Organopalladium chemistry in the '60s and '70s†

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The history of organopalladium chemistry in the 1960s–1970s is briefly outlined. Organopalladium chemistry has a 40 year history. It was born in the late 1950s with the invention of the Wacker process. Inspired by the Wacker reaction, we started our research on Pd chemistry in the early 1960s and discovered the reaction of the $PdCl_2$ complex of COD (cyclooctadiene) with carbonucleophiles, which was the first example of carbon–carbon bond formation by means of a Pd complex. Then we opened the new field of π-allylpalladium chemistry by discovering the reaction of π-allylpalladium chloride with carbonucleophiles. Oxidative carbonylation of alkenes and alkynes mediated by Pd(II) and hydrocarbonylation of alkenes and alkynes catalyzed by Pd(0) were other discoveries made in our laboratory. An account of the development of organopalladium chemistry in our laboratory in the 1960s is presented. In addition, major accomplishments in organopalladium chemistry reported by other groups in the 1960s and 1970s are summarized.

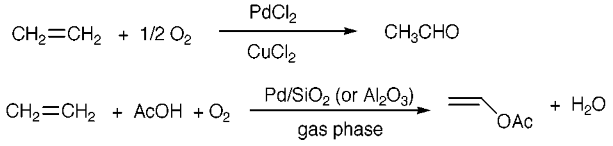
Palladium is now regarded as the most versatile metal among the many transition metals used for OMCOS (Organometallic Chemistry directed towards Organic Synthesis). We started our research on organopalladium chemistry in the early 1960s and discovered several carbon–carbon bond forming reactions promoted by Pd compounds. An account of our research on Pd chemistry and its development is presented.[1] In addition, some important contributions by other groups in the 1960s and 1970s are described. The purpose of this paper is to give young chemists a retrospective of the early history of organopalladium chemistry.

At present, research on OMCOS is in its golden age. In my opinion, OMCOS research has its origin in three kinds of commercial processes involving transition-metal-catalyzed reactions. They are:

1. Carbonylation reactions, which include the hydroformylation of alkenes to give aldehydes, developed by Rölen in 1938, the Reppe processes for acrylate from acetylene catalyzed by $Ni(CO)_4$ and for butanol from propylene catalyzed by $Fe(CO)_5$ (1940–1950s).
2. Production of polyethylene and polypropylene catalyzed by the Ziegler–Natta catalysts (mid 1950s).
3. The Wacker process to produce acetaldehyde from ethylene catalyzed by $PdCl_2$ and $CuCl_2$ (1959).

I started independent research in 1962 at Basic Research Laboratories of Toray Industries, where I had the opportunity to learn these commercial processes and to actually observe polymerization of ethylene and propylene by the Ziegler–Natta catalysts, and Ni-catalyzed cyclization of butadiene to afford COD and CDT (cyclododecatriene), being carried out by other groups at Toray. I was greatly impressed by the fact that the chemistry involved in these commercial processes is clearly different from the chemistry I had studied before when working on natural product synthesis, and I had the firm conviction that applications of transition-metal-catalyzed reactions to organic synthesis had great potential for the future. Thus I planned to study applications of transition-metal-catalyzed reactions to organic synthesis. The Wacker process in particular attracted my attention. Thus I made the fortunate selection of Pd as a target metal.

The Wacker process to produce acetaldehyde from ethylene using $PdCl_2$–$CuCl_2$ as catalysts, invented in 1959 in Germany, is the first example of a homogeneous palladium-catalyzed reaction.[2] Before that time, Pd was known only as a heterogeneous catalyst for hydrogenation. Soon after the invention of the Wacker process, formation of vinyl acetate by the oxidative acetoxylation of ethylene with $PdCl_2$ in AcOH in the presence of NaOAc was reported by Moiseev and coworkers.[3] Vinyl acetate is now produced commercially based on this reaction in the gas phase, using a Pd catalyst supported on silica or alumina.



The Wacker process consists of three stoichiometric reactions, shown below, and smooth cycling of these reactions is the essence of the success of the Wacker process. Formation of acetaldehyde by passing ethylene into an aqueous solution of Pd salts with quantitative precipitation of metallic Pd was known in the 19th century.[4] In my opinion, the most ingenious invention of the Wacker process is the second reaction, namely the oxidation of Pd(0) with $CuCl_2$. Apparently this reaction is expected to be a difficult one when we consider the oxidation-reduction potentials of Pd and Cu. Oxidation of Pd(0), a noble metal, with $Cu(II)Cl_2$, a base metal salt, is unrealistic. Thus the successful application of this reaction to the commercial process by maintaining high concentrations of HCl and $CuCl_2$ is the key to this novel process.

$$\begin{array}{rcl} H_2C{=}CH_2 + H_2O + PdCl_2 & \longrightarrow & CH_3CHO + Pd(0) + 2\,HCl \\ Pd(0) + 2\,CuCl_2 & \longrightarrow & PdCl_2 + 2\,CuCl \\ 2\,CuCl + 2\,HCl + 1/2\,O_2 & \longrightarrow & 2\,CuCl_2 + H_2O \\ \hline H_2C{=}CH_2 + 1/2\,O_2 & \xrightarrow{PdCl_2,\ CuCl_2} & CH_3CHO \end{array}$$

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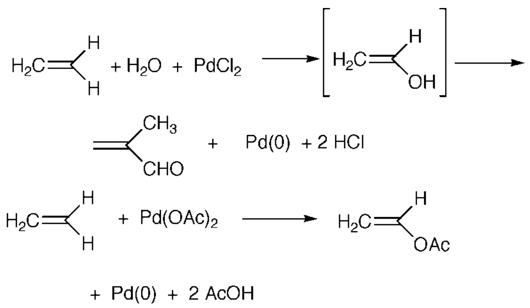
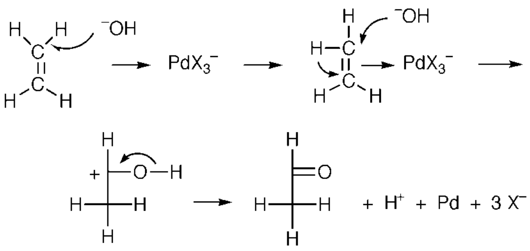
I was very much interested in the reactions involved in these two commercial processes to produce acetaldehyde and vinyl acetate, because formal nucleophilic substitution of ethylene with OH and OAc anions occurs in these reactions. Whatever the mechanism of the reactions, the nucleophilic substitution of alkenes was a new reaction, showing that Pd(II) is a unique compound that can promote this new reaction.



