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CATALYTIC REACTIONS VIA π-ALLYLPALLADIUM COMPLEXES

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Abstract - Various transformations of allylic esters and ethers via π-allylic complexes catalyzed by palladium-phosphine complexes have been studied. Intramolecular reaction of a nucleophile offers a good synthetic method for five-membered ring ketones. Also nucleophiles reacted easily with α-acetoxy-β,γ-unsaturated nitriles and 1,3-diene monoepoxides. It was found that the Carroll rearrangement is catalyzed by palladium complexes under mild conditions. Facile formation of conjugated dienes and terminal olefins from allylic esters and ethers has been studied.

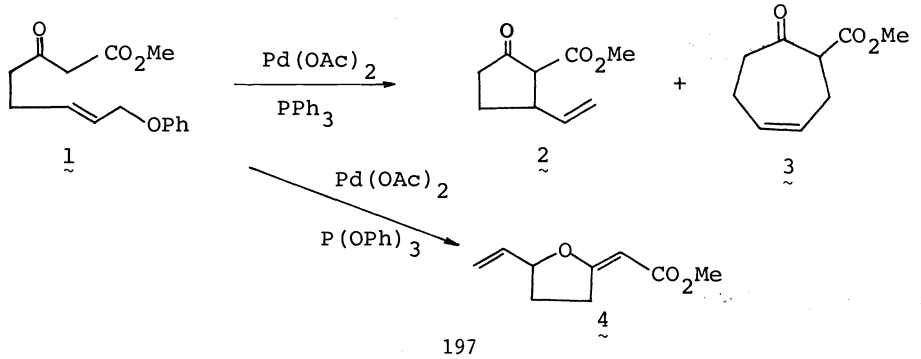
INTRODUCTION

Palladium complexes catalyze numerous reactions (Ref.1). One important and unique group of reactions catalyzed by palladium complexes is the transformation of various allylic compounds. Especially allylic ethers and esters undergo various reactions smoothly in the presence of palladium-phosphine complexes as a catalyst. In the reaction of these allylic compounds, the first step is the oxidative addition of allylic compounds to Pd^0 species to form π-allylpalladium complexes, which then undergo several transformations. In this paper, several transformations of various allylic compounds catalyzed by palladium complexes discovered in our laboratory are presented.

REACTIONS OF NUCLEOPHILES

The reaction of π-allylpalladium complexes with nucleophiles is a well-established reaction. Both stoichiometric and catalytic reactions are possible (Ref.2). Especially the reaction with carbon nucleophiles offers a good method for carbon-carbon bond formation. We have studied further synthetic applications of reactions of allylic compounds via π-allylpalladium complexes.

We have carried out studies aimed at preparing five- and six-membered cyclic ketones by the palladium-catalyzed intramolecular reaction of active methylene with allyl phenyl ether moiety. We have synthesized methyl (E)-3-oxo-8-phenoxy-6-octenoate (1) by the reaction of the dianion of methyl acetoacetate with (E)-1-chloro-4-phenoxy-2-butene (77% yield), and carried out its cyclization using 5-10 mol% of $Pd(OAc)_2$-phosphine or phosphite as a catalyst in various solvents without using a base (Ref.3).



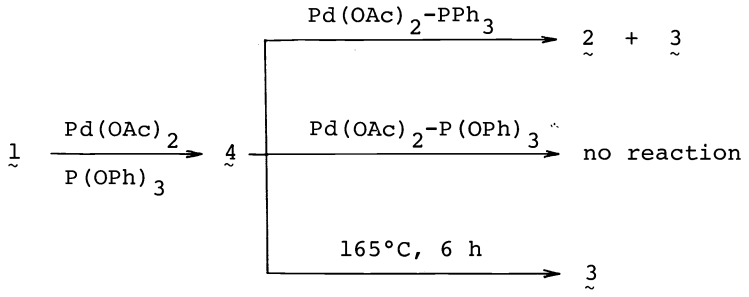
2-Carbomethoxy-3-vinylcyclopentanone (2) and 2-carbomethoxy-4-cycloheptenone (3) were obtained as the C-alkylation products. The ratio of 2 and 3 changed depending on the conditions as shown in TABLE 1. The nature of phosphine ligands was not crucial: PPh_3, PBu_3, and bis(diphenylphosphino)ethane [DIPHOS] gave similar ratios. The largest effect was observed by solvents. The desired 2 was obtained in 87% selectivity when acetonitrile or propionitrile was used (Exp. 8). Dioxane, benzene, and THF gave higher ratios of 3, but the conditions for the selective formation of 3 could not be found. The five-membered ketones were obtained predominantly when 2-alkylated derivatives were subjected to the cyclization. No seven-membered ketones were formed with the larger substituents (Ext. 10-13).

