

Recollections of organopalladium chemistry*

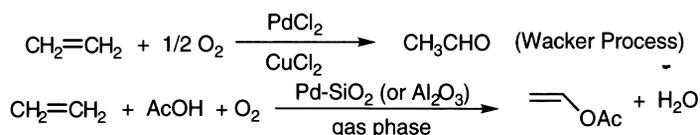
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Abstract: Organopalladium chemistry has 40 years' history. It was born in late 1950s by the invention of the Wacker process. Inspired by the Wacker reaction, we discovered the first example of the carbon–carbon bond formation by means of a Pd complex, and opened the field of π -allylpalladium chemistry. Historical account of organopalladium chemistry, and major accomplishments in our laboratory in 1960s are presented.

INTRODUCTION

Invention of the Wacker process to produce acetaldehyde using $\text{PdCl}_2\text{--CuCl}_2$ as catalysts in 1959 is the first example of the homogeneous palladium-catalyzed reaction [1]. 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 [2]. Vinyl acetate is now produced commercially based on this reaction using supported Pd catalyst in a gas phase (Scheme 1).



Scheme 1

As mechanistic explanation of the formation of acetaldehyde, Smidt and co-workers made the following statement in their review [1].

‘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 hydrogen atoms originally present in ethylene remain there.’

The early 1960s was the dawn of the research on OMCOS. I started independent research in 1962 in Basic Research Laboratories of Toray Industries. By watching polymerization of ethylene and propylene by the Ziegler–Natta catalysts, and Ni-catalyzed cyclization of butadiene, I clearly realized that the chemistry involved in these Ti and Ni-catalyzed reactions is completely new, and I had firm conviction that application of transition metal catalyzed reactions to organic synthesis has high potentiality in future. Thus I planned to study application of transition metal compounds to organic synthesis.

DISCOVERY OF CARBON–CARBON BOND FORMING REACTIONS MEDIATED BY Pd(II)

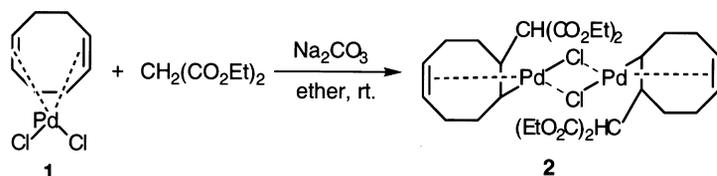
I made fortunate selection of Pd as a target metal of our research project. By studying the reactions of the acetaldehyde and vinyl acetate formation carefully, I realized that hitherto unknown unique reactions are occurring using Pd(II) in these reactions. I was very much interested in the statement by Smidt *et al.*

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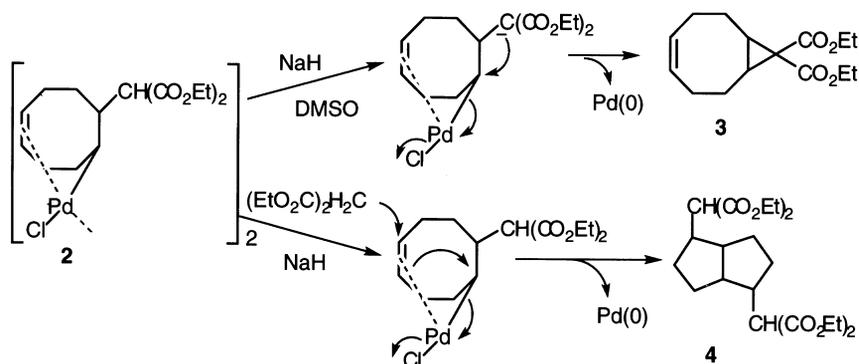
shown above. This statement gave us an important hint for the commencement of our research on organopalladium chemistry. In 1962, we started to investigate two problems: (a) the possibility of carbon–carbon formation using alkenes, and (b) carbonylation of alkenes, alkynes both by means of Pd complexes [3].

