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25 YEARS IN THE ORGANIC CHEMISTRY OF PALLADIUM

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1. Introduction

In response to a kind invitation from the Editors to contribute to this special issue, I am happy to describe our studies on organic chemistry of palladium, which have been continued for nearly 25 years with occasional interruptions. This account comprises two parts. The first part (section 2) deals with reminiscence of the early days of my research on palladium chemistry which started more than 20 years ago, and the second part (section 3) summarizes new aspects of π-allylpalladium chemistry developed recently in our laboratory.

I spent three years at Columbia University under the guidance of Professor G. Stork working for a Ph.D. degree on synthetic approaches to vitamin D and steroidal alkaloids. After gaining the degree, I returned to Japan. It was in 1962 that I started my independent research in the newly opened Basic Research Laboratories of Toray Industries in Kamakura, which is located outside Tokyo. As a research field, I selected organic synthesis with transition metal compounds, particularly palladium compounds, although I knew almost nothing about organotransition metal chemistry. At that time, only very few chemists in the world were working on organic chemistry of palladium.

2. Our work in 1960's

In 1958, a new industrial process for producing acetaldehyde from ethylene using $PdCl_2/CuCl_2$ as catalysts was invented by chemists in Wacker Chemie GmbH [1]. The ingeneous invention of the Wacker process was a harbinger of the modern organic chemistry of palladium. As an extension of the Wacker process, the possibility of producing vinyl acetate by the reaction of ethylene with $Pd(OAc)_2$ was revealed by Moiseev [2]. These reactions gave me important ideas and stimulated my research. I was very much interested in the mechanisms of these reactions of olefins with Pd^{II} salts. As a simplification, in the Wacker reaction ethylene is coordinated by $PdCl_2$ then attack by HO^- leads to formation of acetaldehyde and Pd^0. In vinyl acetate formation, AcO^- attacks the ethylene. In other words, oxypalladation is the

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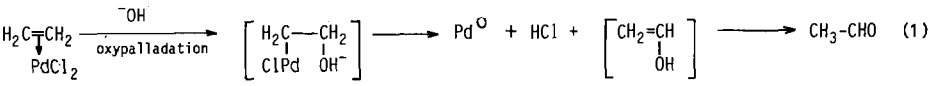
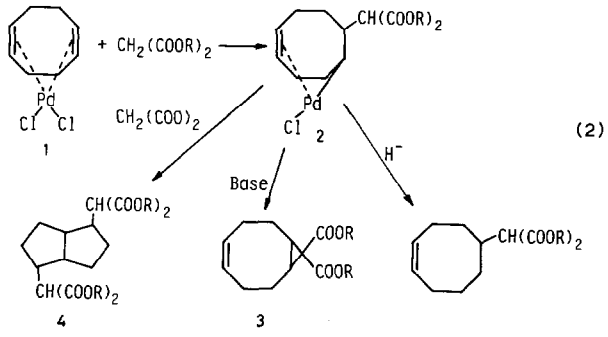
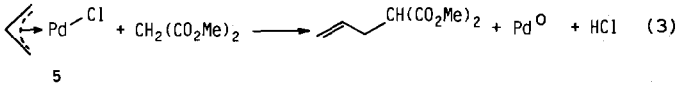
first step, and overall nucleophilic substitution of olefins takes place in these reactions (eq. 1).



Nucleophilic substitution of olefins was virtually unknown and unexplored at that time. This is because I was very interested in. Decrease of the electron density of the olefin by the coordination of Pd^{II} salt allows the attack of HO^- and AcO^- on olefins. For a synthetic organic chemist, the most important reaction is carbon–carbon bond formation and I speculated that carbon–carbon bond formation with olefins might be possible if a carbonucleophile attacked an olefin complex. On the basis of this idea, we attempted the reaction of monoolefins with malonate and acetoacetate as typical carbonucleophiles, but without success [3]. Then we tried the reaction of the more stable cyclooctadiene complex **1** of $PdCl_2$ with malonate. We carried out the reaction of this difficultly-soluble complex **1** with malonate in the presence of sodium carbonate in ether at room temperature under heterogeneous conditions. The yellow complex gradually turned white, and we obtained a quantitative yield of new complex **2**, which contains a newly formed carbon–carbon bond and a stable palladium–carbon σ-bond [4,5]. I was surprised by the facile formation of the carbon–carbon bond under extremely mild conditions. This was the first example of a carbopalladation reaction. A similar complex was obtained from acetoacetate. These complexes, which have π and σ bonds with palladium, underwent further reactions. When treated with a strong base, the bicyclo[6.1.0]nonene derivative **3** was formed. When another molecule of malonate was introduced attack occurred intermolecularly at the π-complexed olefin bond, and was followed by a transannular reaction to form the bicyclo[3.3.0]octane ring species, **4** containing two malonates (eq. 2).



Encouraged by this success, we extended the reaction to π-allylpalladium chloride complex. We carried out the reaction of π-allylpalladium chloride (**5**) with malonate anion in DMSO, and again we observed smooth carbon–carbon bond formation [6]. We also observed the reaction of the complex with enamines to give allyl ketones after hydrolysis (eq. 3) [6].



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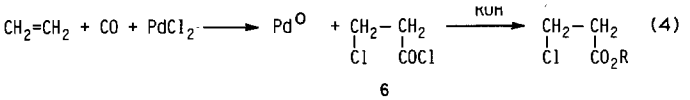
This was the first example of the reaction of π-allylpalladium complexes with a carbonucleophile to form a carbon–carbon bond. After our discovery, formation of carbon–carbon bonds via π-allylpalladium complexes attracted the attention of synthetic organic chemists. Later, a catalytic process for nucleophilic substitution of allylic compounds via π-allylpalladium complexes was introduced [7,8] The catalytic reaction has been explored and used extensively as a synthetic method [9–11].

In parallel with the reaction of carbonucleophiles, we discovered the reaction of carbon monoxide with palladium complexes of olefins. The reaction of the ethylene-$PdCl_2$ complex with carbon monoxide in benzene proceeded smoothly at room temperature to give β-chloropropionyl chloride (**6**) (eq. 4) [12,13]. When the reaction was carried out in ethanol, ethyl β-ethoxypropionate was obtained. On the basis of our oxidative carbonylation of olefins with Pd^{II} salts, a catalytic process aimed at acrylic acid production was explored soon afterwards by Union Oil Company [14].



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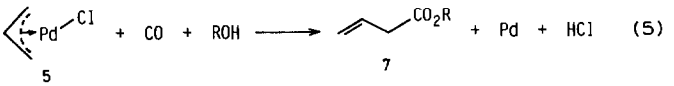
π-Allylpalladium chloride **5** was carbonylated to form 3-butenoate esters **7** in alcohol (eq. 5) [15].



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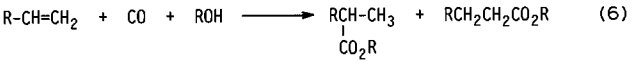
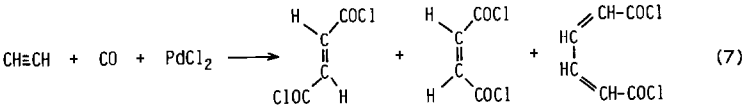
5 7

These carbonylations are stoichiometric reactions. But we observed catalytic carbonylation of olefins in alcohols to give saturated esters (eq. 6) [16]. Carbonylation of olefins catalyzed by palladium phosphine complexes was studied extensively by researchers of BASF [17].



(6)

Catalytic carbonylation of allylic halides was found under somewhat higher pressure by our and other groups [18–20]. We also discovered the catalytic carbonylation of various acetylenic compounds. Some samples are shown in eqs. 7–9 [21–23].



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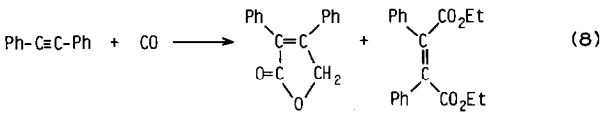

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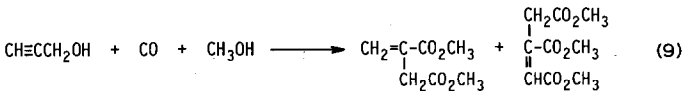
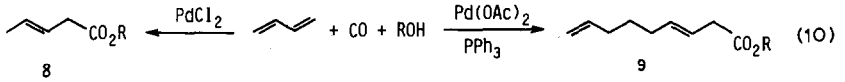


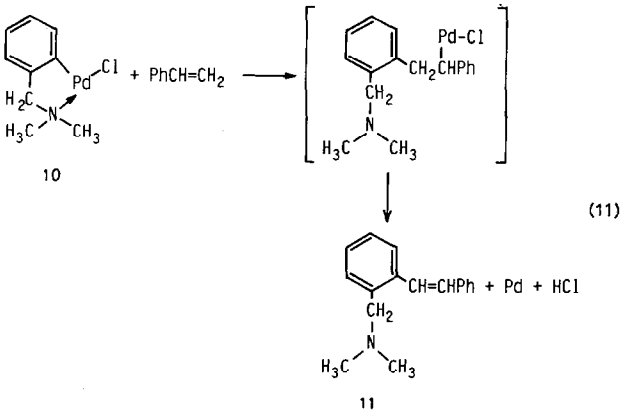
(9)

Butadiene is carbonylated in two ways. Catalytic carbonylation using $PdCl_2$ gave 3-pentenoate (**8**) [24–27]. On the other hand, the reaction catalyzed by $Pd(OAc)_2$ and PPh_3 afforded 3,8-nonadienoate (**9**) (eq. 10) [28,29].