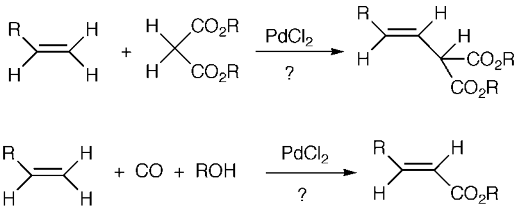
As a mechanistic explanation, Smidt and coworkers made the following statement in their review.[2b]

"Nucleophilic attack on olefin and hydride transfer are characteristic for this reaction. The oxygen required for the oxidation of the olefin is provided by the water. According to our hypothesis only the oxygen atom of the water is transferred to the olefin, while the four atoms originally present in ethylene remain there."



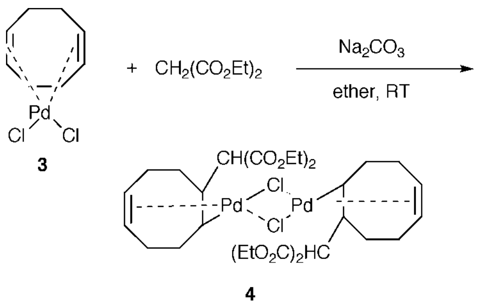
I was very much interested in this statement, which gave me an important hint to initiate our research on organopalladium chemistry. In other words, by studying the formation of the acetaldehyde and vinyl acetate carefully, I realized that hitherto unknown unique reactions were occurring using Pd(II). We understand that coordination of $PdCl_2$ to ethylene decreases its electron density and makes the attack of the oxoanions possible. With present day knowledge, the formation of acetaldehyde and vinyl acetate can be explained as follows. The first step of these reactions is oxypalladation to form **1** and **2**. Pd(II) is a good leaving group and its elimination is accompanied by a hydride shift to give acetaldehyde. On the other hand, elimination of β-hydrogen occurs to give vinyl acetate.

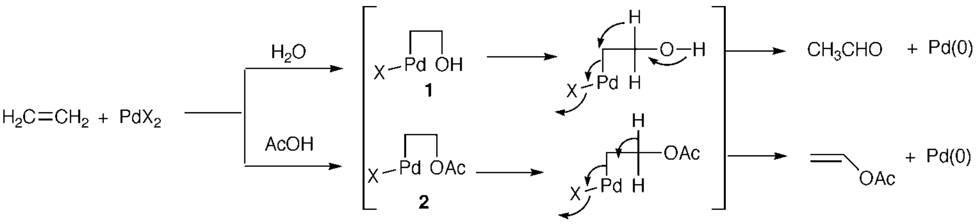
The formation of the carbon–oxygen bond by the attack of the oxoanions on ethylene gave me an important hint as to my research. I expected that it might be possible to discover a carbon–carbon bond forming reaction by the nucleophilic attack of carbanions on alkenes coordinated by Pd(II). Also, we expected that oxidative carbonylation of alkenes should be possible using Pd(II) because CO is a nucleophile. With these two working hypotheses, shown below, we started in 1962 the investigation of two problems: (*a*) the possibility of carbon–carbon bond formation using alkenes and carbonucleophiles and (*b*) carbonylation of alkenes by means of Pd complexes. Summaries of the successful studies were presented.[1,5]



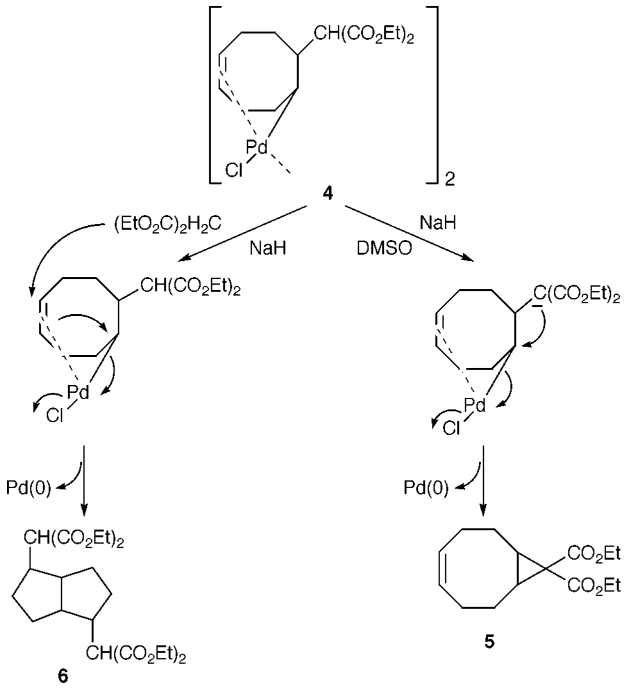
Discovery of carbon–carbon bond forming reactions mediated by Pd(II)

As for carbon–carbon bond formation, we expected that attack of carbanions, typically malonate and acetoacetate anions, on an olefinic bond may occur by the coordination of $PdCl_2$. After unsuccessfully reacting several simple alkenes with malonate, we selected the $PdCl_2$ complex of COD (**3**). This was the right choice and we fortunately obtained facile carbopalladation of one of the olefinic bonds of COD with a soft carbanion. **3** is nearly insoluble in organic solvents. However, when a heterogeneous mixture of the greenish yellow complex **3**, ethyl malonate and Na_2CO_3 in ether was stirred at room temperature overnight, we observed that the greenish yellow mixture gradually turned colorless, suggesting formation of a new complex, which was isolated and recrystallized from ethyl acetate. The new complex, shown as **4**, was obtained in high yield.[6] Formation of **4** suggested that the expected carbon–carbon bond formation took place under extremely mild conditions with malonate or acetoacetate without using a strong base. We were impressed by the ease of the carbon–carbon bond formation and unique reactivity of $PdCl_2$. This reaction is the first example of carbon–carbon bond formation mediated by Pd(II) and marked the beginning of organopalladium chemistry, because carbon–carbon bond formation is the most important process in organic synthesis. The reaction is understood as carbopalladation of the olefinic bond of COD. Of course there was no such word as carbopalladation at that time. Again, decreasing of the electron density of the olefin by the coordination of Pd(II) makes the attack of the carbonucleophile possible. The Pd–carbon σ bond in complex **4** is stabilized by the chelating effect of the remaining double bond.



