BEST SYNTHETIC METHODS

Palladium Reagents in Organic Syntheses

Richard F. Heck

Palladium Reagents
in Organic Syntheses

Richard F. Heck

Department of Chemistry
University of Delaware
Newark, Delaware

1985

This book is a guide to provide general information concerning its subject matter; it is not a procedural manual. Synthesis of chemicals is a rapidly changing field. The reader should consult current procedural manuals for state-of-the-art instructions and applicable government safety regulations. The Publisher and the authors do not accept responsibility for any misuse of this book, including its use as a procedural manual or as a source of specific instructions.

Foreword

There is a vast and often bewildering array of synthetic methods and reagents available to organic chemists today. Many chemists have their own favoured methods, old and new, for standard transformations, and these can vary considerably from one laboratory to another. New and unfamiliar methods may well allow a particular synthetic step to be done more readily and in higher yield, but there is always some energy barrier associated with their use for the first time. Furthermore, the very wealth of possibilities creates an information retrieval problem: How can we choose between all the alternatives, and what are their real advantages and limitations? Where can we find the precise experimental details, so often taken for granted by the experts? There is therefore a constant demand for books on synthetic methods, especially the more practical ones like "Organic Syntheses," "Organic Reactions," and "Reagents for Organic Synthesis," which are found in most chemistry laboratories. We are convinced that there is a further need, still largely unfulfilled, for a uniform series of books, each dealing concisely with a particular topic from a *practical* point of view—a need, that is, for books full of preparations, practical hints, and detailed examples, all critically assessed, and giving just the information needed to smooth our way painlessly into the unfamiliar territory. Such books would obviously be a great help to research students as well as to established organic chemists.

We have been very fortunate with the highly experienced and expert organic chemists who, agreeing with our objective, have written the first group of volumes in this series, "Best Synthetic Methods." We would always be pleased to receive comments from readers and suggestions for future volumes.

A.R.K., O.M.-C., C.W.R.

Preface

Several books concerned with the organometallic chemistry of palladium have appeared in recent years. Is there a need for another one? Aside from the fact that this is a rapidly developing field and new books could be written almost yearly to summarize the advances, a new book, concentrating on the experimental procedures of use in organic syntheses with palladium, is needed. The related literature is extensive, and a summary of the more useful aspects of this area of chemistry should be of significant value to synthetic organic chemists. It is the objective of this volume to fill that need and to provide the summary.

Topics have been selected on the basis of their synthetic value, including availability of the reagents required and convenience of the procedures. The book is not comprehensive, but it does at least mention all of the palladium-promoted organic reactions uncovered in the literature up to mid 1983 that appeared, to the author, to be of possible utility to organic chemists. Experimental procedures have been given wherever possible, and selected examples are also tabulated in order to make the descriptions as complete as possible and to allow reactions to be performed without the necessity of going back to the original literature.

Discussion of reaction mechanisms has been kept to a minimum. An attempt has been made to provide an understanding of the chemistry that is occurring where possible, but many details will have to be found in other places. The emphasis has been on catalytic reactions; however, useful stoichiometric palladium reactions are also included. The cost of palladium often can be compensated for by saving several steps of a synthesis with its use.

Methods of preparation of most of the commonly used complexes and salts of palladium are included as well as the recovery procedure for the metal. The organic reactions produced by palladium include double bond isomerizations, molecular rearrangements, oxidations, allylic substitutions and eliminations, coupling reactions, dimerizations and oligomerizations, carbonylations, cyclopropanations, and reductions. Reductions by hydrogen transfer only will be considered in this volume. Clearly, palladium is a very remarkable reagent in that it catalyzes such a wide variety of known organic reactions and will undoubtedly

此为试读，需要完整PDF请访问：www.ertongbook.com

catalyze others yet to be discovered. We hope this volume will help organic chemists to simplify many organic syntheses with a significant saving of time, effort, and energy.