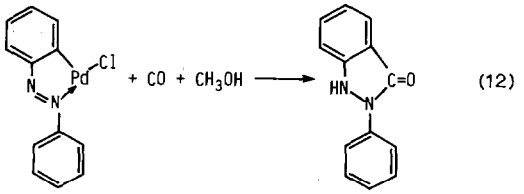
8 9

At the same time, we turned our attention to the reaction of aromatic compounds in the presence of Pd^{II} salts. Although we could not detect the reaction for benzene itself, we studied the reaction of the *ortho*-palladation product of benzylamine and azobenzene derivatives, and found that the *N,N*-dimethylbenzylamine-palladium complex (**10**) reacts smoothly with styrene at room temperature to give the stilbene derivative **11** (eq. 11) [30].



10 11

The azobenzene-$PdCl_2$ complex (**12**) reacts with carbon monoxide in alcohol at 50°C under pressure to give 2-phenyl-3-indazolinone (**13**) in high yield (eq. 12) [31].

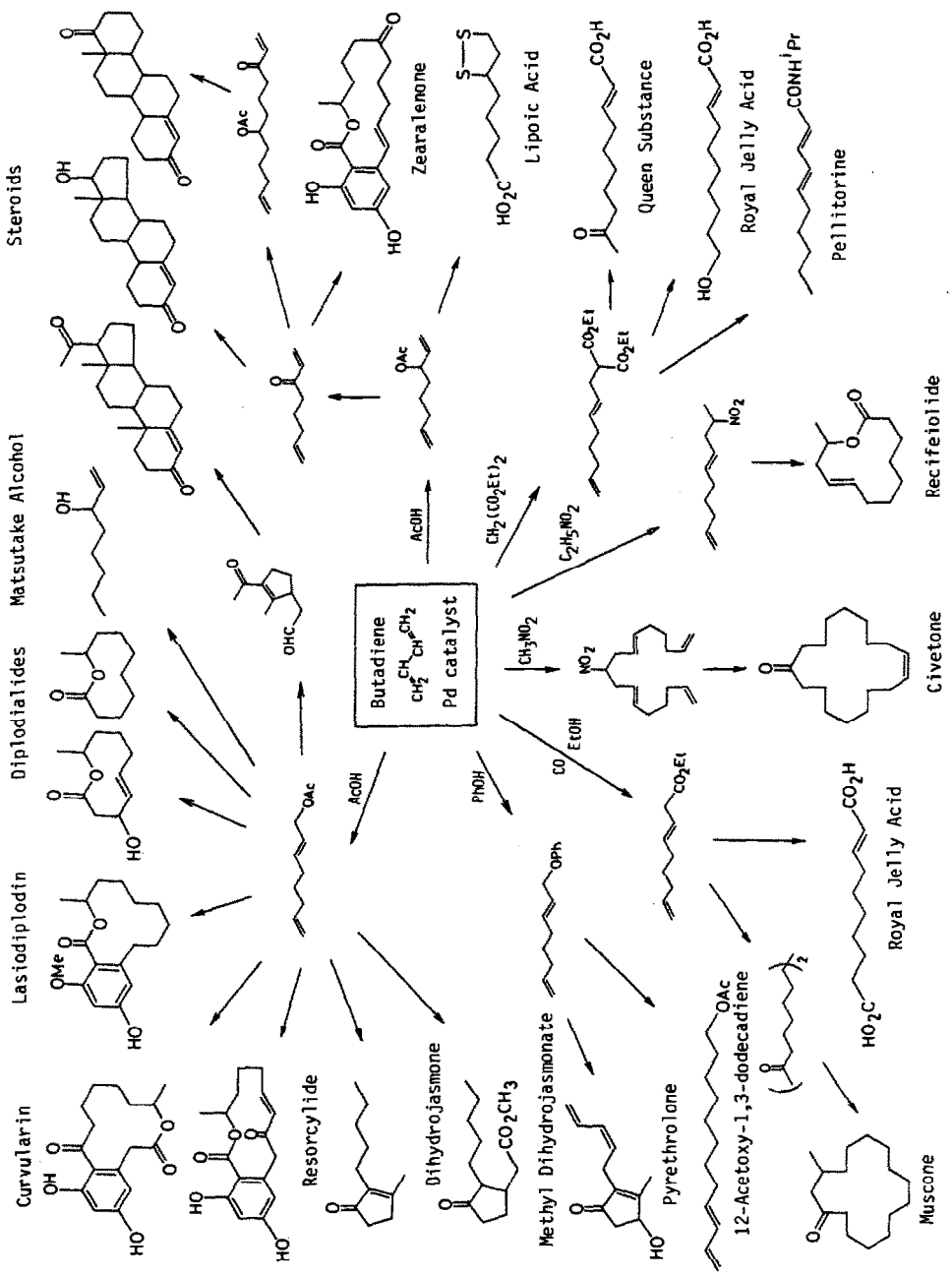


12 13

Thus early in 1960's we discovered a number of new reactions using palladium compounds, both stoichiometric and catalytic. These results were summarized in "Accounts of Chemical Research" [30].

3. Our work in 1980's

Soon after we started our research on palladium chemistry, researches in this field made remarkable progress. In 1980, I published a book entitled "Organic Synthesis with Palladium Compounds" [9] with a kind "Foreword" written by Dr. J. Smidt, who was a main inventor of the Wacker process, just before he passed away. The book included nearly 1000 references.

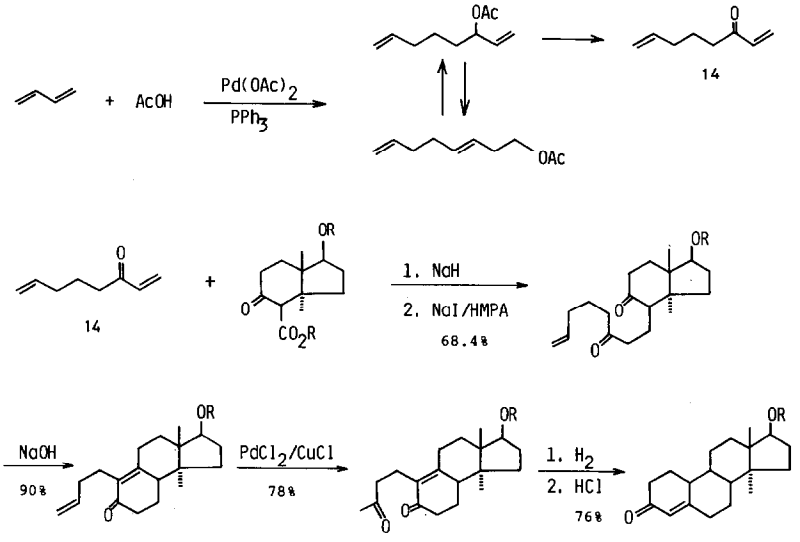

Curvularin
Lasiodiplodin
Diplodialides
Matsutake Alcohol
Steroids
Resorcylide
Dihydrojasmone
Methyl Dihydrojasmonate
Pyrethrolone
12-Acetoxy-1,3-dodecadiene
Muscone
Butadiene
Pd catalyst
AcOH
PhOH
CO EtOH
CH_3NO_2
$CH_2(CO_2Et)_2$
$C_2H_5NO_2$
Civetone
Recifeiolide
Zearalenone
Lipoic Acid
Queen Substance
Royal Jelly Acid
Pellitorine

SCHEME 1

In 1974, I moved from the industry to Tokyo Institute of Technology. After some interruption I again began research on organic chemistry of palladium. We carried out considerable work on application of the Wacker reaction to various olefinic compounds, demonstrating by many examples that the reaction is a very useful method of ketone synthesis, and showed that terminal olefins can be regarded as masked methyl ketones. This work was summarized in a recent review article [32].

Another field of research was the application of butadiene telomers to organic synthesis. Palladium-catalyzed codimerization reactions of butadiene with nucleophiles to afford butadiene dimers and telomers were first reported in 1967 [33,34], and were studied by several groups, including ours [35,36]. These telomers are trifunctional compounds, and we found that they are useful building blocks for a number of natural products. We synthesized steroids, macrolides (diplodialide, lasiodiplodin, zearalenone, recifeiolide), civetone, muscone, royal jelly acids, queen substance in a short sequence using butadiene telomers as main building blocks, as summarized in Scheme 1 [37–39]. A typical example is the synthesis of steroids in a short sequence by using as a bisannelation reagent 1,7-octadien-3-one (**14**), which is derived easily from the telomer of acetic acid. In these steroid syntheses, the oxidation of terminal olefins to methyl ketones with the $PdCl_2/CuCl$ catalyst is a key step (see Scheme 2) [40].

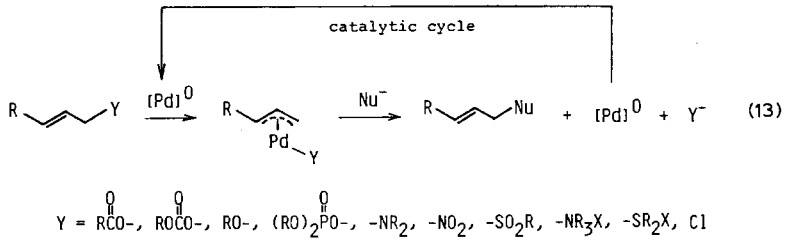
In addition to this, we carried out extensive studies of π-allylpalladium chemistry, discovering a number of new catalytic reactions. In this section, I will summarize new aspects of π-allylpalladium chemistry developed in our laboratory in the last five years.