TABLE 1. Cyclization of methyl 3-oxo-8-phenoxy-6-octenoate and its 2-alkyl derivatives[a)]

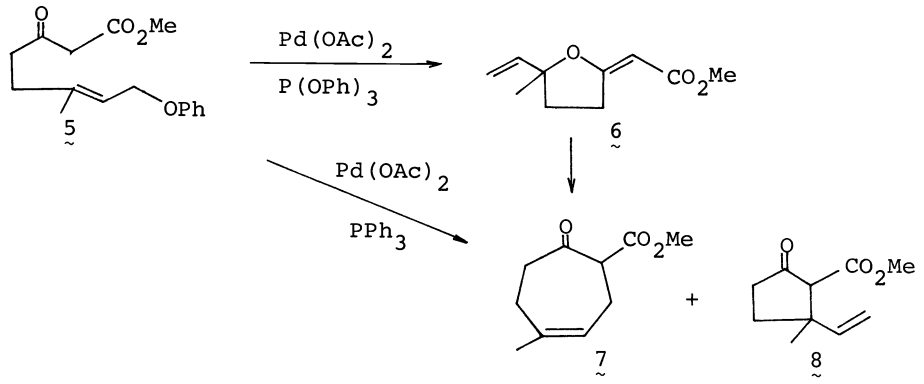
No	R	Solvent	Ligand	Ratios[b)] 2	3	4	Others	Time (h)
1	H	CH_3CN	$P(OPh)_3$	0	0	100	0	8
2	H	CH_3CN	DIPHOS	76	12	0	12	12
3	H	CH_3CN	PBu_3	85	15	0	0	1
4	H	dioxane	PPh_3	46	51	0	3	1/3
5	H	benzene	"	44	49	0	7	2/3
6	H	THF	"	37	57	0	6	8
7	H	acetone	"	60	27	0	13	2.5
8	H	CH_3CN	"	87(59%)[c)]	13	0	0	1
9	CH_3	CH_3CN	"	95(72%)	5	0	0	1/4
10	C_2H_5Ph	CH_3CN	"	(70%)				1/4
11	n-C_5H_{11}	C_2H_5CN	"	(87%)				3
12	Z-$CH_2CH{=}CHC_2H_5$	C_2H_5CN	"	(79%)				2
13	$CH_2C{\equiv}CC_2H_5$	C_2H_5CN	"	(74%)				1.5

a) Reactions were carried out at refluxing temperature of the solvents with $Pd(OAc)_2$ (5-10 mol%) and ligands (20-35 mol%). b) Determined by gas chromatography. c) Isolated yields.

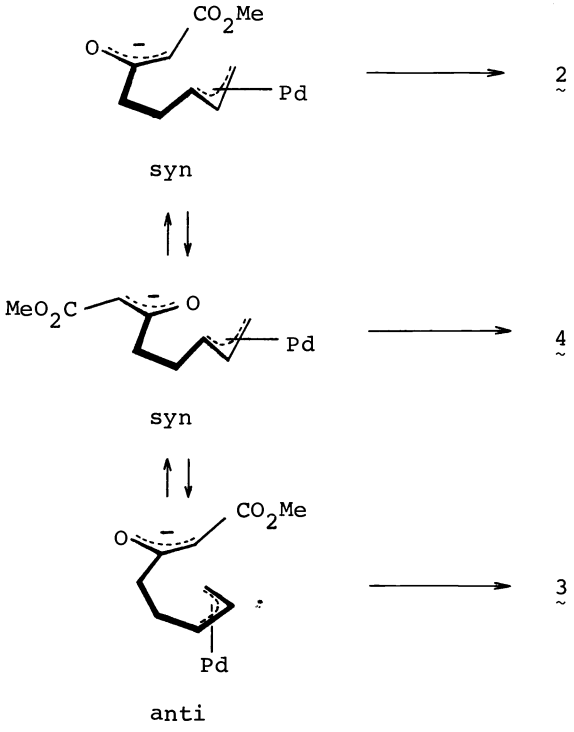
In addition to 2 and 3, which are formed by C-alkylation, 2-carbomethoxymethylidene-5-vinyltetrahydrofuran (4) was obtained as the O-alkylation product. The ratio of this compound to the C-alkylated products 2 and 3 changed depending on the reaction conditions. However, 4 was obtained as the sole product when triphenyl phosphite was used as the ligand. Also it was found that 4 can be rearranged to 2 and 3 by further treatment with $Pd(OAc)_2$ and PPh_3. This is the palladium-catalyzed Claisen rearrangement. No rearrangement took place with $Pd(OAc)_2$-$P(OPh)_3$. Thermal rearrangement afforded only 3 as expected.