RICHARD F. HECK

Contents

-1-

# Palladium Reagents and Palladium Recovery

1.1. Introduction

Palladium compounds are involved in all the reactions to be discussed in this book. It is appropriate, therefore, to begin with a brief description of the various types of palladium complexes and to give their methods of preparation. Normally organopalladium intermediates are formed *in situ* from inorganic palladium complexes or simple salts in catalytic reactions, but occasionally organopalladium compounds have been used as catalysts or stoichiometric reagents. There are instances, for example, where isomeric mixtures may be formed in catalytic reactions where it is desirable to isolate isomerically pure complexes and react them further. The use of stoichiometric quantities of palladium in the synthesis of complex molecules is not as unreasonable as it may seem at first thought. While the initial expense of the palladium compound is high, though comparable to the cost of many organic reagents, the palladium is usually easily recovered, essentially quantitatively, and is reusable. If the palladium reaction saves one or more steps in a synthesis, it indeed could be the most economical as well as the most convenient method to employ.

## 1.2. Zero-Valent Palladium Compounds

Palladium metal in the form of large particles is usually unreactive toward organic reagents. The finely divided metal, especially when it is on a support such as carbon, is more reactive and is commonly used as a catalyst for hydrogenation and for a few other reactions. More often, soluble zero-valent complexes are employed. The most common catalysts of this class

are tetrakis(triphenylphosphine)palladium(0) and bis(dibenzylideneacetone)-palladium(0).
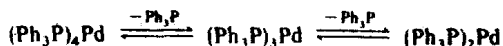
Tetrakis(triphenylphosphine)palladium(0) is commercially available, or it may be prepared easily from dichlorobis(triphenylphosphine)palladium, triphenylphosphine, and hydrazine as the reducing agent (1).

$$2\,(Ph_3P)_2PdCl_2 + 4\,Ph_3P + 5\,N_2H_4 \longrightarrow 2\,(Ph_3P)_4Pd + 4\,N_2H_5{}^+Cl^- + N_2$$
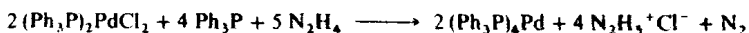
Unfortunately the complex is slowly oxidized by air in the solid state and rapidly in solution. It can be handled quickly in air but is best used under nitrogen or argon. The compound is quite reactive with halogens, acids, and organic halides and undergoes oxidative addition reactions with these materials; for example

$$(Ph_3P)_4Pd + CH_3I \longrightarrow CH_3Pd(I)(PPh_3)_2 + 2\,PPh_3$$
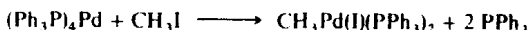
The high reactivity of the complex is due to its ease of dissociation in solution to tris- and bis(triphenylphosphine)palladium(0). These 16- and 14-electron compounds, respectively, are highly electron deficient (coordinatively unsaturated) and therefore very reactive.

$$(Ph_3P)_4Pd \underset{}{\overset{-Ph_3P}{\rightleftharpoons}} (Ph_3P)_3Pd \underset{}{\overset{-Ph_3P}{\rightleftharpoons}} (Ph_3P)_2Pd$$

The tetrakis(triphenylphosphine)palladium(0) is coordinately saturated with 18 electrons (2), having the outer electronic configuration $4s^2, 4p^6, 4d^{10}$. Other zero-valent organophosphine complexes with palladium are known, but they rarely offer any advantage over the triphenylphosphine derivative, with the possible exception of di[bis(diphenylphosphino)ethane]palladium(0). It is interesting that sterically very large phosphines (3) form only bis derivatives with palladium (4).