SCHEME 2

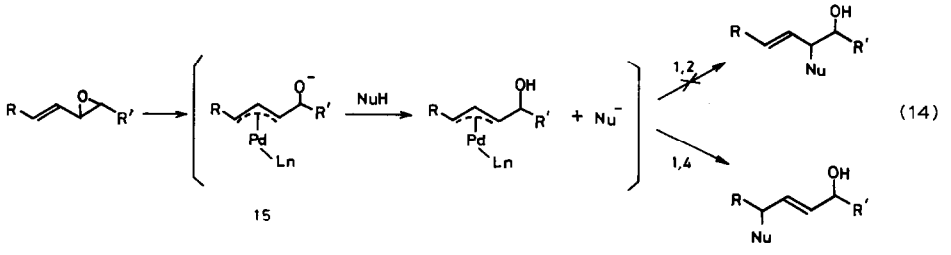
Allylation under neutral conditions with ene oxides and allyl carbonates

The allylation reaction of carbonucleophiles with various allylic compounds has now wide-spread use in organic synthesis. Mainly allylic acetates are used in the presence of bases such as sodium hydride or tertiary amines (eq. 13).

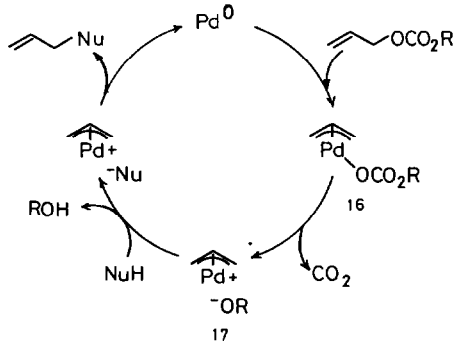


We have developed the allylation reaction under neutral conditions by using allylic carbonates. Furthermore, with allylic carbonates we discovered new reactions which are impossible with allylic acetates.

At first we found that diene monoepoxides behave as very reactive allylating agent for carbonucleophiles [41,42]. The reaction is regioselective 1,4-addition. Also it is stereoselective. We applied this regio- and stereoselective reaction of diene monoxides to the synthesis of natural products such as prostaglandin and steroids [43–45]. More importantly, the palladium-catalyzed reaction of diene monoxides with carbonucleophiles proceeds under neutral conditions. When π-allylpalladium complex is formed as an intermediate, alkoxide anion **15** is formed which behaves as a base, and picks up a proton from carbonucleophiles. This is the reason why the reaction can be carried out under neutral conditions (eq. 14).



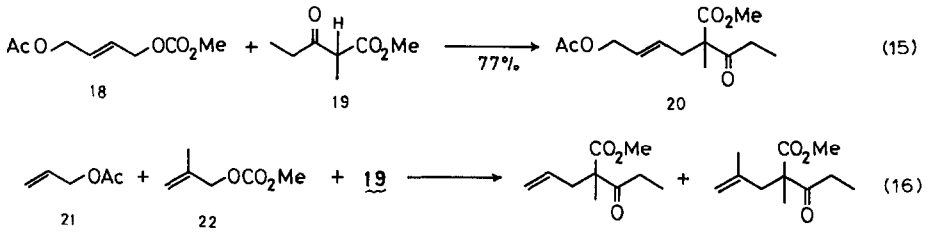
The reaction of diene monoxides under neutral conditions via in situ formation of alkoxide anion gave us an interesting idea for further work. We expected in situ formation of alkoxide anion from allyl carbonates. We found that allylic carbonates are extremely reactive allylating reagents, and allylation of carbonucleophiles pro-



SCHEME 3

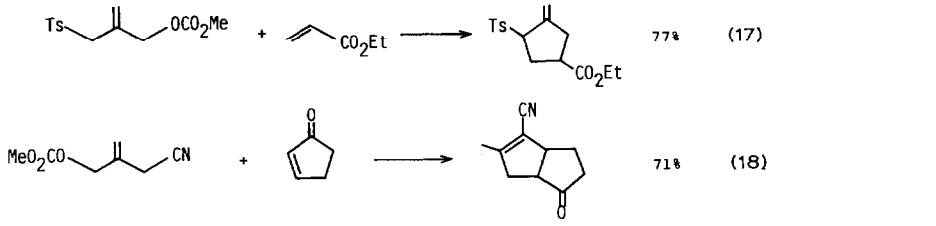
ceeds under neutral conditions [46,47]. Allyl carbamates react similarly [48]. This can be easily understood in terms of the following mechanism. Oxidative addition of allyl carbonates to Pd^0 complex gives the allylpalladium carbonate complex **16**, and this undergoes smooth decarboxylation to give the palladium alkoxide **17**. This alkoxide formed in situ behaves as a base, and abstracts a proton from carbonucleophiles (see Scheme 3).

Thus with allylic carbonates carbon–carbon bond formation is possible under neutral conditions. On the other hand, in the absence of base almost no reaction takes place with allyl acetates and phosphates. Formation of allyl alkyl ethers by the palladium-catalyzed reaction of allyl alkyl carbonates is known [49], but the reaction of π-allylpalladium with carbonucleophiles is much faster than that with alkoxide, and thus no allyl alkyl ether formation takes place in the presence of carbonucleophiles. We have shown clearly that allyl carbonates are more reactive than acetates by using the chemoselective reaction of 4-acetoxy-2-butenyl methyl carbonate (**18**) with the β-keto ester **19**. The reaction takes place only with the allylic carbonate group to give **20** (eq. 15), without an attack on the allylic acetate group under neutral conditions. As another example, in a competitive reaction of allyl acetate (**21**) and methyl methallyl carbonate (**22**) with the β-keto ester **19**, the carbonate reacted predominantly when PPh_3 was used as the ligand, but the selectivity towards reaction of the carbonate was higher when $P(OEt)_3$ was used as the ligand (eq. 16).

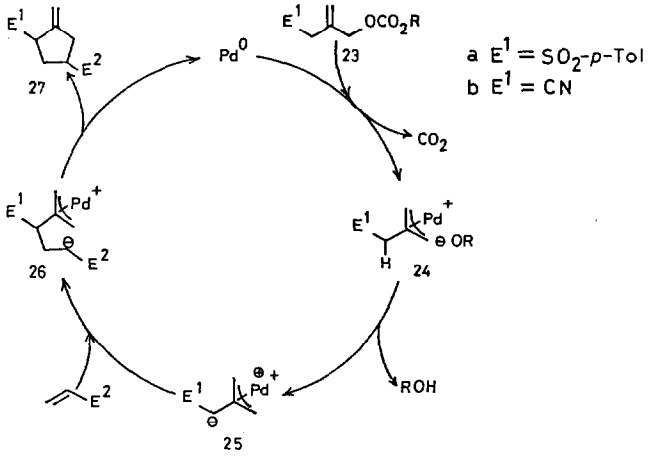


PPh_3	16	84
$P(OEt)_3$	3	97

Facile reaction of allylic carbonates can be applied to the [3 + 2]cycloaddition under neutral conditions, as shown in eqs. 17 and 18 [50]. The allylic carbonates **23**,



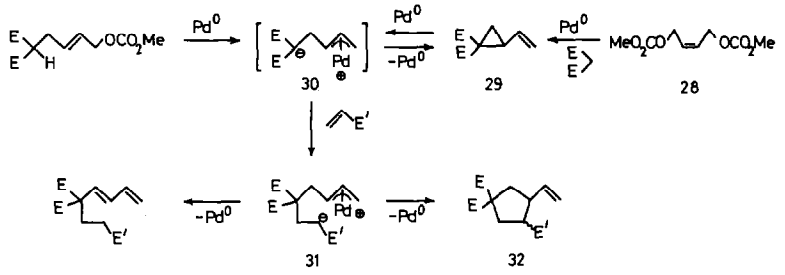
which have an electron-withdrawing group at the methallylic position, undergo decarboxylation by the action of Pd^0 to form **24**, followed by intramolecular deprotonation of active methylene in the same molecule to form the π-allylpalladium complexes **25** (Scheme 4). The carbanion **25** undergoes the Michael addition reaction with olefins containing electron-withdrawing groups to generate carbanion **26**, which then attacks the π-allylpalladium system intramolecularly. Consequently, [3 + 2]cycloaddition occurs to form the five-membered compounds **27** with ex-



SCHEME 4

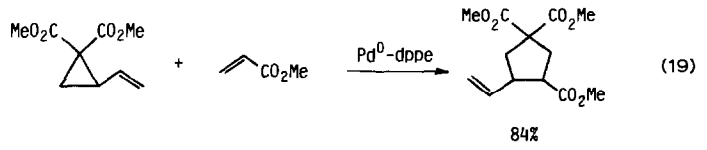
omethylene. A related reaction, reported by Trost et al., involves a [3 + 2]cycloaddition based on the generation of carbanion by desilylation [51].

Vinylcyclopropanes **29** with two electron-withdrawing groups, which are prepared by the palladium-catalyzed reaction of biscarbonate of 2-butenediol (**28**), undergo palladium-catalyzed cycloaddition r with electron-deficient olefins to form vinylcyclopentanes [52]. The reaction involves the formation of π-allylpalladium complexes **30** containing a carbanion centre, which undergoes Michael-type addition to electron-deficient olefins. The generated carbanion **31** then attacks π-allylpalladium complex to form cyclopentane **32** (see Scheme 5).