The five-membered O-alkylation product 6 was obtained exclusively when methyl 3-oxo-6-methyl-8-phenoxy-6-octenoate (5) was treated with $Pd(OAc)_2$ and triphenyl phosphite. However, the seven membered ketone 7 was obtained in a larger amount than that of five-membered ketone 8 by treatment with $Pd(OAc)_2$ and PPh_3. But the yield was not high.



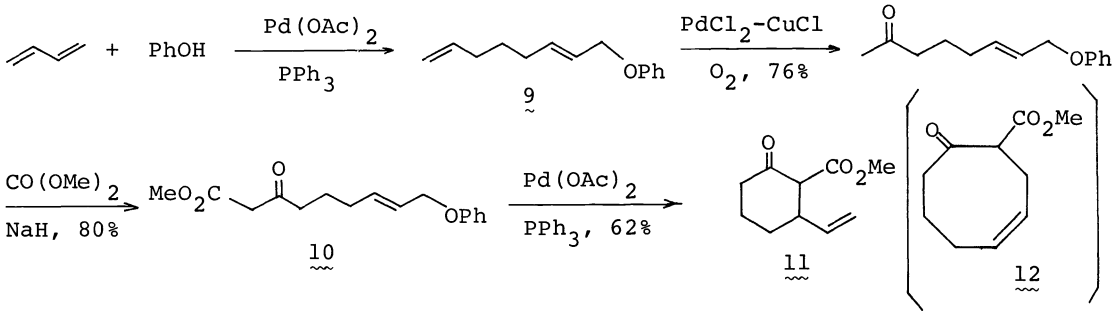
According to Baldwin's rule for ring closure (Ref.4), the formation of the five-membered enol ether 4 by the O-alkylation is the expected product, but actually the unexpected C-alkylation product 2 was formed. Also in this cyclization, the five-membered rings 2 and 4 were formed via the syn form of the intermediate π-allyl complex, and the seven-membered ketone 3 was formed via the anti form.



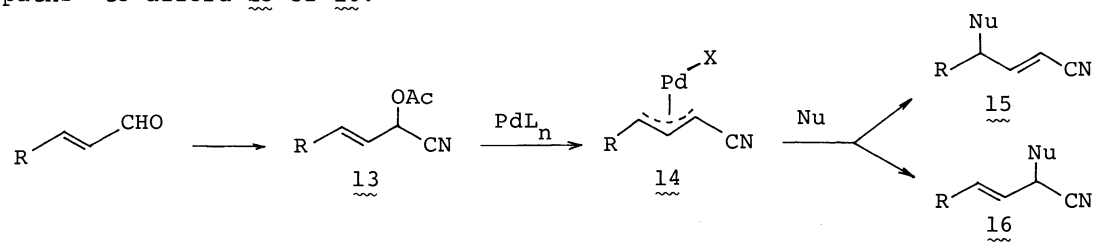
The cyclopentanone derivatives obtained easily by this cyclization reaction are very good starting materials for the syntheses of natural products which have α,β-disubstituted cyclopentanones such as jasmonoides, prostaglandins, and steroids. We have synthesized jasmonate (Ref.3), sarkomycin (Ref.5), coronafacic acid (Ref.5), and 18-hydroxyestrone (Ref.6).

Then methyl 3-oxo-9-phenoxy-7-nonenoate (10) was prepared from the butadiene telomer 9 by the following way, and subjected to the palladium-catalyzed cyclization. 2-Carbomethoxy-3-vinylcyclohexanone (11) was obtained in nearly 90% selectivity using $Pd(OAc)_2$ with PPh_3, DIPHOS, or $P(OPh)_3$ in acetonitrile,

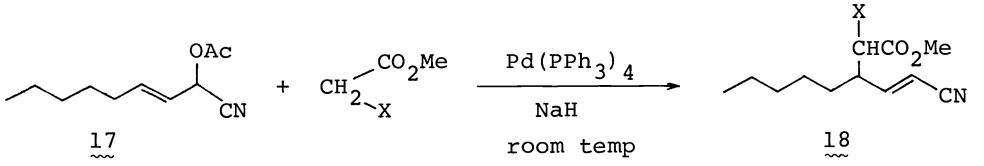
benzene, or dioxane without forming the eight-membered ketone 12.



We studied the effect of substituents in the π-allyl complexes on the regioselectivity of the nucleophilic attack. For this purpose, we studied the reaction of allylic acetates, containing a nitrile group, with nucleophiles in the presence of the palladium complex. The substrates are α-acetoxy-β,γ-unsaturated nitriles (13), which can be prepared easily by the acetylation of cyanohydrins of α,β-unsaturated aldehydes. It is expected that these compounds react with palladium(o) to form π-allylpalladium complexes 14 substituted by a nitrile group, and there are two possible reaction paths to afford 15 or 16.