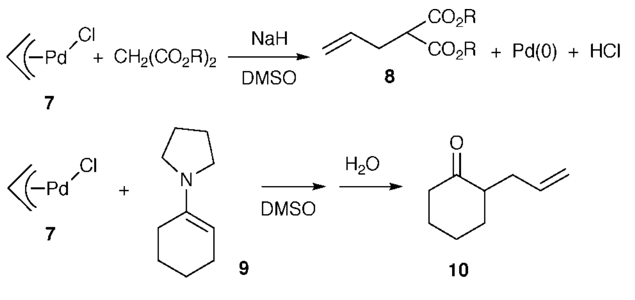


We found that the carbopalladation product **4** underwent further interesting reactions. The carbanion was generated by treatment of complex **4** with NaH in DMSO, and underwent intramolecular attack on the carbon σ-bonded to Pd, giving the cyclopropane **5** by intramolecular nucleophilic attack. Overall, the cyclopropanation occurred by subsequent twofold attack of the carbanion on the olefinic bond activated by Pd(II). Furthermore, the bicyclo[3.3.0]octane **6** was obtained by the intermolecular nucleophilic attack of malonate on the remaining double bond, followed by transannular reaction of the complex **4**. By these reactions, Pd(II) was reduced to Pd(0), which precipitated as black metal.

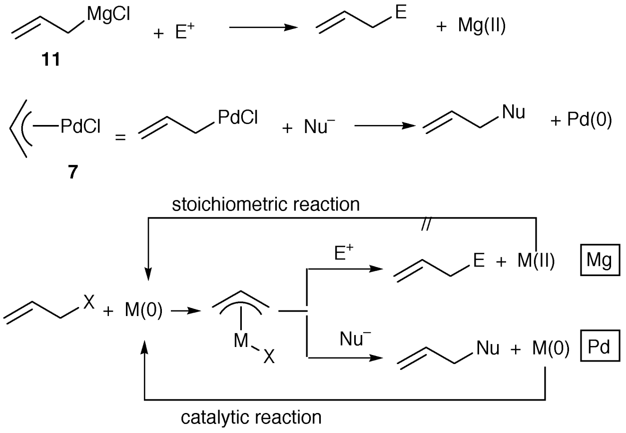


Birth of π-allylpalladium chemistry

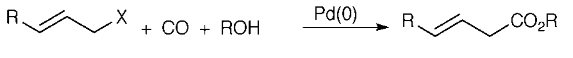
Encouraged by the discovery of the facile carbon–carbon bond formation by the attack of the carbanion on the COD complex **3**, we attempted the nucleophilic attack of the carbanion on π-allylpalladium chloride (**7**).[7] Although **7** was less reactive than the COD complex **3**, the reaction of **7** with the carbanion generated by the treatment of malonate with NaH proceeded in DMSO and allylmalonate **8** was obtained as expected with precipitation of black Pd metal. Use of DMSO as a coordinating solvent was important. No reaction took place in other solvents. Furthermore we found that the reaction of **7** with the enamine **9** of cyclohexanone, which is regarded as a pseudo-carbanion, occurred to afford 2-allylcyclohexanone (**10**) after hydrolysis of the reaction product. These reactions constitute the basis of stoichiometric as well as catalytic π-allylpalladium chemistry. The success of these reactions marked the birth of π-allylpalladium chemistry, which later experienced a remarkable development.



The facile reactions of the COD complex **3** and π-allylpalladium chloride **7** with the carbanions are significant in the history of organometallic chemistry for the following reason. It is well known that the organometallic compounds known at that time, typically allylmagnesium halides (**11**), are nucleophilic, and react with electrophiles, typically carbonyl groups. At the same time Mg(II) is generated, showing that the Grignard reaction involves the oxidation of Mg(0) to Mg(II). Thus the Grignard reaction is intrinsically stoichiometric, because *in situ* reduction of Mg(II) to Mg(0) is practically impossible. On the other hand, the COD–PdCl$_2$ complex **3** and π-allylpalladium chloride **7** were found to be electrophilic, offering a new concept in organometallic chemistry. The reaction of the Pd complexes with nucleophiles accompanies the reduction of Pd(II) to Pd(0). Formation of Pd(0) suggests the possibility of a catalytic reaction. The generation of Pd(0) after the reactions is the most characteristic feature of Pd complexes.



As the catalytic version of π-allylpalladium chemistry, we found the Pd-catalyzed carbonylation of allylic compounds to give β,γ-unsaturated esters **12**. This is the first example of Pd-catalyzed reactions of allylic compounds.[8]



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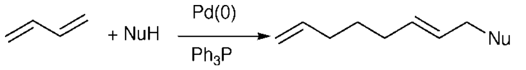
Concerning the catalytic allylation of nucleophiles, Pd-catalyzed telomerization of butadiene with nucleophiles such as carboxylic acids, alcohols and amines to afford **13** was discovered in 1967, which involved catalytic allylation of the nucleophiles. [9,10]



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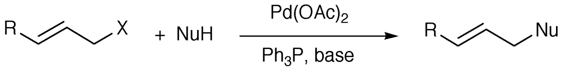
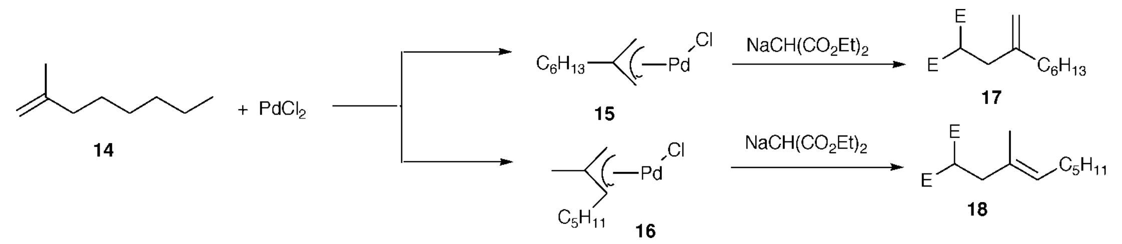
Further studies on the Pd-catalyzed telomerization of butadiene lead to the discovery of catalytic allylation of nucleophiles, including carbonucleophiles with allyl acetate and allyl phenyl ether, by two groups in 1970.[11,12] Thus, catalytic allylation of nucleophiles was discovered five years after the discovery of the stoichiometric allylation. In this way the basis of π-allylpalladium chemistry was established.



NuH = ROH, PhOH, RNH$_2$, RCO$_2$H, CH$_2$E$_2$

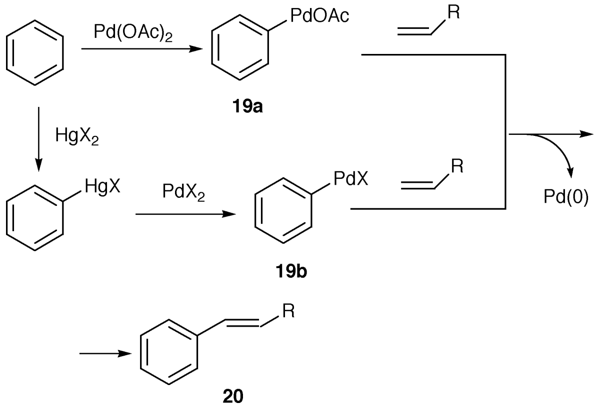
X = OPh, OAc, OH



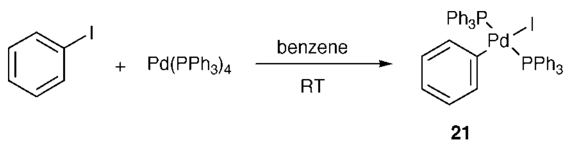
After the establishment of π-allylpalladium chemistry, studies on its synthetic application were initiated by other groups. The Trost group carried out "alkylation of alkenes" by combining two known reactions, namely the formation of π-allylpalladium complexes from alkenes and $PdCl_2$ [13] and our allylation reaction of carbonucleophiles with the π-allylpalladium complex. For example, the terminal alkene **14** was converted to a mixture of π-allylic complexes **15** and **16**, which were allowed to react with malonate in THF in the presence of Ph_3P to give the alkylated alkenes **17** and **18**.[14] Allylation of nucleophiles is called the Tsuji–Trost reaction.