Preparation of Tetrakis(triphenylphosphine)palladium(0) (5). A mixture of palladium dichloride (17.72 g, 0.10 mol), triphenylphosphine (131 g, 0.50 mol), and 1200 ml dimethyl sulfoxide was placed in a single-necked, 2-liter round-bottom flask equipped with a magnetic stirring bar and a dual-outlet adapter. A rubber septum and a vacuum–nitrogen system were connected to the outlets. The system was then placed under nitrogen with provision made for pressure relief through a mercury bubbler. The yellow mixture was heated by means of an oil bath with stirring until complete solution occurs ($\sim 140°C$). The bath was then taken away, and the solution was rapidly stirred for approximately 15 min. Hydrazine hydrate (20 g, 0.40 mol) was then rapidly added over approximately 1 min from a hypodermic syringe. A vigorous reaction took place with evolution of nitrogen. The dark solution was then immediately cooled with a water bath; crystallization began to occur at $\sim 125°C$. At this point the mixture was allowed to cool without external cooling. After the mixture reached room temperature. it was filtered under

nitrogen on a coarse, sintered-glass funnel. The solid was washed successively with two 50-ml portions of ethanol and two 50-ml portions of ether. The product was dried by passing a slow stream of nitrogen through the funnel overnight. The resulting yellow crystalline product weighed 103.5–108.5 g (90–94% yield).

The melting point of the product in a sealed capillary under nitrogen was 116°C dec (uncorrected). The melting point is not very reproducible, however, and is not a good indicator of purity.

Di[1,2-bis(diphenylphosphino)ethane]palladium(0) (6). In acetone 1 equiv of PdBr$_2$ ($\sim 10^{-4}$ M) and 2 molar equiv of bisdiphenylphosphinoethane were dissolved and diluted with an equal volume of water. Then a concentrated solution of 3 molar equivalents of sodium borohydride in water was added dropwise with stirring to the solution under nitrogen. Hydrogen was evolved and the product precipitated. Recrystallization of the product from benzene–ethanol gave a 68% yield of yellow solid mp 234°C). The compound is air sensitive and should be handled under nitrogen or argon.

Bis(dibenzylideneacetone)palladium(0). Bis(dibenzylideneacetone)palladium(0) is more air stable than tetrakis (triphenylphosphine)palladium(0) and can be handled for short periods in air in the solid state. The dibenzylideneacetone ligands are easily replaced by other ligands such as organophosphines and phosphites. The compound was prepared by adding 3 equiv sodium acetate in a saturated aqueous solution to a solution of sodium tetrachloropalladite (Na$_2$PdCl$_4$) and 3 equiv dibenzylideneacetone in hot methanol under nitrogen. Cooling caused precipitation of the product as brown crystals. The product was filtered under nitrogen, washed with water and acetone, and dried in a stream of nitrogen (mp 135°C dec) (7).

1.3. σ-Bonded Organopalladium(II) Complexes

As is found with many organo transition metal complexes, the σ-organopalladium derivatives are generally not stable unless certain stabilizing ligands are present in the complexes. Most often triarylphosphines are the ligands employed, and of these triphenylphosphine is usually the one of choice for catalytic reactions because of its low cost and availability.

Two general methods are available for the preparation of σ-bonded organopalladium(II) complexes; metathesis reactions of main organometallics with palladium salts, usually the halides or acetate, and oxidative addition

of organic halides to palladium(0) complexes:
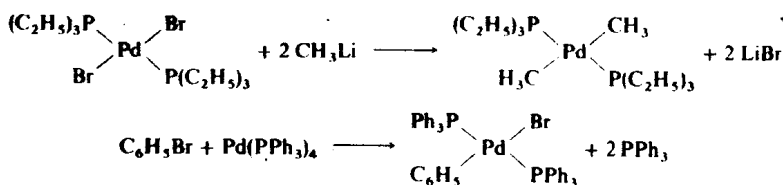
The first method allows the preparation of mono- or dialkyl- or arylpalladium(II) complexes depending upon the ratio of reactants and reactivity of the alkylating agent. The second method is only useful for preparing monoalkyl, vinyl, heterocyclic, or arylpalladium derivatives. A third method of preparation generally useful only *in situ* is direct metallation of arenes with palladium(II) compounds (usually the acetate or acetylacetonate). The presumed σ-arylpalladium compounds formed this way are generally unstable under the conditions required for their formation ($>100°C$) and must be formed in the presence of reactants to be useful or the complexes decompose into biaryls (see Chapter 6).