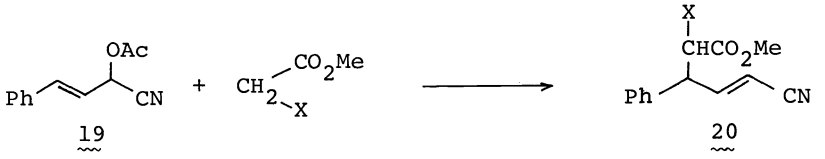


We found that the compounds 13 reacted smoothly with malonate and acetoacetate regioselectively to give only one product in the presence of the palladium catalyst (Ref.7). Reaction of 2-acetoxy-3-nonenonitrile 17 in THF with anion of malonate proceeded smoothly at room temperature to give 4-substituted 2-nonenonitrile 18 in good yields.



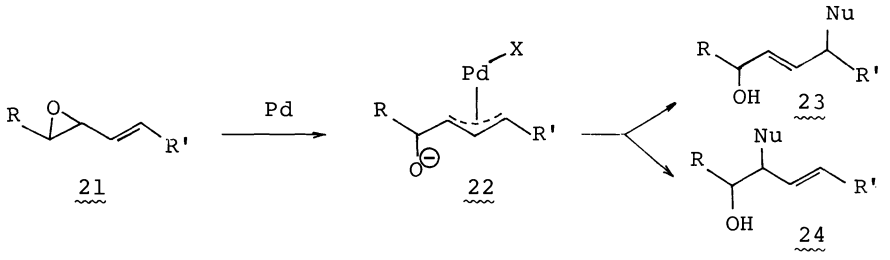
X = CO_2Me 54% (30 min)
COMe 97% (60 min)

2-Acetoxy-3-phenyl-3-propenonitrile 19 prepared from cinnamaldehyde reacted similarly to give the 3-substituted nitrile 20 regioselectively in 87% yield in 10 min.

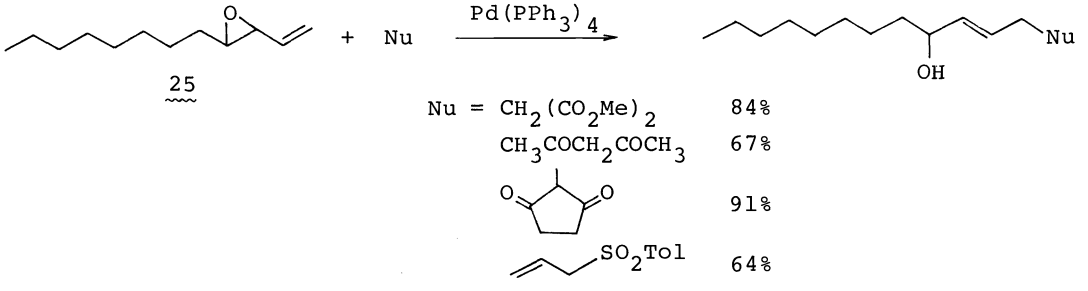


X = CO_2Me 87% (10 min)
COMe 78% (60 min)

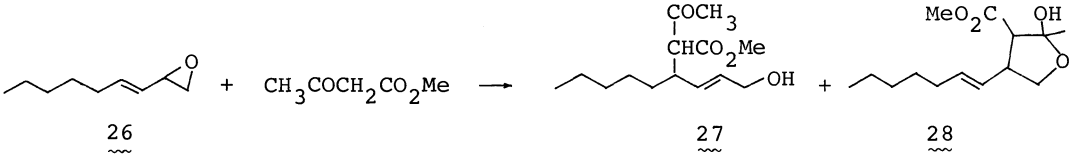
Then we carried out the reaction of nucleophiles with the monoepoxide of conjugated dienes 21. We considered that π-allylpalladium complexes 22 are formed by the treatment of the diene monoxides with palladium, because they can be regarded as reactive allylic ethers. If the complex formation takes place, then nucleophilic attack should be possible.



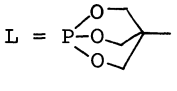
The reaction of 3,4-epoxy-1-dodecene 25 with various nucleophiles proceeded rapidly even at room temperature, and the nucleophiles were introduced selectively at the terminal carbon (Ref.8).



The reaction of 1,2-epoxy-3-nonene (26) took place mostly at C-4, but the reaction was not completely selective when $Pd(PPh_3)_4$ was used as the catalyst. The attack at C-2 was observed as a minor path. However, we found that ligands affect the regioselectivity. The uses of DIPHOS and particularly phosphites afforded the C-4 product 27 with high regioselectivity.



