134. Catalytic Intramolecular Palladium-Ene Reactions

Preliminary Communication[1])

by **Wolfgang Oppolzer*** and **Jean-Marc Gaudin**

Département de Chimie Organique, Université de Genève, CH-1211 Genève 4

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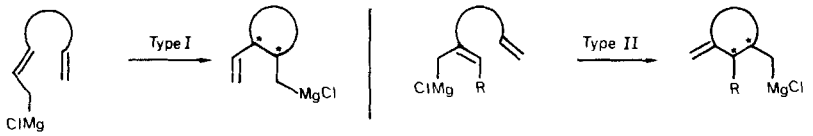
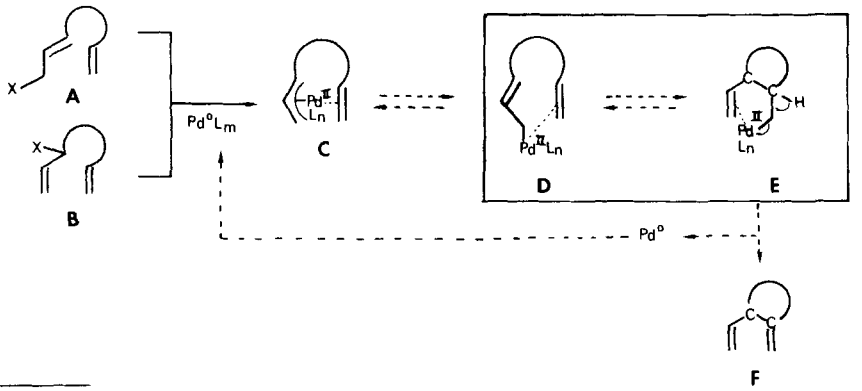
$Pd(dba)_2$[dba = dibenzylideneacetone]/PPh_3-or $Pd(PPh_3)_4$-catalyzed cyclizations of acetoxy-dienes **2** → **3** and **10** → **11** gave 1-vinyl-2-methylidene-substituted cyclopentanes and cyclohexanes in high yield, consistent with a palladium-ene/β-elimination mechanism (**D** → **E** → **F**, *Scheme 2*). The efficient and highly stereoselective cyclizations **4** → **7** and **8** → **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** → **14** → **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 reactions[2]) (*Scheme 2*).

Scheme 2



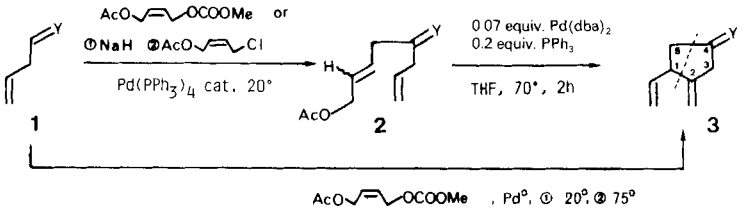
[1]) Presented at the '4th IUPAC-Symposium on Organometallic Chemistry Directed towards Organic Synthesis' (OMCOS IV), July 28, 1987, Vancouver, Canada.

[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** ⇆ **E**.

In-situ preparation of the olefinic allylpalladium intermediates **C** could be accomplished by oxidative addition of Pd° 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* $Pd(PPh_3)_4$-catalyzed alkylation of 1-acetoxy-4-chloro-2-butene [6] or, preferably, (4-acetoxy-2-butenyl)methyl carbonate[3])[4]) with a 3(4)-alkenyl-1,1-disulfone[3]), or with 3-alkenyl-malonates as exemplified by the transformation **1a**[4])→**2**[4]) (*Scheme 3*).

Scheme 3



Heating diene **2a** with bis(dibenzylideneacetone)palladium [$Pd(dba)_2$ (= bis[η-1,5-diphenyl-1,4-pentadien-3-one]palladium); 0.07 equiv.] and PPh_3 (0.2 equiv.) in THF at +70° 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.), $Pd(dba)_2$ (0.07 equiv.), and PPh_3 (0.2 equiv.) in THF at +20° (2 h) and then at +75° (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. *$Pd(dba)_2$/PPh_3-Catalyzed Cyclizations* **2**→**3**

Entry	Series	Y	Solvent	mol-equiv. PPh_3	Reaction temp. [°C] (Reaction time)	Yield [%] of **3**
1	**a**	$(SO_2$-*p*-MePh$)_2$	THF	0.2	+70° (2 h)	82
2[a])	**a**	$(SO_2$-*p*-MePh$)_2$	THF	0.2	'1-pot'[a])	76[a])
3	**b**	$(COOMe)_2$	THF	0.2	+80° (40 h)	20
4	**b**	$(COOMe)_2$	MeOH	0.2	+80° (8 h)	65
5	**b**	$(COOMe)_2$	AcOH	0.2	+80° (1.5 h)	77
6	**b**	$(COOMe)_2$	AcOH	–	+80° (3 h)	–
7	**c**	$(COO)_2CMe_2$	AcOH	0.2	+80° (1.5 h)	75

[a]) $Pd(dba)_2$ (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°→ +20°, < 95% yield. **1a** was prepared by mono-alkylation of bis(tolylsulfonyl)methane [8].