Palladation is best regarded as electrophilic substitution since electron-donating substituents accelerate palladation at the ortho and para positions. Exceptions to the general instability of organopalladium complexes under the conditions required for their preparation by palladation occur when certain substituents (usually a trivalent nitrogen group) are present in the aromatic ring or side chains of the ring that, most often, form five- or six-membered chelated rings with the palladium in the metallated product. This metallation with prior coordination of the aryl derivative is known as ortho metallation or cyclometallation because metallation occurs only ortho to the chelating substituents. The chelating substituent both facilitates the palladation and stabilizes the organopalladium product; for example
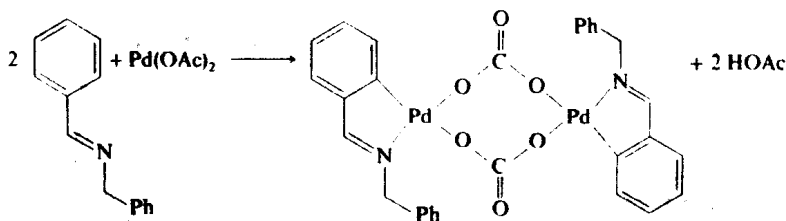
σ-Alkyl- and arylpalladium(II) complexes are intermediates in many palladium-catalyzed reactions. They may be added initially as the catalyst but generally this is not necessary because the complexes usually form *in situ* easily from simple palladium salts and the appropriate ligands. The ortho-

palladated complexes have been used stoichiometrically for the synthesis of a variety of organic products (see Chapters 6 and 8).

***trans*-Dimethyl(bistriethylphosphine)palladium(II) (8).** A solution of dibromo(bistriethylphosphine)palladium(II) was prepared in anhydrous ether (200 ml) under nitrogen from palladium bromide (5.32 g, 0.020 mol) and triethylphosphine (7.20 g, 0.061 mol) (caution, pyrophoric). After the palladium salt dissolves, the solution was cooled to $-60°C$ in a dry ice bath, and methyllithium (0.045 mol) in ether (38 ml) was added during 15 min with stirring. The stirring was continued for an additional 15 min while the reaction mixture was allowed to warm up to room temperature. Water (50 ml) was then added and the mixture was shaken. The ether phase was separated, dried with anhydrous magnesium sulfate, and concentrated *in vacuo*. The solid remaining was recrystallized from hexane to give 7.4 g (90%) of colorless, air-stable crystals of the product (mp 47–49°C).

A similar reaction with methylmagnesium bromide in place of methyllithium gave the monomethyl complex (8). Other complexes prepared by this method are listed in Table 1.

***trans*-Bromo(phenyl)bistriphenylphosphinepalladium(II) (9).** A mixture of tetrakis(triphenylphosphine)palladium(0) (2.2 g) and bromobenzene (1 g) in degassed benzene (15 ml) was heated overnight in a capped, thick-walled polymer tube under nitrogen at 80°C. After cooling to room temperature, the benzene was removed *in vacuo*, and the resulting solid was triturated with ether and the ether discarded. The product was further purified by recrystallization from methylene chloride–hexane. The yield of colorless airstable crystals (mp 216°–220°C dec) was 95% of theory.

TABLE 1

σ-Bonded Organopalladium Complexes Prepared
by Alkylation or Arylation[a]

Compound	Yield (%)	mp (°C) (dec)
$[CH_3)_2Pd[As(C_2H_5)_3]_2$	--	49
$(C_6H_5)_2Pd[P(C_2H_5)_3]_2$	55	95
$(CH_3)_2Pd(Bipy)$[b]	57	155
$C_6H_5Pd[P(C_2H_5)_3]_2Br$	--	89
$(p-CF_3C_6H_4)(C_6H_5)Pd[P(C_2H_5)_3]_2$	85	74–75
$[p-(CH_3)_2NC_6H_4]_2Pd[P(C_2H_5)_3]_2$	80	99–100
$[C_6H_5C≡C]_2Pd[P(C_2H_5)_3]_2$	66	162–164