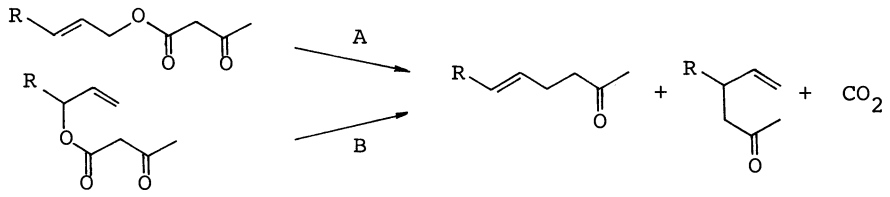
Catalysts	Solv.	Yield	Ratio (27 : 28)
$Pd(PPh_3)_4$	THF	67%	78 : 22
$Pd_3(TBAA)_3$ + DIPHOS	THF	61%	85 : 15
$Pd_3(TBAA)_3$ + L	THF	65%	92 : 8
$Pd_3(TBAA)_3$ + L	CH_3CN	60%	95 : 5



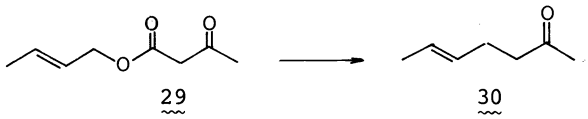
Thus the nucleophilic attack took place in these reactions preferentially at the carbon remote from the hydroxy group.

PALLADIUM-CATALYZED CARROLL REARRANGEMENT

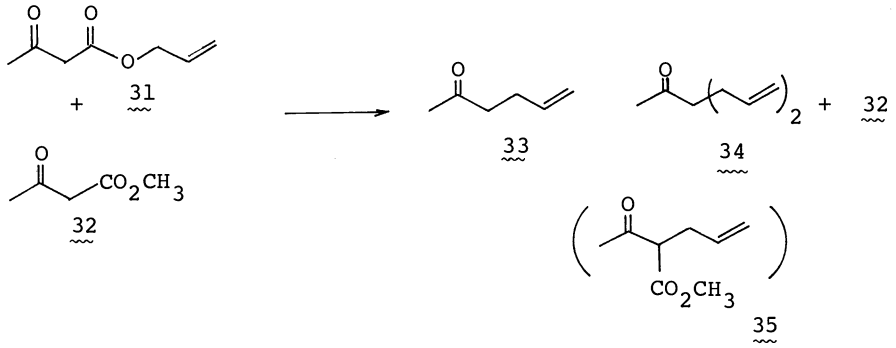
We found that allylic esters of acetoacetate undergo the palladium-catalyzed rearrangement to give γ,δ-unsaturated methyl ketones with elimination of carbon dioxide as expressed by the following general scheme (Ref.9,10).



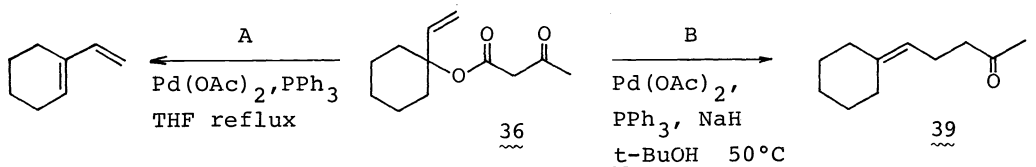
The reaction route B in the scheme is called the Carroll rearrangement, which proceeds thermally above 170°C (Ref.11,12). The palladium-catalyzed reaction, we have discovered, proceeds in refluxing THF, or at lower temperature by using catalytic amounts of $Pd(OAc)_2$ and PPh_3 to give the rearranged products in high yields. For example, (E)-4-methyl-5-hepten-2-one (30) was obtained in nearly quantitative yield with retention of the E form of the double bond.

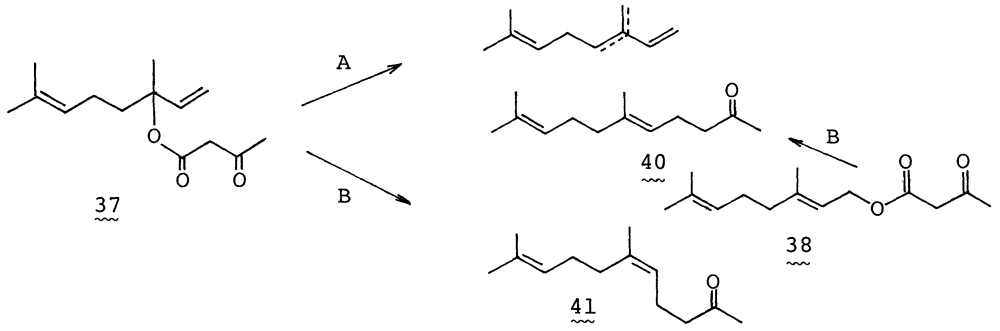


When the reaction of allyl acetoacetate (31) was carried out in the presence of methyl acetoacetate (32) which is a strong nucleophile, 2-allylated acetoacetate (35) was not formed. However, in this reaction diallylacetone (34) was a major product and allylacetone (33) was a minor product. This result suggests the mechanism of intramolecular reaction, but the formation of diallylacetone 34 can not be explained.