SCHEME 5

A typical example is the following (eq. 19):



84%

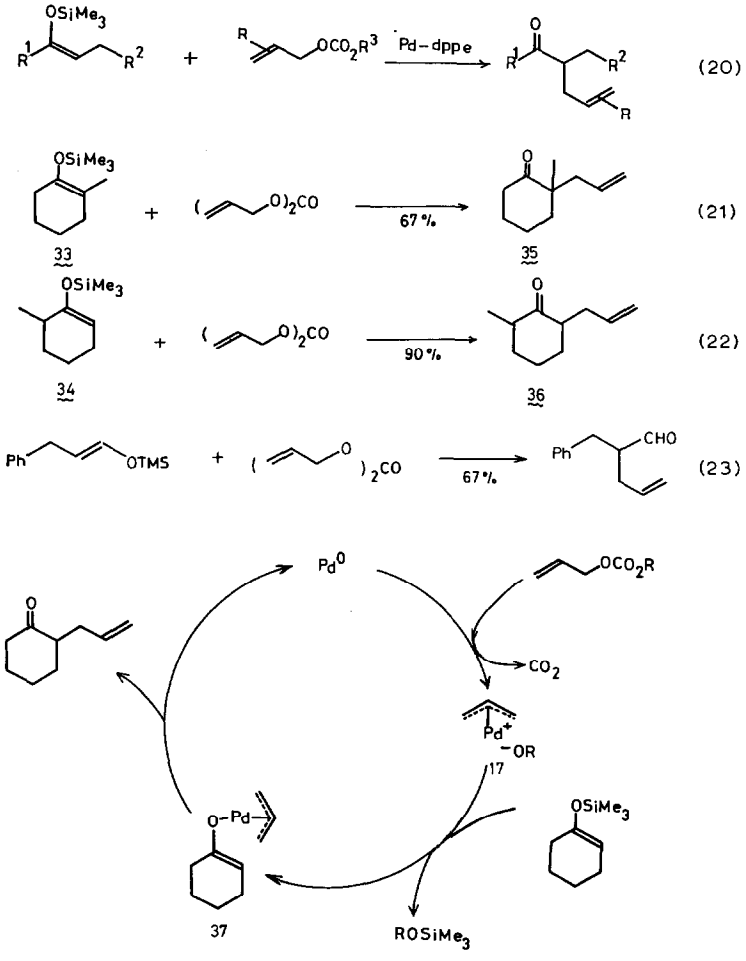
(19)

It is known that 1,3-butadienylcyclopropanes activated by two electron-withdrawing groups smoothly rearrange to vinylcyclopentanes by ring opening via π-allylpalladium complex [53,54].

Decarboxylation-allylation and decarboxylation-dehydrogenation reactions with allyl carbonates

Palladium-catalyzed allylation of simple ketones is not easy. They are allylated by allyl acetates via their lithium [55], boron [56], and tin [57] enolates. Recently palladium-catalyzed allylation of simple ketones with *O*-allylisourea was reported [58].

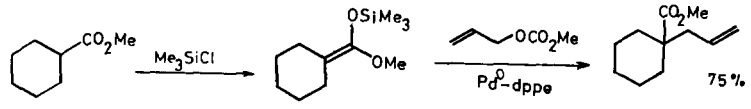
The palladium-catalyzed reaction of silyl enol ethers with allyl acetate or allyl ammonium salt gave poor results. We found that by the reaction of silyl enol ethers with allyl carbonates, monoallylation at α-position of ketones and aldehydes is possible [59]. The reaction is regioselective. For example, two isomeric silyl enol ethers **33** and **34** were prepared from 2-methylcyclohexanone via thermodynamic and kinetic enolates. Their allylation regioselectively gave 2-allyl-2-methylcyclohexanone (**35**) and 2-methyl-6-allylcyclohexanone (**36**), respectively, without forming a mixture of these isomers. For this reaction, dppe is a better ligand than PPh_3 (eqs. 20–23).



SCHEME 6

The reaction can be interpreted in terms of the following mechanism. There is initial oxidative addition of allyl carbonates to Pd^0, followed by decarboxylation to give π-allylpalladium alkoxide **17**, which undergoes transmetalation with silyl enol ethers to give π-allylpalladium enolate **37** and alkoxysilane. Finally reductive elimination gives allylated carbonyl compound with regeneration of Pd^0 species, which starts a new catalytic cycle (see Scheme 6).

Ketene silyl acetals are prepared by silyation of ester enolates. They were found to react with allyl carbonates under catalysis by Pd-phosphine to give α-allylated esters in high yields [60]. The reaction can be applied also to the allylation of lactones (eqs. 24, 25).



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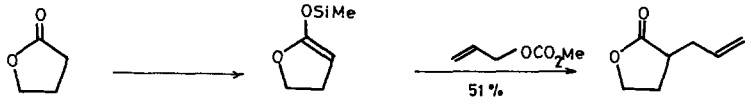
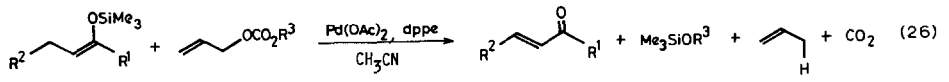


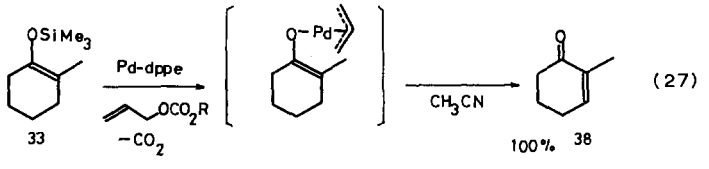
(25)

In the reaction of silyl enol ethers with allyl carbonates, we observed a very interesting solvent effect on the course of the reaction. Silyl enol ethers can be converted in one step in good yields to α,β-unsaturated carbonyl compounds by the reaction of allyl carbonates in CH_3CN using palladium complex as a catalyst (eq. 26) [61,62]. The enone and enal formation proceeds satisfactorily only in nitriles, and



(26)

CH_3CN is the most convenient. From 2-methylcyclohexanone, the kinetic and thermodynamic silyl enolates **33** and **34** were prepared, and subjected to the palladium-catalyzed dehydrogenation to give 2-methyl-2-cyclohexenone, **38**, regioselectively from **33**, and likewise 6-methyl-2-cyclohexenone, **39**, from **34** (eqs. 27–29).



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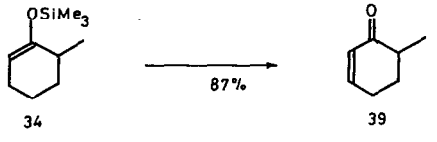

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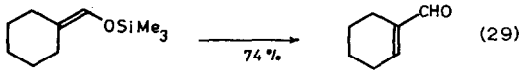
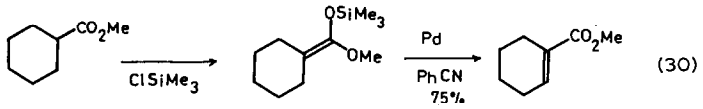


(29)

As in the palladium-catalyzed allylation of silyl enol ethers with allyl carbonates (Scheme 6), the allylpalladium enolate **40** is formed by the transmetalation between palladium and silicon as the common intermediate, which is in equilibrium with the carbon bonded complex **41**. The enone is formed by the elimination of PdH species from **41** (see Scheme 7). Finally reductive elimination of the allylpalladium hydride complex produces propene and regenerates the Pd^0 species.

The palladium-catalyzed decarboxylation-dehydrogenation of ketene silyl acetals derived from saturated esters and lactones can be carried out most satisfactorily in boiling CH_3CN in the presence of $Pd(OAc)_2$ without using a phosphine ligand [60]. In the presence of phosphine ligand, allylation proceeds to a considerable extent (eqs. 30,31).



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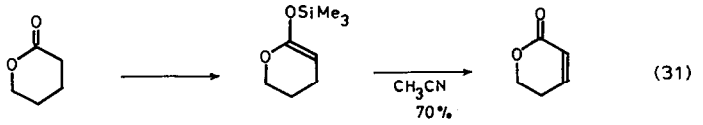
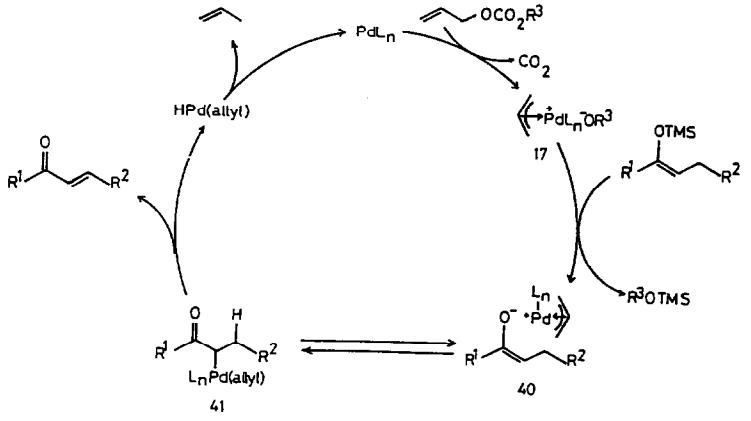
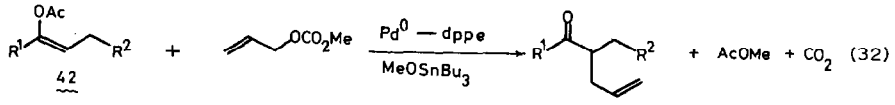