Discovery of the Mizoroki–Heck reaction

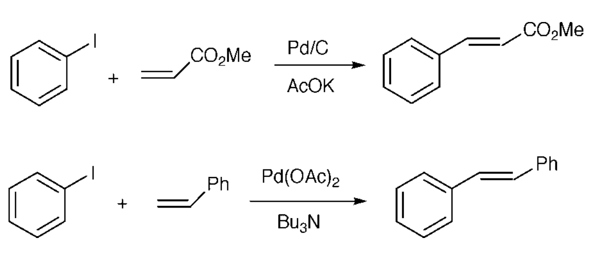
Another important event in the history of organopalladium chemistry is the discovery of the Mizoroki–Heck reaction, which is the arylation or alkenylation of alkenes to afford aryl alkenes and conjugated dienes. At first stoichiometric versions were discovered by two groups in 1967. Fujiwara discovered the formation of stilbene by the reaction of benzene with styrene in the presence of $Pd(OAc)_2$. In this reaction, the phenylpalladium species **19a** is generated as an intermediate.[15] Heck prepared the phenylpalladium intermediate **19b** by mercuration of benzene, followed by transmetallation with $Pd(OAc)_2$.[16] Alkene insertion in the phenylpalladium intermediates **19a,b**, followed by β-elimination, afforded the aryl alkenes **20**. The reactions are stoichiometric, because the reactions start from Pd(II), which is reduced to Pd(0) at the end of the reaction.



One paper published at that time stimulated the discovery of the catalytic reaction. In 1968, Fitton and coworkers showed the first experimental evidence of the oxidative addition of iodobenzene to $Pd(Ph_3P)_4$ to form the phenylpalladium iodide complex **21**.[17] The oxidative addition of iodobenzene to Pd(0) is now the most basic and well-established reaction.

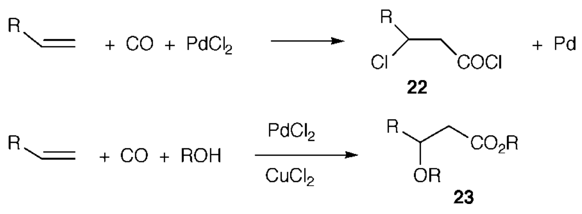


This report on the oxidative addition of iodobenzene to Pd(0) to form **21** led Mizoroki and Heck to try the reaction of iodobenzene with alkenes in the presence of a catalytic amount of Pd(0). Thus, Mizoroki and coworkers reported the coupling of iodobenzene with acrylate catalyzed by Pd on carbon to give cinnamate in 1971.[18] Heck and Nolley discovered independently in 1972 the reaction of iodobenzene with styrene to afford stilbene using $Pd(OAc)_2$ as a catalyst.[19] These reactions marked the discovery of the useful Mizoroki–Heck reaction. Interestingly, both groups carried out the reactions using phosphine-free Pd catalysts.

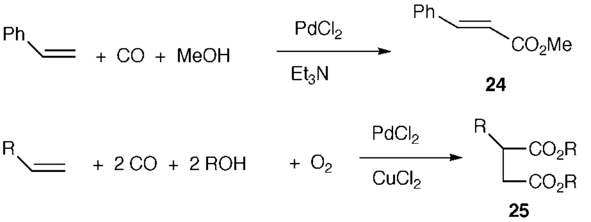


Pd(II)-mediated oxidative carbonylations

Based on our working hypothesis, we discovered that Pd(II) species mediate oxidative carbonylations. Since CO behaves as a nucleophile, we expected that CO should attack alkenes in the presence of $PdCl_2$, and that, if the nucleophilic substitution of alkenes with CO takes place, unsaturated carboxylates or their equivalents should be obtained by oxidative carbonylation. Based on this expectation, we tried the reaction of alkenes with CO in benzene in the presence of $PdCl_2$ under CO pressure and obtained the β-chloroacyl chlorides **22**.[20] This is a unique oxidative carbonylation of alkenes with Pd(II) salts, which is mechanistically different from hydrocarbonylation of alkenes catalyzed by Pd(0) and other metal carbonyls. The oxidative carbonylation of alkenes in alcohol gave the β-alkoxy esters **23**. These reactions are the first examples of the oxidative carbonylation of alkenes mediated by Pd(II), which is specific to Pd(II), and impossible with other metal carbonyls.

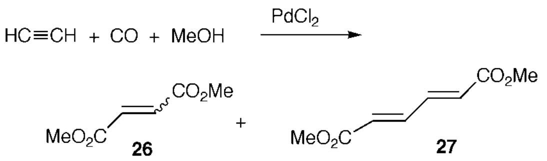


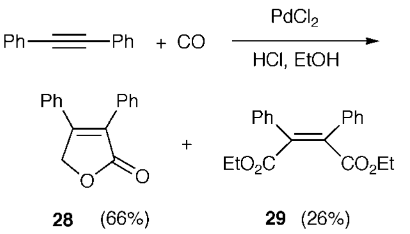
After our discovery of the oxidative carbonylation of alkenes, Yukawa and Tsutsumi discovered the formation of cinnamate (**24**) by the oxidative carbonylation of styrene under basic conditions.[21] The oxidative carbonylation was then modified by Fenton and Steinwand and by Heck to afford α,β-unsaturated esters similar to **24** and succinates **25**.[22] Thus the oxidative carbonylation of alkenes in alcohol to give three kinds of products, namely β-substituted esters **23**, α,β-unsaturated esters, such as **24**, and succinate derivatives **25**, was established.