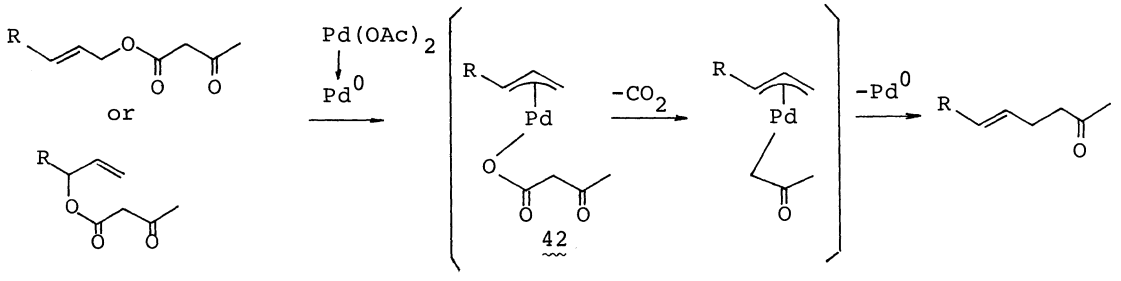


In the reactions of 36, 37, and 38, the acetonyl group was introduced exclusively at the terminal position. Reactions of esters of tertiary allyl alcohols such as 36 and 37 with $Pd(OAc)_2$-PPh_3 in refluxing THF gave the dienes as the elimination products predominantly. But reaction of 36 in the presence of NaH, $Pd(OAc)_2$, and PPh_3 in t-BuOH at 50°C for 1 h gave the γ,δ-unsaturated ketone 39, without elimination, in 51% yield after chromatographic purification. Under the same conditions linalyl acetoacetate (37) gave geranylacetone (40) and nerylacetone (41) in a ratio of 3 : 2, but geranyl acetoacetate (38) was converted to geranylacetone (40) with retention of E form of the double bond.



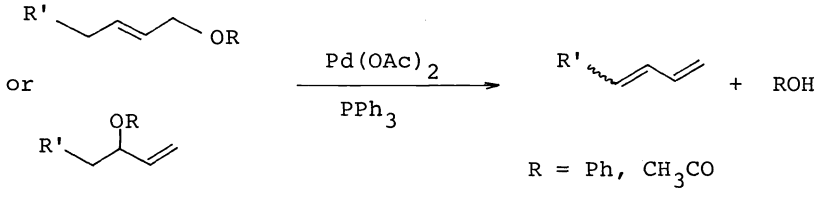


This reaction can be explained by the following mechanism. The first step is the oxidative addition of allylic esters to Pd^0 species formed from $Pd(OAc)_2$ and PPh_3 to form the π-allyl palladium complex 42, coordinated by acetoacetate anion, which undergoes decarboxylation. Similar facile decarboxylation was observed with coordinated formate anion to form palladium hydride species in the palladium catalyzed hydrogenolysis of allylic esters. Then the nucleophilic attack of the coordinated carbanion of acetone mainly at the less substituted side of the π-allylic system gives the product.

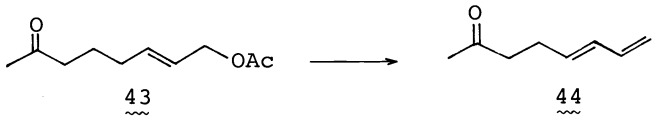


CONVERSION OF ALLYLIC COMPOUNDS TO TERMINAL DIENES

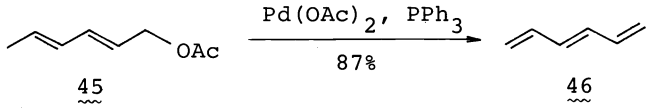
We have found a simple preparative method for terminal conjugated dienes based on the elimination of acetic acid and phenol from easily available allylic acetates and allylic phenyl ethers respectively using a palladium catalyst as shown below (Ref.13).



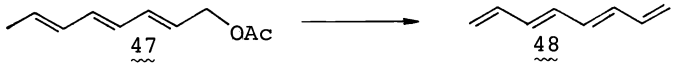
The reaction proceeds under mild conditions to give dienes in high yields. Thus allylic acetates and phenyl ethers can be regarded as useful synthons of dienes. For example, 8-acetoxy-6-octen-2-one (43) was heated in dioxane with a catalytic amount of $Pd(OAc)_2$ and PPh_3 at 100°C for 1 h. Gas chromatographic analysis of the reaction mixture showed complete conversion of the acetate to 5,7-octadien-2-one (44). The diene was isolated by distillation in 78% yield.