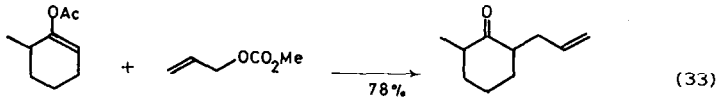
(31)

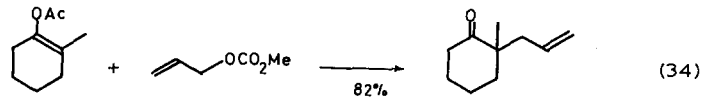
Enol acetates **42** are other enolate equivalents, easily prepared from ketones. Enol acetates can be allylated with allyl carbonates by using Pd-phosphine and tributyltin methoxide as a bimetallic catalyst to give α-allyl ketones in high yields [63]. For this reaction, dppe is the most suitable ligand. The allylation is regioselective, as shown in eqs. 32–34. This unique bimetallic catalysis can be interpreted in terms of the



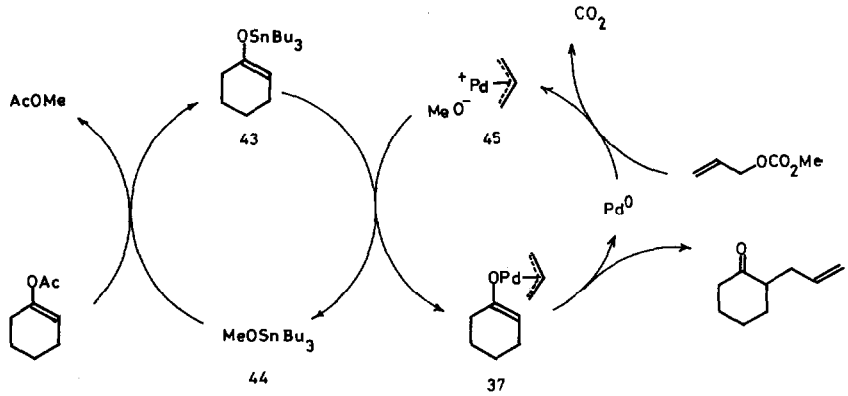
SCHEME 7





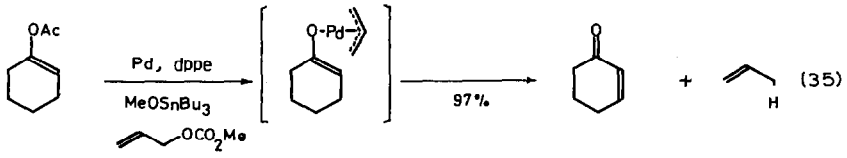


following mechanism. The in situ formation of tin enolates 43 by the reaction of enol acetates with tin methoxide 44 is known [64]. The transmetalation of tin enolates **43** with π-allylpalladium alkoxide complex **45**, formed by the oxidative addition of allyl carbonates to Pd^0 complex and subsequent decarboxylation, gives π-allylpalladium enolates **37**, which undergo reductive elimination to give allyl ketones [57]. Regeneration of the tin alkoxide **44** and Pd^0 makes the reaction catalytic (Scheme 8).

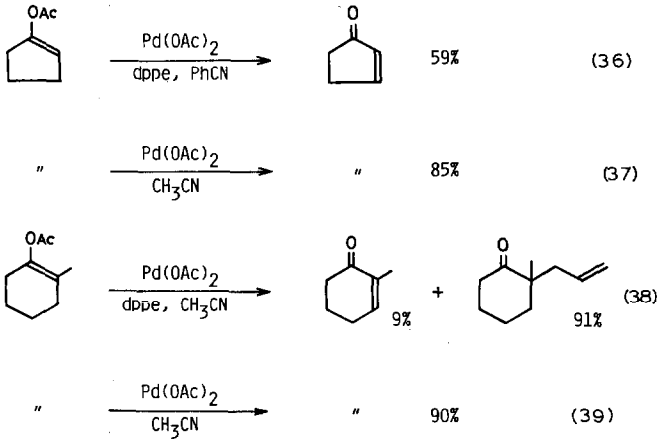


SCHEME 8

In this reaction, solvents have a crucial effect. Enol acetates are converted to enones selectively in CH_3CN (eq. 35) [65]. Somewhat poor results are obtained with

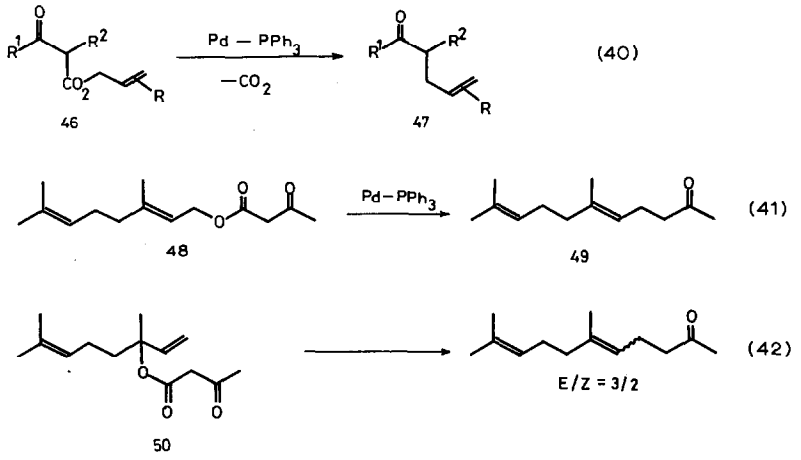


five-membered and eight-membered ketones, and α-substituted ketones by using a Pd-Sn-dppe catalyst, but in these cases enone formation takes place satisfactorily with the phosphine-free palladium catalyst, [66]. For example, cyclopentenone was obtained in 59% yield by using Pd-Sn-dppe catalyst but the phosphine-free Pd-Sn catalyst gave the enone in 85% yield. Similarly, 2-methyl-2-cyclohexenone was obtained in 90% yield from the enol acetate of 2-methylcyclohexanone in the absence of a phosphine ligand (eqs. 36–39).

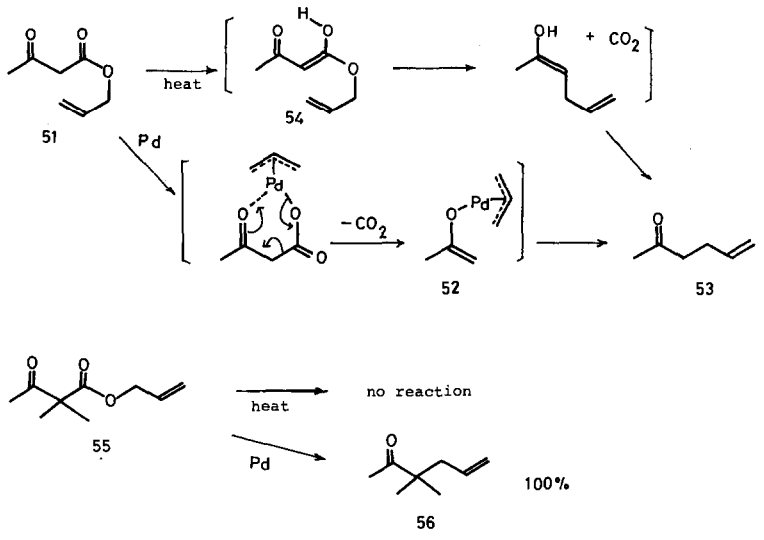


Decarboxylation-allylation and decarboxylation-dehydrogenation of allyl β-keto carboxylates and allyl alkenyl carbonates

Thermal rearrangement of the allyl β-keto carboxylates **46** with decarboxylation to give the α-allyl ketones **47** is known as the Carroll rearrangement, and proceeds at 170–200°C [67]. The same rearrangement proceeds in boiling THF or even at a room temperature when a Pd-phosphine catalyst is used [68,69]. Geranylacetone (**49**) was obtained from geranyl acetoacetate (**48**) in a high yield with retention of the configuration of double bond in boiling THF. From linalyl acetoacetate (**50**), a mixture of geranylacetone and nerylacetone was obtained in a 3/2 ratio (eqs. 40–42).



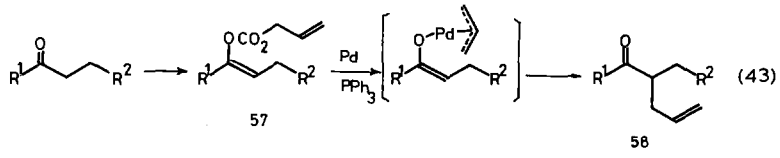
The palladium-catalyzed Carroll rearrangement can be accounted for by the following mechanism. Oxidative addition of allylic ester **51** is followed by facile decarboxylation to give the π-allylpalladium enolate **52**, which then undergoes reductive elimination to give allyl ketones **53** (see Scheme 9). This mechanism is completely different from the mechanism of the thermal rearrangement, which involves the [3,3]sigmatropic rearrangement of the enol form **54** of the allyl β-keto ester. In order to confirm the difference in the mechanisms, the reaction of the allylic

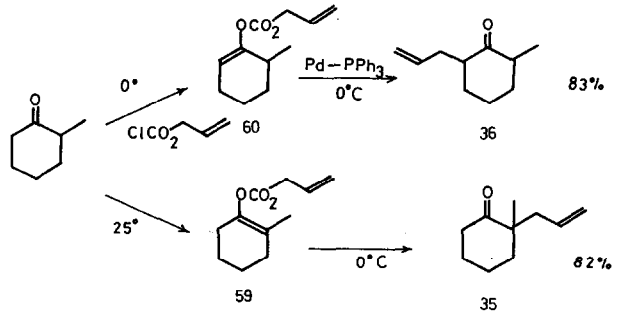


SCHEME 9

ester **55**, which has no hydrogen at the α-position, so that enolization is impossible, was examined. No thermal reaction took place, but a smooth palladium-catalyzed reaction gave the allyl ketone **56** in a nearly quantitative yield. The reaction was regioselective, and the allyl group was introduced at the more crowded carbon (Scheme 9).