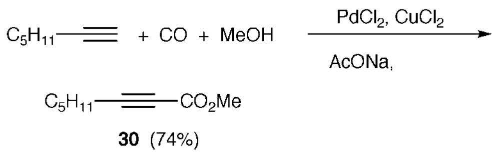


We then found two types of oxidative carbonylation of alkynes. Reaction of acetylene with CO in the presence of $PdCl_2$ under pressure afforded maleyl and fumaryl chlorides, which were isolated as their esters **26**. In addition, we observed the formation of muconyl chloride by dimerization and carbonylation, and isolated as methyl muconate (**27**).[23] Later, Chiusoli and coworkers modified the reaction to produce muconate (**27**) as the main product by the addition of thiourea.[24] We found that the oxidative carbonylation of diphenylacetylene in ethanol afforded α,β-diphenyl-γ-crotonolactone (**28**) as the main product with some ethyl α,β-diphenylmaleate (**29**), using only a catalytic amount of $PdCl_2$ in the presence of HCl.[25] Interestingly, concomitant reduction of one of the carbonyl groups occurred to give the lactone **28**.

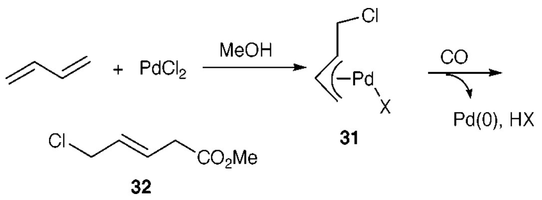
As another example of the oxidative carbonylation of alkynes, we found a useful synthetic route to alkynoates, *e.g.* **30**, by the oxidative carbonylation of terminal alkynes using catalytic amounts of $PdCl_2$ and $CuCl_2$ in the presence of a base.[26]



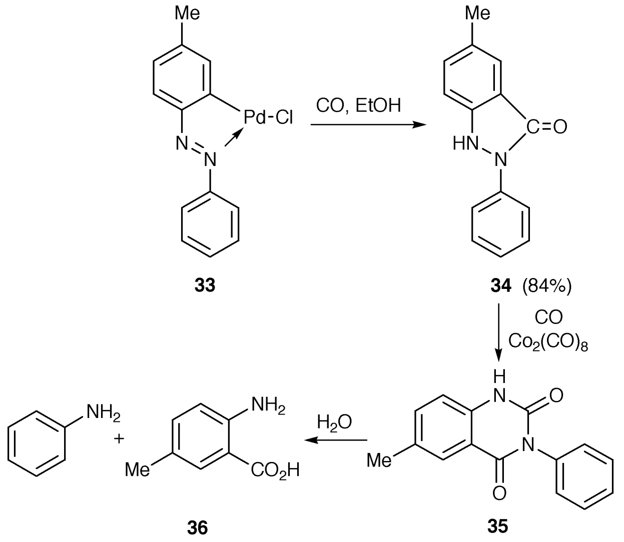




Reaction of butadiene, MeOH and $PdCl_2$ afforded the complex **31**. Treatment of the complex with CO gave methyl 5-chloro-3-pentenoate (**32**) as the product of the oxidative carbonylation of conjugated dienes.[27] This is the first example of the oxidative carbonylation as well as the oxidative 1,4-difunctionalization of conjugated dienes.

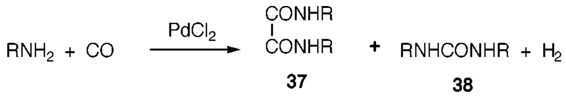


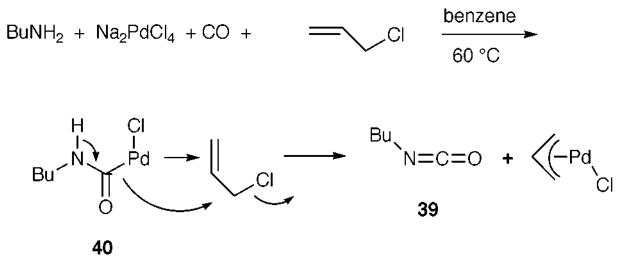
Encouraged by the facile oxidative carbonylation of alkenes, alkynes and dienes, we tried the oxidative carbonylation of aromatic rings. Although attempted direct oxidative carbonylation of benzene was unsuccessful, we found facile insertion of CO in an *ortho*-palladated complex. 2-Aryl-3-indazolone **34** was produced in high yield by the carbonylation of the azobenzene complex **33**.[28] Further carbonylation of **34** catalyzed by $Co_2(CO)_8$, reported by Murahashi and Horiie,[29] afforded the quinazolinedione **35**, which was hydrolyzed to afford the substituted anthranilic acid **36**. Thus, anthranilic acid was prepared by the oxidative carbonylation of aniline *via* the *ortho*-palladated complex **33**. This is the first example of the oxidative carbonylation of the aromatic ring.



We found that oxidative carbonylation of amines to give oxamide **37** and *N*,*N*′-dialkylurea **38** with generation of H_2 occurred under somewhat severe conditions using $PdCl_2$ or Pd on carbon as catalysts.[30] Later, a preparative method for oxalate and carbonate by oxidative carbonylation was reported.[31]

As another example of oxidative carbonylation of amines, Stern and Spector reported the formation of isocyanate by the reaction of amine, CO, and $PdCl_2$ in the presence of a base.[32]

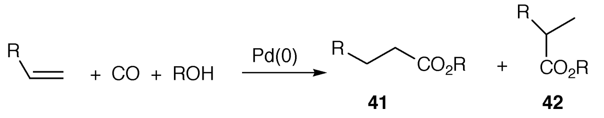


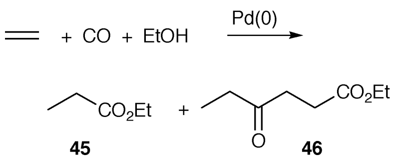


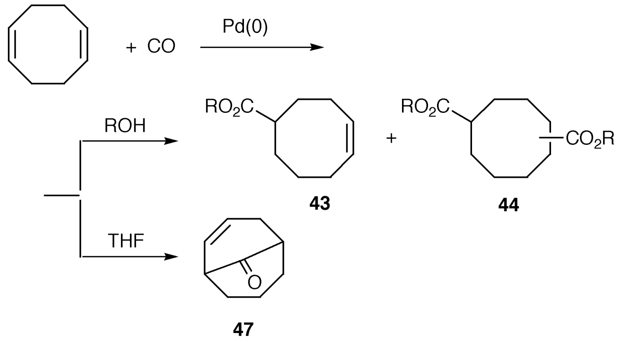
Concerning the mechanism of the oxidative carbonylation of amines to give isocyanates, such as **39**, we found that the isocyanate and π-allylpalladium chloride were formed by the reaction of a primary amine, allyl chloride, and $PdCl_2$. This interesting reaction can be explained by the generation of the intermediate **40**.[33] The net result is the abstraction of two hydrogens from the amine with Pd(II).