[4]) All isolated intermediates and products were characterized by IR, ^{1}H-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** → **6**; *Scheme 4*, *Table 2*).

Scheme 4

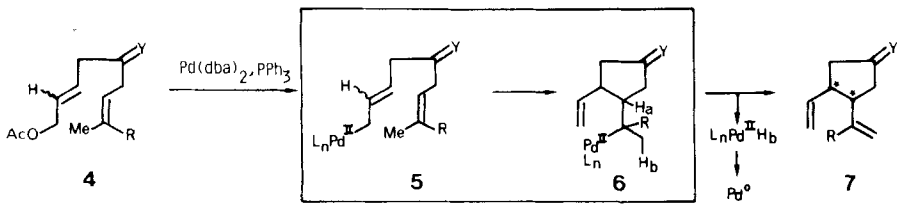


Table 2. *Pd(dba)$_2$/PPh$_3$-Catalyzed Cyclizations* **4** → **7**

Entry	Series	R	Y	Solvent	Reaction temp. [°C] (Reaction time)	Yield [%] of **7**
8	**a**	H	$(SO_2$-*p*-MePh$)_2$	THF	+25° (15 h)	80
9[a])	**a**	H	$(SO_2$-*p*-MePh$)_2$	AcOH	+75° (1.5 h)	91
10	**b**	Me	$(SO_2$-*p*-MePh$)_2$	THF	+85° (40 h)	40
11	**b**	Me	$(SO_2$-*p*-MePh$)_2$	AcOH	+75° (1.5 h)	71

[a]) $Pd(dba)_2$ (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°).

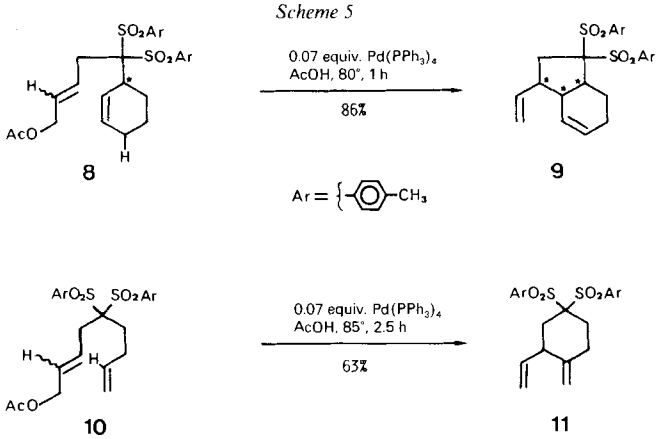
Thus, Pd°-catalyzed cyclizations of 1-acetoxy-2,7-dienes **4a**[4]) and **4b**[4]) gave in each case a single 1,5-diene product **7a**[4])[5]) and **7b**[4])[5]), respectively. It follows that the ene-step **5** → **6** is highly stereoselective in both cases and that the intermediates **6** eliminate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

As expected, $Pd(PPh_3)_4$ (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.

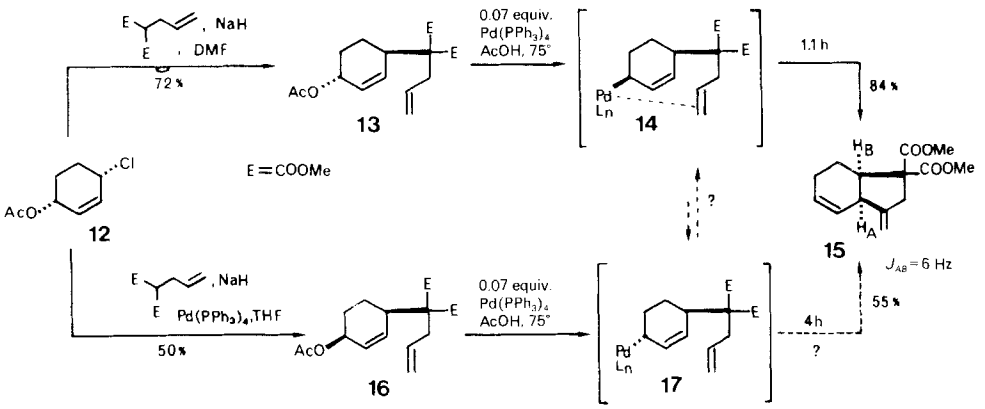
[5]) The relative configuration of this single stereoisomer has not yet been established.

Scheme 5



The palladium-ene unit may also be part of a ring as shown by the smooth $Pd(PPh_3)_4$-catalyzed cyclization of the *trans*-acetoxydiene **13**[4,6]) which was complete after 1.1 h to give the *cis*-fused hydrindene **15**[4]) in 84% yield (*Scheme 6*).

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.

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[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 groups[7]) 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].