The allyl enol carbonates (allyl alkenyl carbonates) **57**, readily prepared by the reaction of allyl chloroformates with enolates of ketones or aldehydes, undergo facile palladium-catalyzed rearrangement to give the allyl ketones **58** in high yields [70]. Allyl enol carbonates are more reactive than allyl β-keto carboxylates, and the reaction proceeds even at 0°C when Pd-PPh_3 is used as the catalyst (eq. 43).

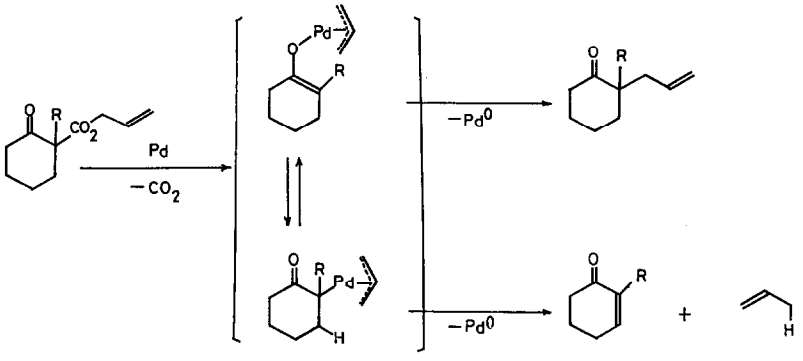




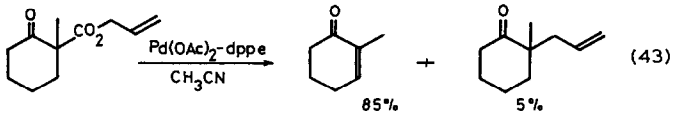
SCHEME 10

High regioselectivity was confirmed by the reaction of 2-methylcyclohexanone. The thermodynamically stable enol carbonate was obtained as a 93/7 mixture of **59** and **60**. The reaction of **59**, without separation of **60**, gave a mixture of 2-allyl-2-methylcyclohexanone (**35**) and 6-methyl-2-allylcyclohexanone (**36**) in 82% yield (**35**/**36** = 95/5). On the other hand, the allyl alkenyl carbonate **60**, prepared from kinetically generated potassium enolate at 0°C (99/1 mixture of **60**/**59**), was converted into **36** (**36**/**35** = 98/2) in 83% yield (Scheme 10).

In the palladium-catalyzed reaction of allyl β-keto carboxylates, solvents can have remarkable effects on the course of the reaction. Selective enone formation, or intramolecular decarboxylation-dehydrogenation is achieved by carrying out the reaction in CH_3CN [71]; aprotic polar solvents such as CH_3CN and DMF are the best. On the other hand, in acetone or t-butyl alcohol, the allylated products are the main products (Scheme 11). Some examples are shown in eqs. 43 and 44.



SCHEME 11



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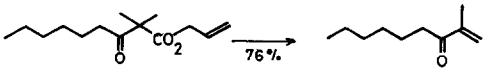
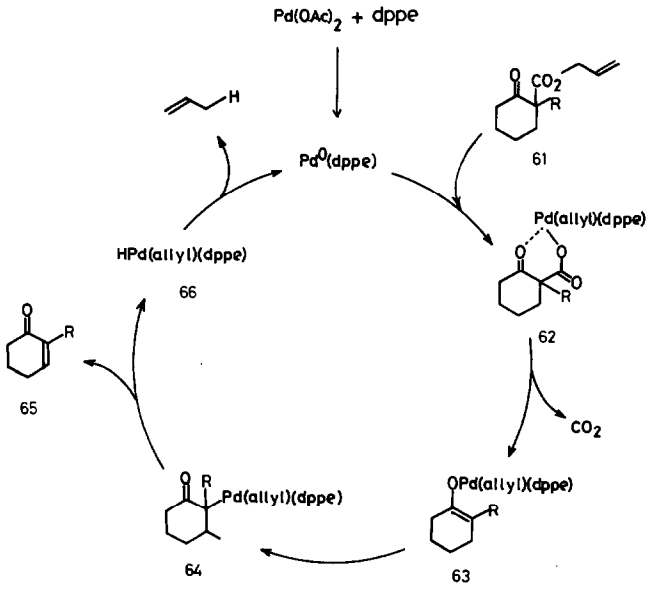


(44)

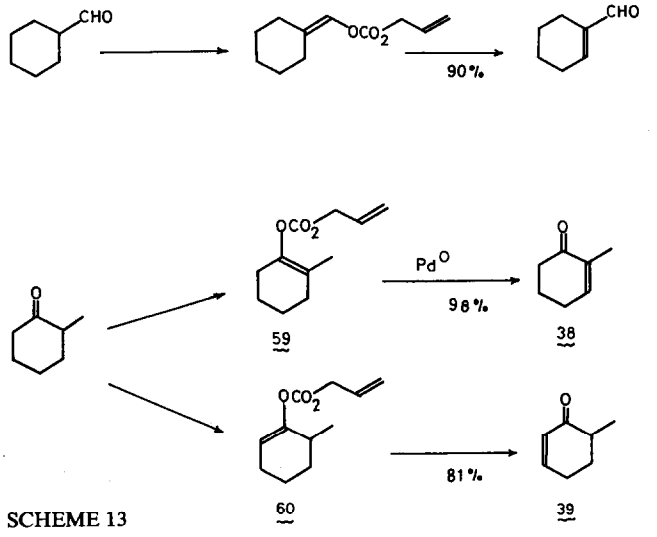
The enone formation can be accounted for by the following mechanism. The oxidative addition of the allyl ester **61** to Pd^0 species, formed in situ from $Pd(OAc)_2$, affords the allylpalladium β-keto carboxylate **62**, which undergoes decarboxylation to give the allylpalladium enolate complex **63**, which is in equilibrium with the carbon-bonded complex **64**. The enone **65** is then formed by elimination of Pd–H from **64**. Finally reductive elimination of the allylpalladium hydride complex **66** produces propene and regenerates the Pd^0 species (Scheme 12).

Intramolecular decarboxylation-dehydrogenation can also be brought about by the palladium-catalyzed reaction of allyl alkenyl carbonates to give enones selectively at 80°C in CH_3CN in the presence of $Pd(OAc)_2$ and dppe [72]. When the reaction is carried out at 20°C, allylation takes place to give allyl ketone, rather than



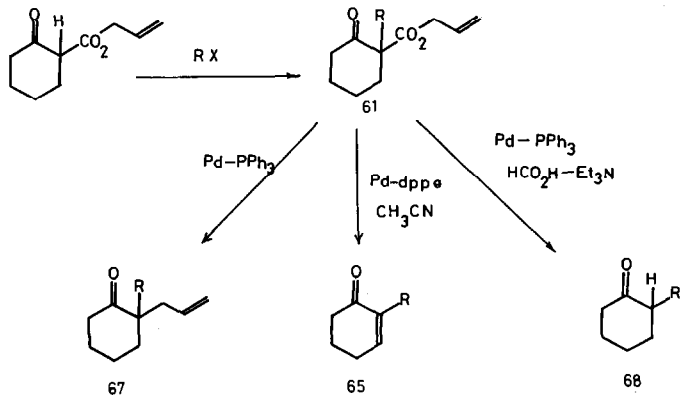
SCHEME 12

enone. By this method, not only ketones, but also aldehydes can be converted into α,β-unsaturated aldehydes. The reaction of allyl enol carbonates of unsymmetrical ketones is regioselective. The reaction of allyl enol carbonate obtained from thermodynamic enolate **59** of 2-methylcyclohexanone gave 2-methyl-2-cyclohexenone (**38**) selectively. On the other hand, the allyl enol carbonate from the kinetically generated enolate **60** gave 6-methyl-2-cyclohexenone (**39**) in 81% yield (Scheme 13).



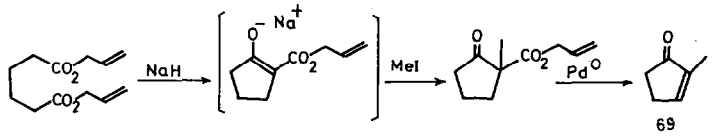
SCHEME 13

In preparative organic chemistry, β-keto esters are used for selective monoalkylation of ketones by removing the carboxylate by hydrolysis and decarboxylation after the alkylation. Three palladium-catalyzed reactions of allyl β-keto carboxylates **61** have now been discovered, namely, decarboxylation-allylation to form **67**, dehydro-



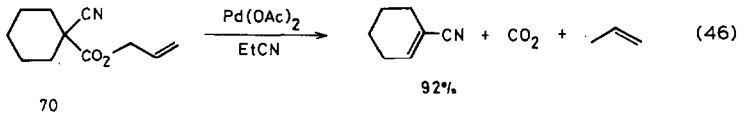
SCHEME 14

genation to give enone **65**, and hydrogenolysis to form **68** by careful selection of reaction conditions (see Scheme 14). These palladium-catalyzed reactions greatly enhance the usefulness of β-keto carboxylates. In particular the facile enone formation has a high synthetic value, since it is difficult to achieve by other means. For example, 2-methyl-2-cyclopentenone (**69**) can be prepared in a short sequence as shown in eq. 45 [73]. Furthermore, methyl jasmonate is now produced in Japan in an industrial scale as application of this palladium-catalyzed reaction.