[a] Adapted from Calvin and Coates (8).
[b] Bipy = 2,2'-dipyridyl.
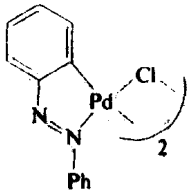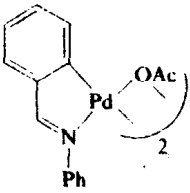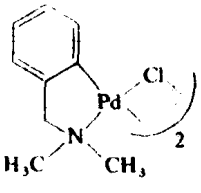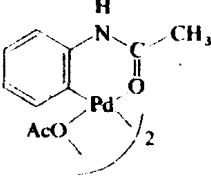
TABLE 2

σ-Bonded Organopalladium Complexes Prepared by Oxidative Addition

Compound	Yield (%)	Reaction temp (°C)	mp (°C) (dec)	Reference
3-$O_2NC_6H_4Pd(PPh_3)_2Cl$	86	135	208–210	9
4-$CH_3O_2CC_6H_4Pd(PPh_3)_2Cl$	83	135	172–178	9
4-$CH_3COC_6H_4Pd(PPh_3)_2Cl$	93	135	180–183	9
4-$O_2NC_6H_4Pd(PPh_3)_2I$	90	25	192–196	9
$CH_3Pd(PPh_3)_2I$	"Good"	25	151–154	10
$CH_3COPd(PPh_3)_2Cl$	"Good"	25	166–172	10
$C_2H_5OCOPd(PPh_3)_2Cl$	"Good"	25	232–237	10

TABLE 3

Chelated, σ-Bonded Organopalladium Complexes Prepared
by ortho Palladation

Compound	Yield (%)	mp (°C) (dec)	Reference
	---	279–281	12
	96	210–220	13
	96	185–187	14
	60	141–142	15,16

Numerous other aryl-, heterocyclic, vinylic, and alkylpalladium derivatives have been prepared by similar methods. Alkyl derivatives with β hydrogens are generally unstable with respect to elimination of a hydridopalladium group, however. Other examples of complexes prepared by oxidative addition of organic halides to tetrakis(triphenylphosphine)palladium(0) are given in Table 2.
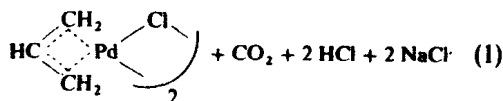
A typical procedure for ortho metallation is given below and other examples appear in Table 3.

Di-μ-acetatobis[o-(N-benzylformidoyl)phenyl]dipalladium(II) (*11a*). A mixture of palladium acetate (2.24 g, 10 mmol) and 2.05 g N-benzylbenzaldehyde imine in 50 ml acetic acid was heated to boiling for 50 min. After cooling, water was added, and the solid formed was separated by filtration. After washing with water and air drying, the product was crystallized from benzene to give 3.00 g (80%) of golden yellow crystals of the ortho-palladated product (mp 194°C dec).

1.4. π-Allylic Palladium Complexes

The π-allylic palladium complexes, in general, are more stable than σ-allylic derivatives because of the delocalized π-electron system of the allylic group bonding to two coordination positions of the metal. The π-allylic palladium group is generally in dynamic equilibrium with the coordinately unsaturated σ-allyl species, and the compounds may react in either form. These compounds are frequently encountered as intermediates in reactions of conjugated dienes and of vinylic palladium derivatives.

