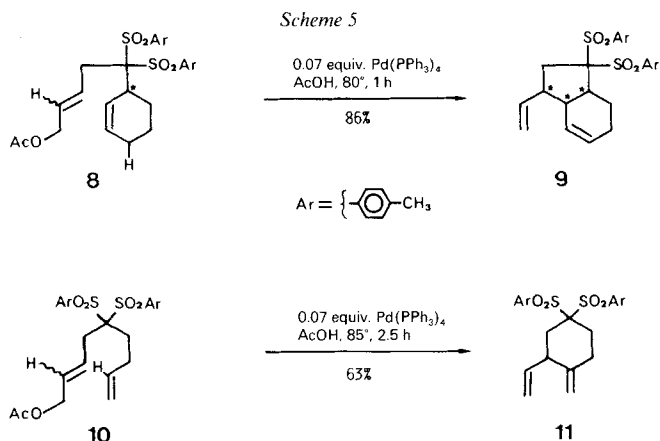
^{a)} $\text{Pd}(\text{dba})_2$ (8 mg) and PPh_3 (11 mg) were added to **4a** (98 mg) in AcOH (3 ml). Heating the mixture at +75–80° for 1.5 h, addition of sat. aq. Na_2CO_3 , workup, and flash chromatography furnished pure **7a** (86 mg, 91% yield; m.p. 136–137°).

Thus, Pd^0 -catalyzed cyclizations of 1-acetoxy-2,7-dienes **4a**⁴⁾ and **4b**⁴⁾ gave in each case a single 1,5-diene product **7a**⁴⁾⁵⁾ and **7b**⁴⁾⁵⁾, respectively. It follows that the ene-step **5** $\rightarrow$ **6** is highly stereoselective in both cases and that the intermediates **6** eliminate the exocyclic H_β preferentially over H_α , in agreement with the conformational constraints of a *syn*- β -elimination process [2]. Again, the cyclizations **5** $\rightarrow$ **6** proceeded significantly faster in AcOH as compared to THF without change of the stereochemical outcome. In contrast, attempts to effect a Pd^0 -catalyzed cyclization of **4a** in THF, while trapping the generated AcOH by finely powdered Na_2CO_3 , gave only unchanged **4a**.

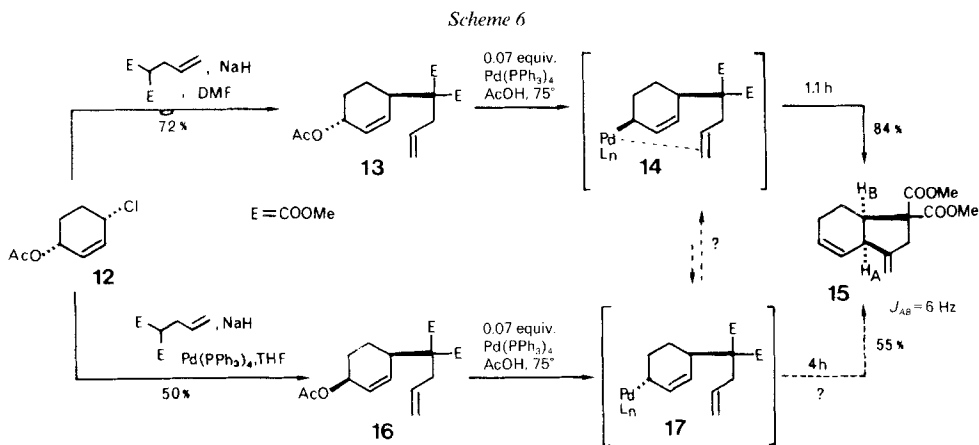
As expected, $\text{Pd}(\text{PPh}_3)_4$ (0.07 equiv.) turned out to be an equally efficient catalyst for intramolecular palladium-ene reactions (Scheme 5).

Thus, 1-acetoxy-2,7-diene **8**⁴⁾ containing a cyclic 'enophile' unit furnished stereoselectively the bicyclic product **9**⁴⁾⁵⁾ (m.p. 176–177°) in 86% yield. Similar conversion of the 1-acetoxy-2,8-diene **10**⁴⁾ to **11**⁴⁾ illustrates the feasibility of this method for 6-membered-ring formation.

⁵⁾ The relative configuration of this single stereoisomer has not yet been established.



The palladium-ene unit may also be part of a ring as shown by the smooth $\text{Pd(PPh}_3)_4$ -catalyzed cyclization of the *trans*-acetoxydiene **13**^{4,6}) which was complete after 1.1 h to give the *cis*-fused hydriodene **15**⁴) in 84% yield (Scheme 6).



Under similar conditions, the *cis*-substituted acetoxydiene **16**^{4,6}) reacted slower, affording after 4 h the identical *cis*-product **15**⁴) in only 55% yield. These results indicate that the olefin inserts into the allylpalladium unit preferentially *cis* relative to the Pd, consistent with the intermediacy of **14**⁶). However, in the epimeric complex **17**⁶), coordination of the Pd with the *trans*-disposed enophile is excluded. Therefore, the slower conversion of **16** to **15** may imply that **17** isomerizes to **14** (e.g. via the corresponding π -allyl complex), or that **17** undergoes a relatively slow 'enophile'-insertion *trans* to the Pd.

⁶) Preparation of **12**: [10]. The relative configurations of intermediates **13**, **14**, **16**, and **17** were assigned on the basis that oxidative additions of Pd^0 to allyl chlorides and allylacetates proceeds with inversion and that the resulting allylpalladium complexes are substituted by malonate anions *trans* relative to the Pd^{II} [2].

In summary, we have shown here that catalytic intramolecular palladium-ene reactions are simple to carry out, compatible with various functional groups⁷⁾ as well as applicable to 1,2-dialkyl-, trialkyl-, and cycloalkenyl enophiles, thus, complementing advantageously the analogous magnesium-ene process. Further extensions and applications of this novel methodology are presently under investigation in our laboratories.

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⁷⁾ For the smooth hydrogenolytic removal (Na, Hg) of geminal disulfones without reduction of isolated olefinic bonds, see [11].