(45)

Allyl alkylcyanoacetates **70** also undergo the palladium-catalyzed decarboxylation-dehydrogenation to give α,β-unsaturated nitriles in propionitrile (eq. 46) [74].



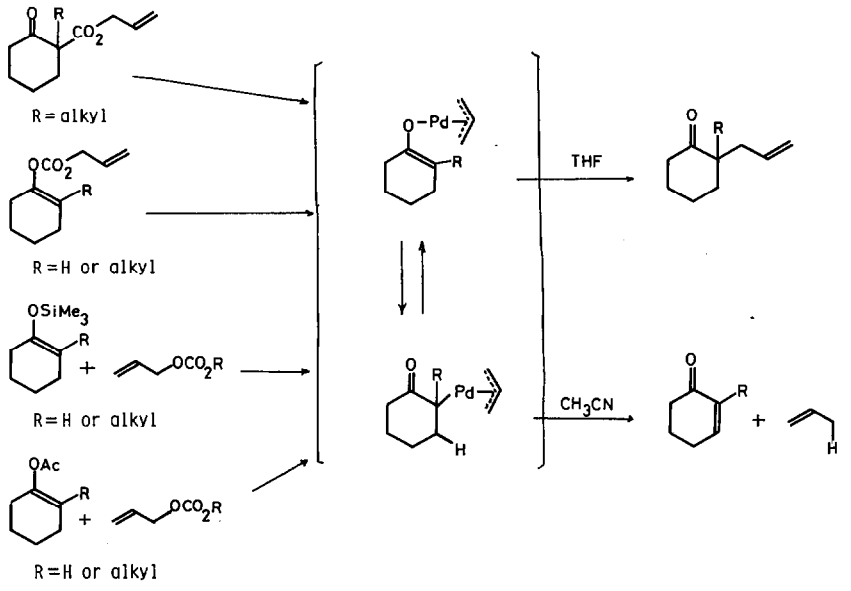
70

(46)

The palladium-catalyzed decarboxylation-allylation and decarboxylation-dehydrogenation reactions from four different species have now been explored. Intramolecular reactions take place with allyl β-keto carboxylates and allyl alkenyl carbonates. Intermolecular reactions of allyl carbonates with silyl enol ethers, ketene silyl acetals, and enol acetates are also possible. In all these reactions π-allylpalladium enolates are formed as common intermediates, which undergo dehydrogenation reaction in nitriles and allylation in other solvents. All these reactions proceed with high selectivity under neutral conditions, and have a high synthetic utility (see Scheme 15).

Oxidation of alcohols via their allyl carbonates

As described before, facile palladium-catalyzed elimination of β-hydrogen proceeds in CH_3CN. Consideration of the mechanism of the elimination of β-hydrogen

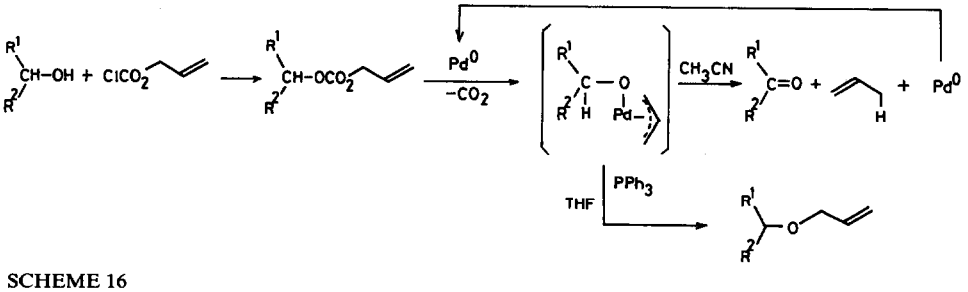


SCHEME 15

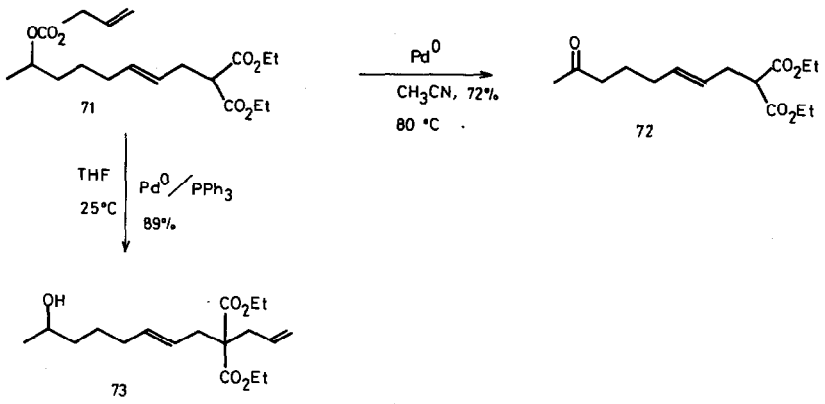
suggested the possibility of oxidation of alcohols via their allyl carbonates, and a new method of palladium-catalyzed oxidation of alcohols via their allyl carbonates, which are easily prepared by the reaction of alcohols with allyl chloroformate, was found [75]. The reaction produces only carbon dioxide and propene as by-products, and hence is very clean (see Scheme 16).

The phosphine-free palladium catalyst is active for this reaction. In the presence of PPh_3, decarboxylation-ether formation takes place without oxidation [49]. A high chemoselectivity was observed in the reaction of the compounds **71**. Use of the phosphine-free palladium catalyst afforded the ketone **72**. On the other hand, simple allylation of the malonate took place, without oxidation of alcohol, to give **73** when palladium/PPh_3 in THF was used (Scheme 17).

The selection of solvent is important, and CH_3CN is the most suitable. The reaction can be applied to various alcohols except simple primary alcohols, which give aldehydes in somewhat lower yields, and a considerable amount of alcohol is recovered. But primary benzyl and allyl alcohols can be oxidized smoothly. This



SCHEME 16

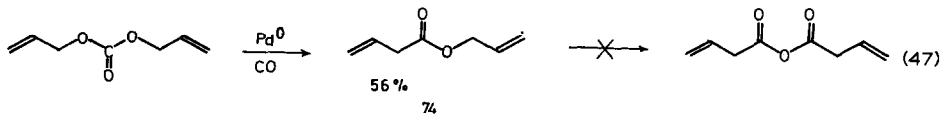


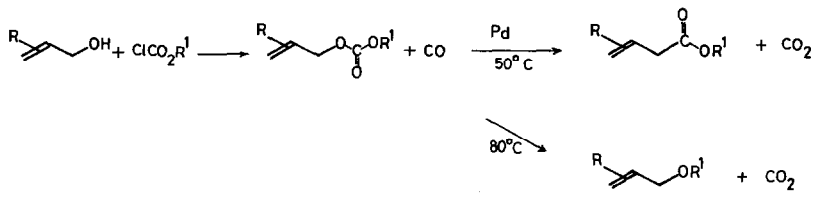
SCHEME 17

oxidation proceeds under neutral conditions without attacking functional groups. We later found that a ruthenium hydride complex is more active than palladium for this dehydrogenation [76].

Palladium-catalyzed decarboxylation-carbonylation of allylic carbonates

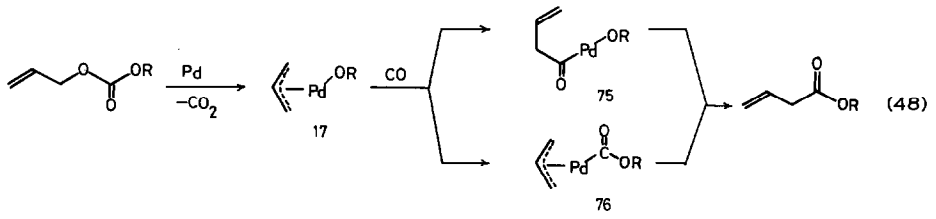
We found that allylic carbonates react with carbon monoxide under mild conditions [77,78]. Decarboxylation-carbonylation takes place, to give β,γ-unsaturated esters in high yields. In other words, there is exchange between carbon dioxide and carbon monoxide. (Scheme 18). The reaction proceeds even under atmospheric pressure of carbon monoxide using a rubber balloon filled with carbon monoxide. The reaction is somewhat accelerated by increasing the pressure up to 10 atm. The choice of reaction temperature is important; at room temperature, almost no reaction takes place, while at temperatures higher than 80°C, simple decarboxylation takes place, to give allylic ethers. The optimum temperature for the carbonylation is about 50°C. The following chemoselective carbonylation of diallyl carbonate was found to give **74**; no carbonylation of the allyl ester **74** was observed, showing that only allyl carbonate is carbonylated, with no attack on the allyl carboxylate (eq. 47).