There are at least five general methods of preparation of π-allylic palladium complexes: (1) oxidative addition of allylic halides or esters to palladium(0) compounds or metal; (2) metathesis of main group allylic derivatives with palladium(II) salts; (3) reactions of alkenes with palladium(II) salts; (4) addition of σ-bonded organopalladium compounds to conjugated dienes; and (5) reactions of vinylic palladium complexes with alkenes. Typical examples of these methods are formulated below in the order just listed. Experimental procedures and tables of examples follow.

$$CH_2{=}CHCH_2Cl + Na_2PdCl_4 + CO + H_2O \xrightarrow{CH_3OH}$$

$$\cdots + CO_2 + 2\,HCl + 2\,NaCl \quad (1)$$

In this reaction, the commercially available sodium tetrachloropalladite is reduced by the aqueous carbon monoxide to palladium(0) which oxidatively adds the allyl chloride (17). In catalytic reactions, allylic acetates are generally employed to form the π-allylic complexes. These additions proceed by a nucleophilic displacement of the leaving group with inversion of configuration.

$$H_2C\!\!=\!\!\overset{\overset{\displaystyle CH_3}{|}}{C}\!-\!CH_2MgCl + (Ph_3P)_2PdCl_2 \xrightarrow{-MgCl_2} \xrightarrow{H_2O}$$

$$\left[H_3C\!-\!C \underset{CH_2}{\overset{CH_2}{\langle}} Pd \underset{PPh_3}{\overset{PPh_3}{\langle}} \right]^+ \quad Cl^- \cdot 2H_2O \quad (2)$$

The above example illustrates the use of the metathesis method for preparing π-allylic complexes (18).

$$+ \text{PdCl}_2 + \text{NaOAc} \xrightarrow[\text{HOAc, Ac}_2\text{O}]{\text{CuCl}_2,\ \text{NaCl}} \qquad + \text{NaCl} + \text{HOAc} \qquad (3)$$

$$\text{CO}_2\text{CH}_3 + \text{Pd(O}_2\text{CCF}_3)_2 \xrightarrow{\ \text{Cl}^-\ }$$

The two equations above (19,20) illustrate the direct conversion of alkenes to π-allylic complexes. The use of the highly reactive palladium trifluoroacetate is preferred when the mildest conditions are desired for the metallation. The reaction may be selective with nonconjugated dienes. The formation of terminal π-allylic complexes is preferred over similar internal ones as shown in the following example (21,22).

$$+ \text{Pd(O}_2\text{CCF}_3)_2 \xrightarrow[\text{RT}]{\text{CH}_3\text{COCH}_3} \xrightarrow{\ \text{Cl}^-\ }$$

83%

2-Alkenes prefer to form the more substituted π-allylic complexes while branched alkenes tend to form mixtures of isomers. The 1-methyl cycloalkenes generally produce the less substituted isomers (21).

72%   11%

92%

Electron-attracting substituents on a double bond generally deactivate the compound to allylic palladation. Thus, the triene ester below gives mainly the terminal π-allylic complex and none of the carbomethoxy-substituted isomer (21).

35%   5%

In the above example of method 4, the organopalladium reactant is formed *in situ* and adds to the diene to form the π-allylic adduct in good yield (23,23a).

$$(CH_3)_3CCH=CHHgCl + PdCl_2L_2 \longrightarrow [(CH_3)_3CCH=CHPdCl] + HgCl_2$$

$$[(CH_3)_3CCH=CHPdCl] + CH_2=CHCO_2C_2H_5 \longrightarrow$$

$$[(CH_3)_3CCH=CHCH_2\overset{\underset{\textstyle |}{PdClL_2}}{C}HCO_2C_2H_5] \xrightarrow{L}$$