The method was applied to the syntheses of conjugated trienes and tetraenes. 2E,4E-Hexadienyl acetate (45) was converted to 1,3E,5-hexatriene (46) in 87% yield. The reaction proceeded stereoselectively.

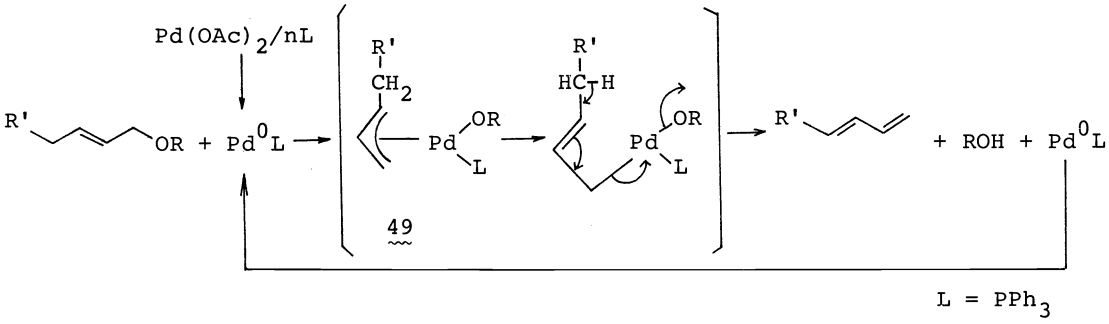


Similarly, 2E,4E,6E-octatrienyl acetate (47) was converted to 3E,5E-octatriene (48) in 48% yield.



For this reaction, $Pd(OAc)_2$ combined with PPh_3 is a suitable catalyst. The presence of an excess of PPh_3 (about 8-10 mols for one mol of Pd) is desirable for maximum catalytic activity. About one mol% of the catalyst for the substrate was found to be enough. $PdCl_2(PPh_3)_2$ was not an active catalyst. As the substrates, allylic acetates and phenyl ethers were found most satisfactory. No elimination was observed with allylic methyl ethers, alcohols, and amines. Also a simple acetate was not eliminated. The allylic isomers were converted to the same products in the same yields.

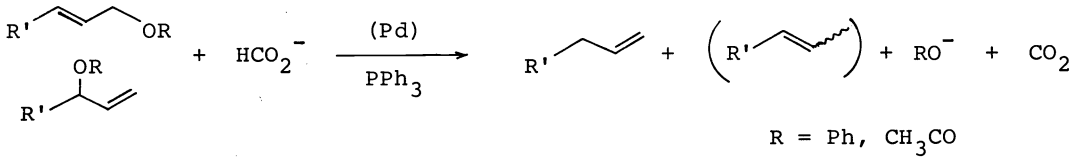
This elimination reaction can be explained via the formation of a π-allylic complex 49, by the oxidative addition of allylic compounds to zerovalent palladium. Elimination of acetic acid or phenol from the complex 49 liberates the diene and regenerates the zerovalent palladium, which recycles.



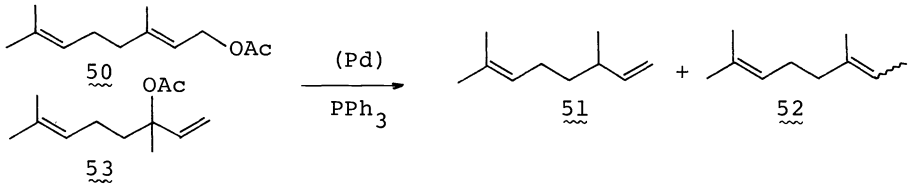
CONVERSION OF ALLYLIC COMPOUNDS TO 1-OLEFINS

We found that allylic esters and ethers are converted to 1-olefins in high yields under mild conditions by the reaction of ammonium formate using a palladium catalyst (Ref.14). In this reaction, 1-olefins were obtained predominantly with 2-olefins as minor products.

Thus allylic acetates and phenyl ethers can be regarded as useful synthons of 1-olefins.



In a typical example, a mixture of geranyl acetate (50) and ammonium formate was refluxed in dioxane in the presence of $PdCl_2(PPh_3)_2$ (1 mol%) for 1 h. Gas chromatographic analysis of the reaction mixture showed nearly quantitative conversion of geranyl acetate to give 1-olefin [dihydromyrcene (51)] and 2-olefin [cis- and trans-dihydromyrcene (52)] in a ratio of 94 : 6. A similar product ratio was obtained by the reaction of linalyl acetate (53).