SCHEME 18

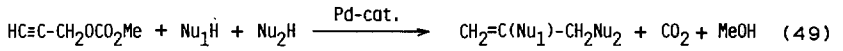
The decarboxylation-carbonylation can be explained in terms of the following mechanism. The first step is the oxidative addition of allyl carbonate to give π-allylpalladium alkoxide **17**. There are two possible reaction paths for carbon monoxide insertion. The first involves the insertion of carbon monoxide into the π-allylpalladium bond to give 3-butenoylpalladium complex **75**. The second involves insertion into the palladium–alkoxide bond to give (carboalkoxy)(π-allyl)palladium complex **76**. There is as yet no evidence which permits discrimination between these two possibilities. The final step is the reductive elimination to give β,γ-unsaturated ester, the Pd^0 species being regenerated at the same time (eq. 48).



(48)

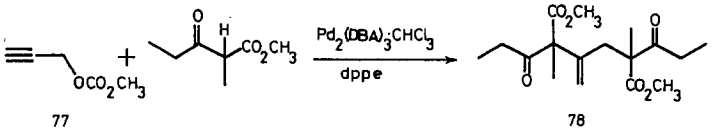
Reactions of propargyl carbonates with carbonucleophiles and carbon monoxide under neutral conditions

In contrast to the extensive studies on the palladium-catalyzed reactions of allylic compounds, very few studies have been carried out on the palladium-catalyzed reactions of propargyl compounds. Conversion of propargyl esters into 1,2-dienes by the reaction of hard carbonucleophiles such as organomagnesium [79] and zinc compounds [80,81] has been reported. We found that propargyl carbonates react with soft carbonucleophiles to give 2,3-disubstituted propenes under neutral conditions via the formation of π-allylpalladium complexes [82] (eq. 49).



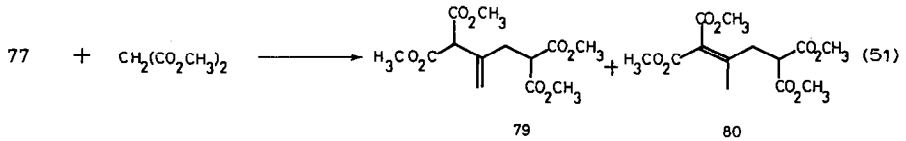
(49)

Reaction of methyl propargyl carbonate (**77**) with two equivalents of methyl 2-methyl-3-oxopentanoate in boiling THF for 2 h in the presence of $Pd_2(DBA)_3CHCl_3$ and dppe (Pd/dppe = 1/2, 5 mol%) gave the adduct **78** in 69% yield (eq. 50). Reaction of dimethyl malonate with **77** in boiling THF for 2 h also afforded a 1 : 1 mixture of the adducts **79** and **80** in 49% yield. In boiling dioxane for 9 h the yield of **80** was 69% (eq. 51).



(50)

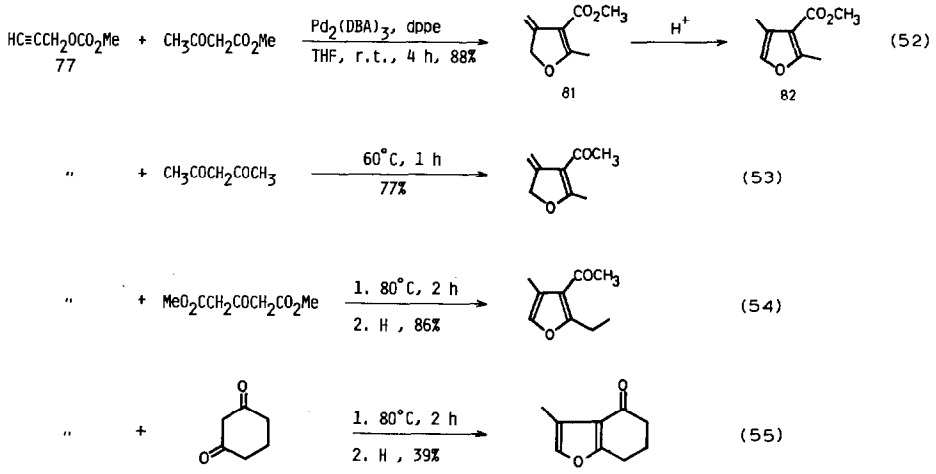
77 78



(51)

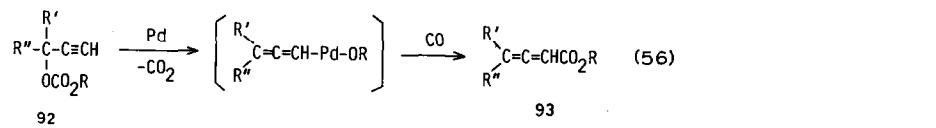
79 80

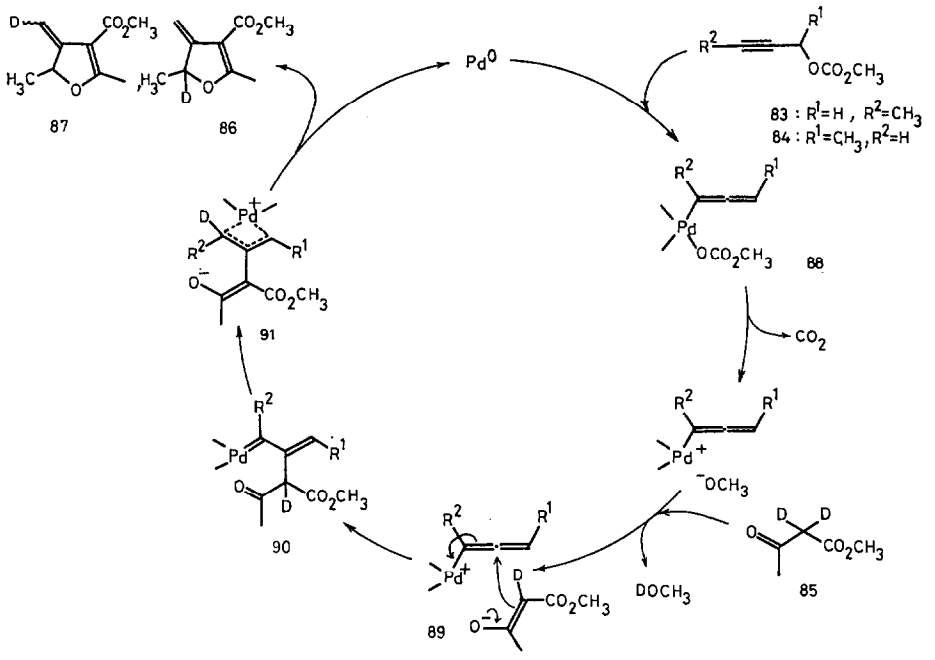
β-Keto esters and β-diketones bearing two active hydrogens react with propargyl carbonates in 1/1 ratio to give 4-methylene-4,5-dihydrofurans and 4-methylfurans by *C*- and *O*-alkylations. Reaction of **77** with methyl acetoacetate in THF at room temperature for 2 h in the presence of Pd-dppe catalyst (5 mol%) gave 3-methoxycarbonyl-2-methyl-4-methylene-4,5-dihydrofuran (**81**) in 88% yield. This smooth cyclization proceeds under completely neutral conditions. The methylenefuran **81** is unstable, and isomerizes to the stable furan **82** quantitatively under acidic conditions. Acetylacetone, dimethyl 3-oxoglutarate, and 1,3-cyclohexanedione reacted similarly with **77**, to give the corresponding furans (eqs. 52–55).



The reaction of methyl-2-butynyl carbonate (**83**) with methyl 2,2-bisdeuterioacetoacetate (**85**) gave the 5-deuteriofuran **86** (97%) as a sole product, but the reaction of methyl 1-methylpropargyl carbonate (**84**) afforded the furan **87** deuterated at the methylene carbon (1/1 *E*/*Z* mixture, 67%). One deuterium from **85** was transferred to **83** or **84** at a different carbon. These results can be accounted for in terms of the following mechanism (see Scheme 19). Initially an S_N2' type reaction of propargyl carbonate with palladium phosphine complex takes place, to give 1,2-propadienylpalladium carbonate **88**. Then the palladium carbonate **88** undergoes decarboxylation to give a methoxide ion, which picks up an acidic hydrogen (or deuterium) from active methylene compound **85** to give the complex **89**. Then the enolate anion attacks the *sp*-carbon of the 1,2-propadienyl moiety to form the palladium carbene complex **90**, which isomerizes to the π-allylpalladium complex **91** by intramolecular proton (or deuterium) transfer. Finally, the π-allyl complex **91** undergoes intramolecular *O*-alkylation at carbonyl oxygen at more substituted side of the π-allyl system to give the exomethylenefurans **86** or **87**.

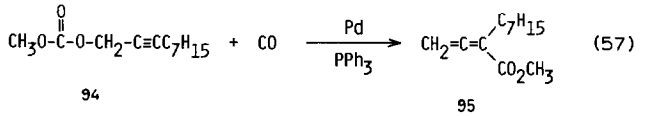
Propargyl carbonates **92** react smoothly with carbon monoxide in alcohol to give the 2,3-butadienoates **93** when Pd/PPh_3 is used as catalyst (eq. 56) [83].





SCHEME 19

This is a good preparative method for these reactive esters. For example, reaction of 2-decynyl methyl carbonate (**94**) with carbon monoxide (10 atm) at 50°C in methanol afforded methyl 2-heptyl-2,3-butadienoate (**95**) in 82% yield (eq. 57).



(57)

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