$$[(CH_3)_3CCH=\overset{\underset{\textstyle \uparrow}{H-Pd-Cl}}{\overset{\textstyle |}{C}}HCH=CHCO_2C_2H_5] \longrightarrow$$ (5)
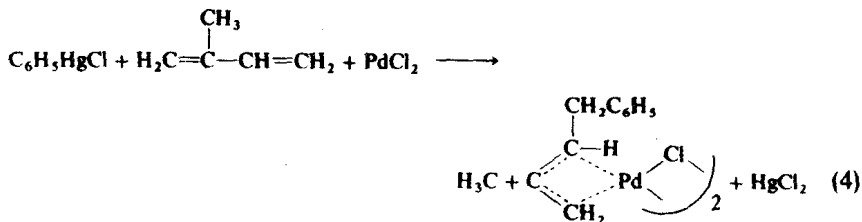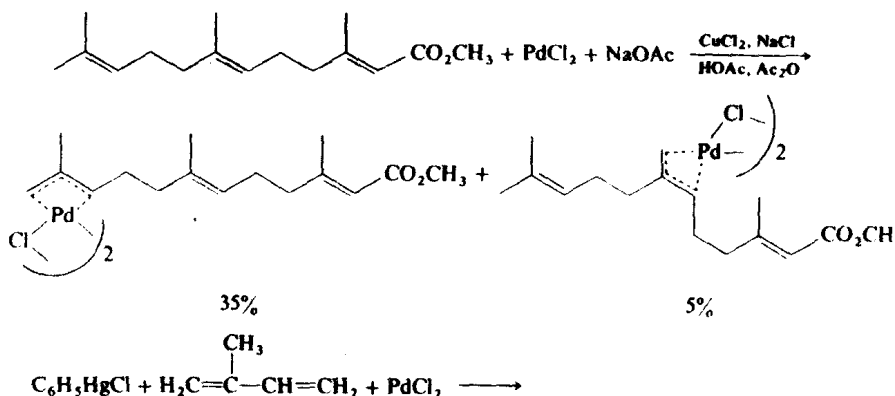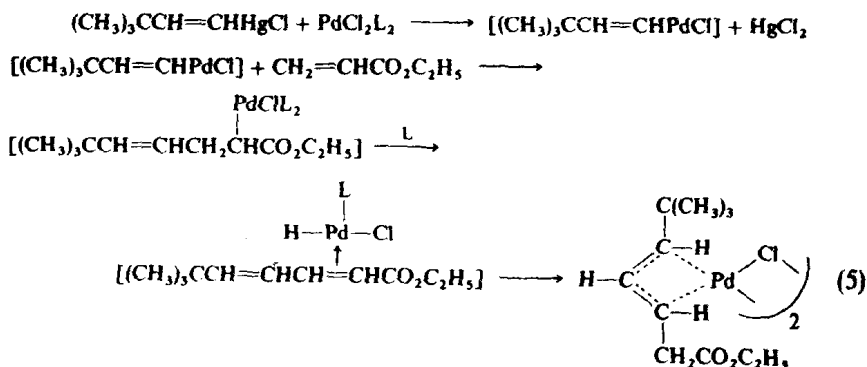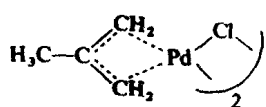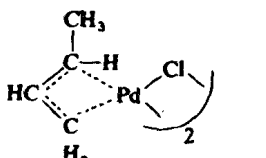
L = a weakly bonding ligand such as solvent or halide ion

Vinylpalladium complexes generally add to alkenes with subsequent elimination of a hydridopalladium group (24). Often the hydridopalladium group re-adds in the reverse direction before the π-hydrido complex dissociates.

Chloro-π-allylpalladium Dimer Prepared by Oxidative Addition (17). A mixture of palladium chloride (17.7 g) and calcium chloride (11.1 g) in 150 ml methanol and 10 ml water was stirred, and allyl chloride (27.9 g) was added. Carbon monoxide was passed into the stirred solution at a rate of about 2–2.5 liters/min for 30 min. The reaction mixture was then diluted with a liter of water, and the product was extracted with three portions (100 ml each) of chloroform. The combined extracts were dried over magnesium sulfate. Evaporation of the solvent under reduced pressure at room temperature gave yellow crystals of the air-stable complex (mp 158°C dec). The yield was 67.5% of theory (Table 4).

TABLE 4

Chloro-π-allylic Palladium Complexes Prepared
by Oxidative Addition[a]

Compound	Yield (%)	mp (°C)
	92.5	166–168 (dec)
	100	136–137

[a] Adapted from Dent et al. (17).