However, the selectivity of the reaction is influenced by ligands. The preferential formation of 1-olefin from geranyl acetate (50) was observed by using PPh_3, but the selectivity to 1-olefin decreased by the use of other ligands. 2-Olefin became the main product when phosphites were used as the ligands, as shown below.

ligand	1-olefin	2-olefin
PPh_3	91.1	8.9
$P(OMe)_3$	60.3	39.7
$P(OEt)_3$	41.2	58.8
$P(O\text{-}\underline{i}Pr)_3$	32.0	58.3

By this method, allyl esters can be used as a protecting group of carboxylic acids. Octanoic acid was obtained in 82% yield from allyl octanoate by the treatment with the palladium catalyst.

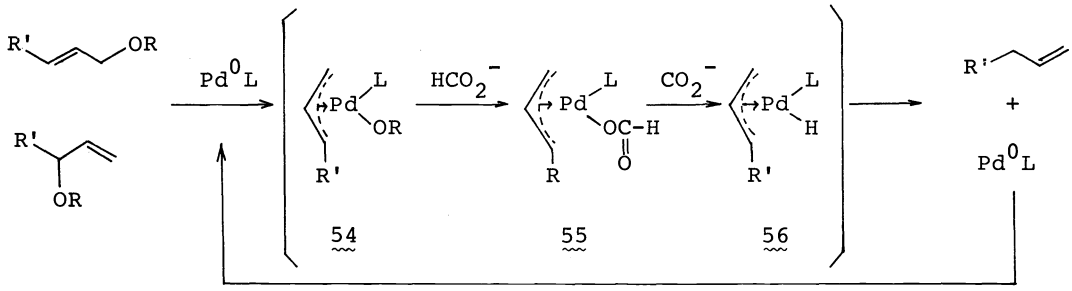
$$CH_3(CH_2)_6CO_2CH_2CH{=}CH_2 \xrightarrow[\text{[Pd]}]{HCO_2NH_4} CH_3(CH_2)_6CO_2H$$

Similarly allyl cinnamate was treated with ammonium formate in the presence of the palladium catalyst, and cinnamic acid was obtained in 93% yield. In this reaction, the allyl group was removed by hydrogenolysis, but the double bond in the acid molecule remained intact. Therefore, the palladium catalyzed removal of the allyl protecting group is superior to the commonly used method of removing the benzyl ester group by hydrogenation.

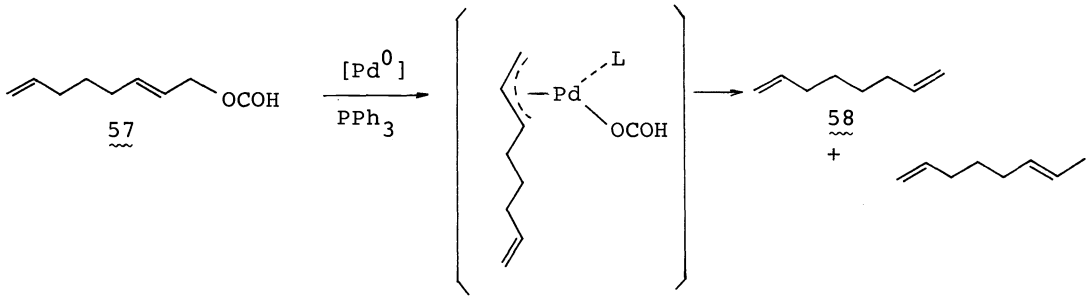
$$PhCH{=}CHCO_2CH_2CH{=}CH_2 \xrightarrow[PPh_3]{\text{[Pd]}} PhCH{=}CHCO_2H$$

The present reaction can be explained by the following mechanism. Oxidative addition of the allylic compounds to Pd^0 species takes place to form the π-allylic complex 54. Displacement reaction by formate affords the formate complex 55, which is then converted to the palladium-hydride 56 with generation of carbon dioxide. Then the olefins are liberated by the reductive elimination with regeneration of the Pd^0 species. In this step, the hydride attacks preferentially the more substituted side of the π-allylic system 56 to afford 1-olefins predominantly.

The selectivity to 1-olefins (above 90%) was observed with geranyl and linalyl acetates, but it was 80% with the less substituted 3-phenoxy- or 3-acetoxy-1,7-octadiene. A 2-methyl group somewhat lowered the selectivity. 2-Acetoxy-3-decene afforded nearly equal amounts of 2- and 3-decene (54 : 46) as expected.



In order to obtain supporting evidence for the formation of the formate complex 55 in the above mechanism, 2,7-octadienyl formate (57) was treated with the palladium catalyst in the absence of ammonium formate, and 1,7-octadiene (58) was obtained as a main product.



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