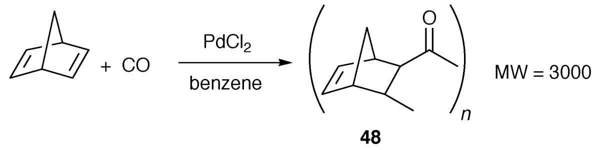
Pd(0)-catalyzed hydrocarbonylation of alkenes, dienes, and alkynes

During our studies on the oxidative carbonylation of alkenes, we observed the formation of saturated esters **41** and **42** from alkenes in alcohol by hydrocarbonylation. We soon realized that these esters were formed with a catalytic amount of $PdCl_2$, which is a precatalyst and reduced *in situ* to Pd(0), which then catalyzed the hydrocarbonylation of the alkenes.[34,35] For example, carbonylation of COD in alcohol afforded the monoester **43** and diesters **44**.[36] Carbonylation of ethylene in ethanol catalyzed by Pd(0) afforded ethyl propionate (**45**) as a major product and ethyl 4-ketohexanoate (**46**) as a minor product.[34] Formation of a ketone is a general reaction in an aprotic solvent. Brewis and Hughes reported that the carbonylation of COD in THF afforded bicyclo[3.3.1]-2-nonen-9-one (**47**).[37] The formation of the keto ester **46** suggested the possibility of polyketone formation. Actually, we observed formation of the polyketone **48** by the carbonylation of norbornadiene, which has strained double bonds.[38] This is the first example of Pd-catalyzed polyketone formation from alkenes. Pd-catalyzed polyketone formation from ethylene and propylene is now attracting attention from an industrial standpoint.[39]

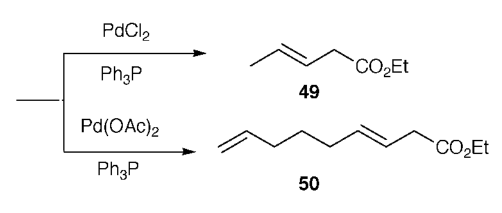




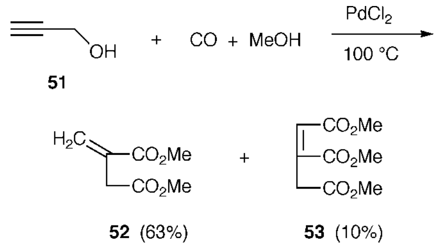




Pd(0) is a good catalyst for the hydrocarbonylation of conjugated dienes and alkynes. Pd-catalyzed carbonylation of butadiene in alcohol afforded two products, depending on the catalytic species. When $PdCl_2$ was used as a catalyst, 3-pentenoate (**49**) was obtained.[40] In this case, Pd(0) and HCl is formed, and the presence of Cl anions gives **49**. On the other hand, dimerization of butadiene and carbonylation took place to afford ethyl 3,8-nonadieonate (**50**) when $Pd(OAc)_2$ and Ph_3P were used as the catalyst.[41] The presence or absence of Cl anions gives the different products **49** or **50**.



Hydrocarbonylation of akynes proceeded smoothly. Dimethyl itaconate (**52**) was obtained as a main product and trimethyl aconitate (**53**) as a minor product by the carbonylation of propargyl alcohol (**51**) in MeOH.[42]

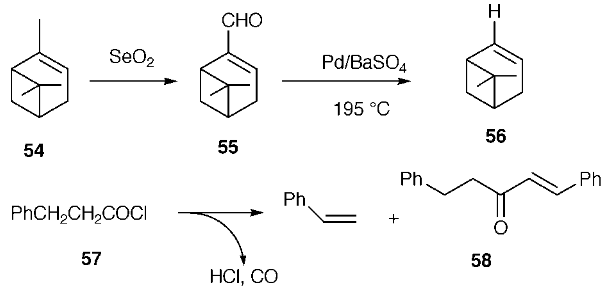


Although selectivity was low, we obtained propanal by the Pd-catalyzed hydroformylation of ethylene with CO and H_2. The main reaction was hydrogenation of ethylene to afford ethane.[43]

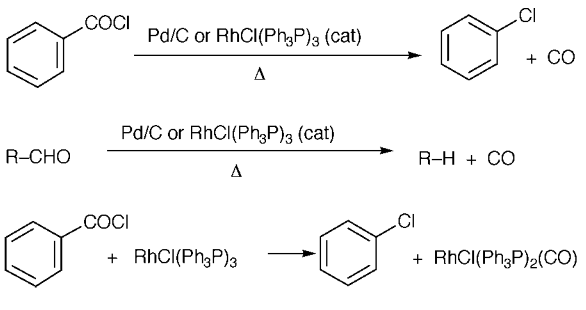
$$H_2C{=}CH_2 + CO + H_2 \longrightarrow CH_3CH_3 + CH_3CH_2CHO$$

Pd- and Rh-catalyzed decarbonylation of aldehydes and acyl halides

During our mechanistic studies on Pd(0)-catalyzed hydrocarbonylation and hydroformylation, we attempted Pd-catalyzed decarbonylation of acyl halides and aldehydes under high temperature to give alkanes and alkenes based on the assumption that CO insertion is reversible.[44] The Pd-catalyzed decarbonylation of aldehydes was known before and used for synthetic purposes.[45] For example, Eschinazi and Pines converted α-pinene (**54**) to myrtenal (**55**), which was decarbonylated with Pd on $BaSO_4$ at 195 °C to give apopinene (**56**).[46] We obtained styrene as the major product (53%), accompanied by 10% of 1,5-diphenyl-1-penten-3-one (**58**) by the Pd-catalyzed decarbonylation of phenylpropionyl chloride (**57**).[44] The formation of the ketone **58** can be explained by the insertion of styrene in the intermediate acylpalladium bond.



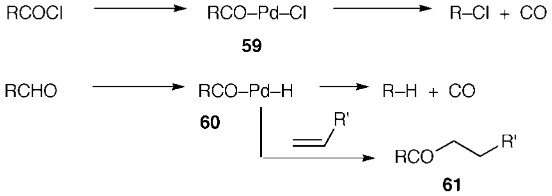
At that time, a report on the preparation and properties of the Wilkinson complex attracted our attention,[47] and we found that the Rh-catalyzed or promoted decarbonylation of

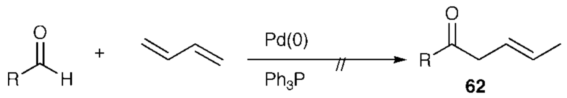


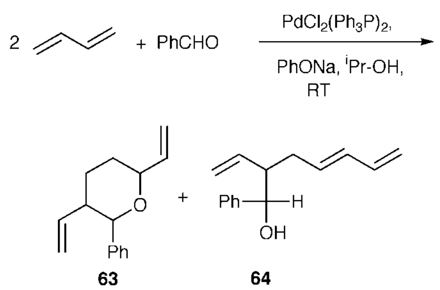
acyl halides and aldehydes proceeds more smoothly.[48] Stoichiometric decarbonylation of acyl halides and aldehydes with the Wilkinson complex took place at room temperature, and catalytic decarbonylation at high temperature.

Pd-catalyzed reaction of butadiene *via* amphiphilic bis-π-allylpalladium

We proposed that the first step of the Pd and Rh-catalyzed decarbonylation is the oxidative addition of acyl halides and aldehydes to form the acylpalladiums **59** and **60**, and we could actually isolate acylrhodium complexes by the treatment of acyl chlorides with the Wilkinson complex.[49] Based on the formation of the unsaturated ketone **58**, we speculated that alkene insertion in the acylpalladium complex **60** may afford the ketone **61**, and we tried ketone synthesis by the Pd-catalyzed reaction of aldehydes with alkenes. Unfortunately, we had little success. However, when we attempted formation of the ketone **62** by the reaction of butadiene with benzaldehyde, we obtained the divinyltetrahydropyran **63** and the unsaturated alcohol **64**, completely unexpected products.[50] The same reaction was reported by Haynes and by Manyik and coworkers independently.[51,52]

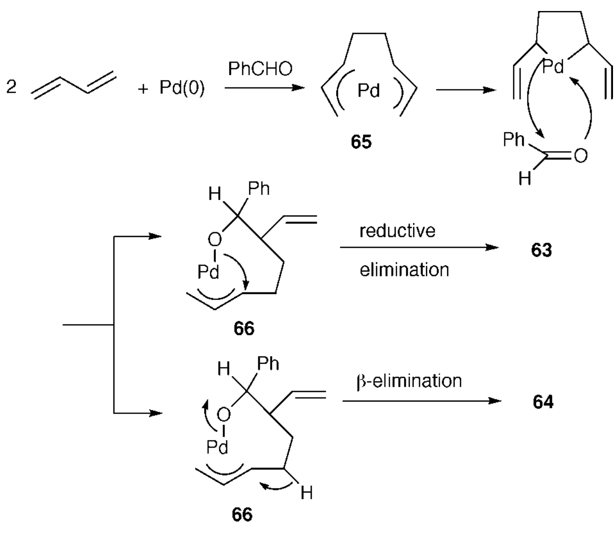




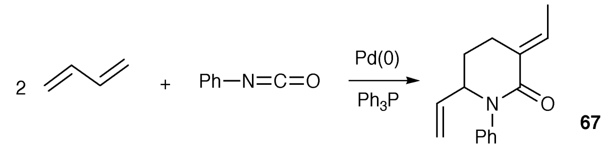


(Combined yield 72%)

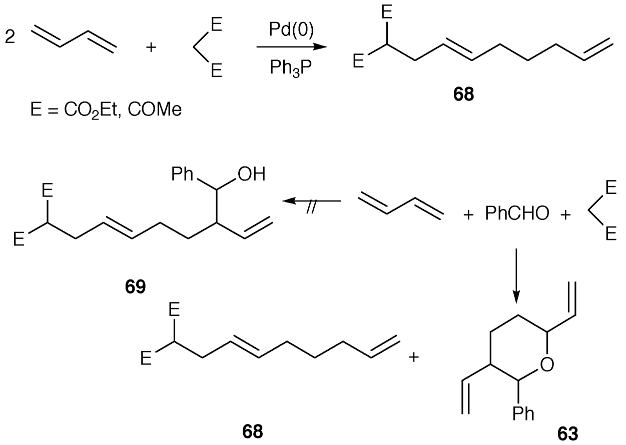
The first step of the Pd-catalyzed reaction of butadiene is the formation of bis-π-allylpalladium **65**. Formation of the pyran **63** is interesting, because benzaldehyde, an electrophile, attacks the bis-π-allylpalladium intermediate **65**. The formation of the pyran **63** can be explained by the following mechanism. At first, nucleophilic attack of **65** on the aldehyde generates the π-allylpalladium alkoxide **66** as an intermediate. Then, electrophilic attack of the π-allyl group on the alkoxide, or reductive elimination of **66**, affords the pyran **63**. The formation of the pyran is expected to be favored by a higher ratio of Ph_3P to Pd, because it is reasonable to expect that coordinative saturation accelerates the reductive elimination. Elimination of β-hydrogen from **66** gives the unsaturated alcohol **64**, the formation of which is favored when the ratio of Ph_3P to Pd is small. In fact, the unsaturated alcohol **64** was obtained as the main product when the ratio of Ph_3P to Pd was 1 ~ 2, and the pyran **63** was formed by reductive elimination as the main product when the ratio was larger than 3.



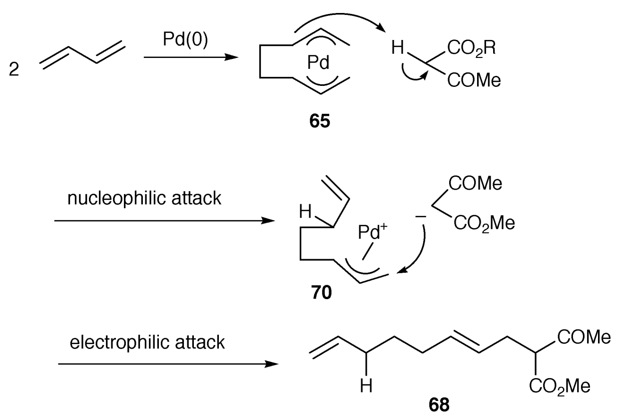
Formation of the pyran **63** by the reaction of aldehydes showed for the first time that the bis-π-allylpalladium system **65** generated from butadiene has amphiphilic nature. **65** at first reacts as a nucleophilic π-allylpalladium, followed by electrophilic attack of the remaining π-allylpalladium. In addition to aldehydes, we found that the reaction with isocyanates, another electrophile, gives the piperidone **67**.[53]



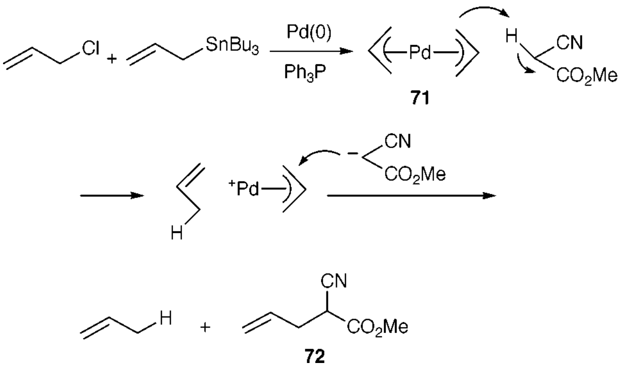
Hata and coworkers reported the Pd-catalyzed telomerization of butadiene with pronucleophiles, such as malonate, to afford the telomer **68**.[54] Thus interestingly, butadiene reacts with pronucleophiles as well as with electrophiles such as aldehydes under similar conditions. Then we attempted the three-component reaction of butadiene, benzaldehyde, and methyl acetoacetate, expecting the formation of **69**. However the expected product was not obtained. Instead, benzaldehyde and acetoacetate reacted independently to give the pyran **63** and the telomer **68**.[55]



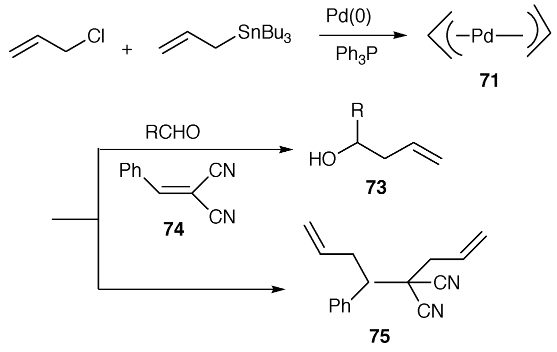
The reaction of methyl acetoacetate with butadiene can be explained by the following mechanism, based on the amphiphilicity of the bis-π-allylpalladium intermediate **65**. The first step is the protonation of **65** with an acidic hydrogen of acetoacetate as a pronucleophile to generate the π-allylpalladium intermediate **70** and acetoacetate anion. This reaction can be regarded as the nucleophilic attack of one of the π-allyl groups in **65** on acetoacetate to generate the acetoacetate anion and the π-allylpalladium **70**, which then undergoes electrophilic attack by the acetoacetate anion, as expected, to give **68**.[55] A similar mechanism was proposed by Jolly and coworkers.[56]



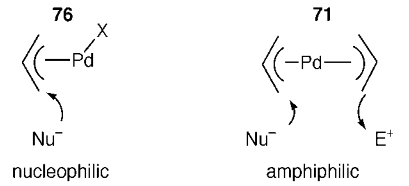
We generated another bis-π-allylpalladium (**71**) *in situ* by the reaction of Pd(0), allyl chloride and allylstannane, and confirmed its reaction with a pronucleophile (methyl cyanoacetate) to give propylene and methyl allylcyanoacetate (**72**).[55] The reaction can be explained by the nucleophilic (protonation) and electrophilic attacks of **71**.

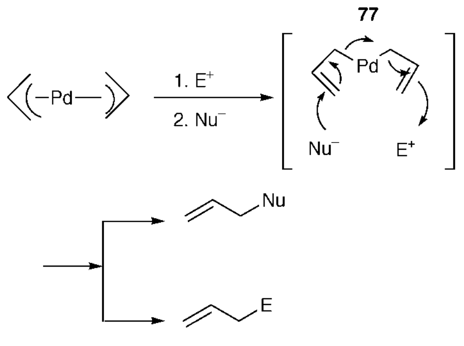


Recently Yamamoto and coworkers showed the amphiphilic nature of **71** generated *in situ*.[57] **71** reacts with aldehydes to give the unsaturated alcohols **73**, and its reaction with the highly polar double bond **74** affords the α,β-diallylated product **75**.



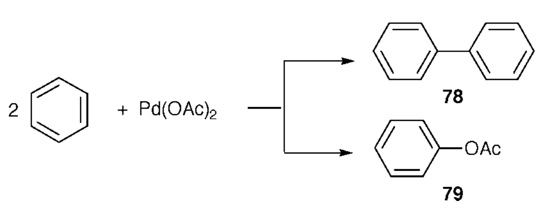
Thus, we can conclude that π-allylpalladium halide **76** is electrophilic, and bis-π-allylpalladium **71** is amphiphilic, undergoing nucleophilic attack at first, followed by electrophilic attack, as shown by **77**.





Pd-catalyzed cross coupling reactions

In addition to the Tsuji–Trost and Mizoroki–Heck reactions, another important Pd-catalyzed reaction is the coupling of aromatic rings. At first stoichiometric oxidative homocoupling of benzene using $Pd(OAc)_2$ to afford biphenyl (**78**) was reported.[58] Acetoxybenzene (**79**) was also obtained.[59]



Further improvement was achieved by the discovery of Pd-catalyzed cross couplings of aryl halides with organometallic reagents. The cross coupling of aryl halides with Grignard reagents catalyzed by Ni-phosphine complexes, reported by two groups, was the breakthrough.[60,61]

$$\text{Ar–X} + \text{R–MgX} \xrightarrow{\text{NiCl}_2(\text{PR}_3)_2} \text{Ar–R} + \text{MgX}_2$$

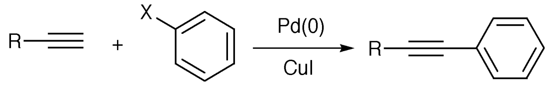
Inspired by the Ni-catalyzed cross coupling reaction, several groups published Pd-catalyzed cross couplings of aryl and alkenyl halides with various organometallic compounds, showing that Pd is the more versatile and superior catalyst compared to Ni for cross coupling. Pd complexes were found to catalyze the cross coupling of Grignard reagents efficiently.[62–64] The coupling reactions of organoaluminium reagents,[65] and organozinc reagents[66] were reported by Negishi and coworkers. Smooth coupling of organostannanes with allyl and acyl halides (called Kosugi–Migita–Stille coupling) was first reported by Kosugi, Migita and colleagues[67] and then with acyl halides by Milstein and Stille in the following year.[68] The cross coupling of halides with organoboron compounds was reported in 1979 and is called Suzuki–Miyaura coupling.[69]

$$\text{Ar–X} + \text{R–M–X} \longrightarrow \text{Ar–R} + \text{MX}_2$$

$\text{R–MX} = \text{RMgX, RZnX, R}_2\text{AlX, RSnR'}_3\text{, BR}_3$

R = aryl, alkenyl, alkynyl

Synthetically useful coupling of terminal alkynes with halides was also developed at about the same time. The Pd-catalyzed coupling of aryl and alkenyl halides with terminal alkynes was reported in 1975 by Dieck and Heck and by Cassar.[70,71] Then Sonogashira and coworkers discovered that the use of CuI as a cocatalyst with Pd(0) is the more versatile catalyst.[72]



Thus three of the most important Pd-catalyzed reactions, namely the Tsuji–Trost reactions, the Mizoroki–Heck reactions, and the cross coupling reactions, were established at the end of the 1970s. The golden age of organopalladium chemistry could then begin and remarkable progress in organopalladium chemistry is still continuing.

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