As for the carbon–carbon bond formation, we expected an attack of a carbanion, typically malonate and acetoacetate anion, on olefinic bonds may occur. After unsuccessful trial of reacting simple olefins with malonate, we selected PdCl₂ complex of COD (**1**). This was the right selection and we fortunately found a facile carbopalladation of the olefin bond of COD with soft carbanions. PdCl₂ complex of COD (**1**) is nearly insoluble in organic solvents. When a heterogeneous mixture of the yellow complex **1**, ethyl malonate, and Na₂CO₃ in ether was stirred at room temperature overnight, we observed that yellow color of the mixture gradually turned white, suggesting formation of a new complex, which was somewhat soluble in organic solvents. The new complex as shown by **2** was obtained [4]. Formation of **2** suggested that the expected carbon–carbon bond formation took place under extremely mild conditions with malonate without using a strong base. The facileness of the carbon–carbon bond formation and unique reactivity of PdCl₂ impressed us. This reaction is the first example of the carbon–carbon bond formation mediated by Pd(II), and marked the beginning of organopalladium chemistry. The reaction is understood as carbopalladation of the olefinic bond of COD, which becomes electron deficient by the coordination of Pd(II), and attack of the carbon nucleophile becomes possible. The Pd–carbon σ -bond in the complex **2** is stabilized by the chelating effect of the remaining olefinic bond (Scheme 2).



Scheme 2

We found the carbopalladation product **2** undergoes further interesting reactions. The carbanion was generated by the treatment of the complex **2** with NaH in DMSO, and underwent intramolecular attack on the carbon σ -bonded to Pd. The cyclopropane **3** was formed by the intramolecular nucleophilic attack. Overall, the cyclopropanation occurred by the attack of the carbanion twice on the olefinic bond activated by Pd(II). Furthermore, the bicyclo(3.3.0)octane **4** was obtained by the intermolecular nucleophilic attack of malonate on the remaining olefin, followed by transannular reaction of the complex **2**. By these reactions, Pd(II) was reduced to Pd(0), which precipitated as black metal (Scheme 3).

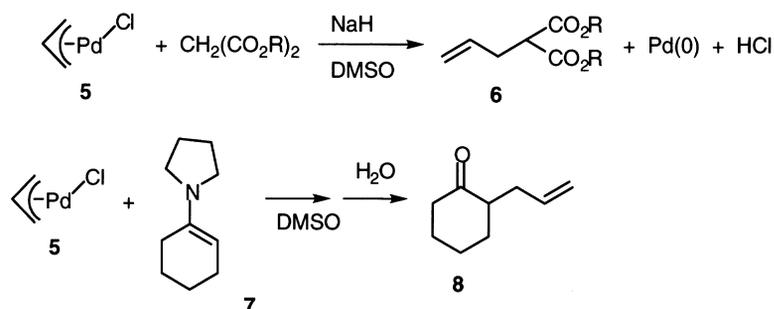


Scheme 3

BIRTH OF π -ALLYLPALLADIUM CHEMISTRY

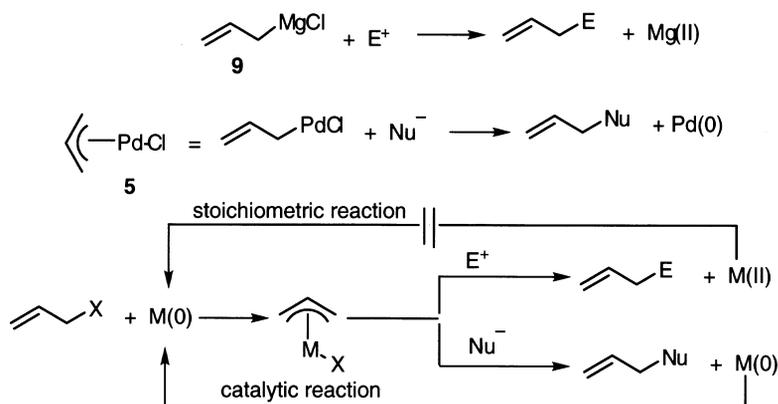
Encouraged by the facile carbon–carbon bond formation by the attack of the carbanion on the COD complex **1**, we attempted the nucleophilic attack of the carbanions on π -allylpalladium chloride (**5**) [5]. Although π -allylpalladium chloride (**5**) is less reactive than the COD complex, the reaction of **5**

proceeded in DMSO using malonate anion generated by the treatment of malonate with NaH, and allylmalonate **6** was obtained as expected with precipitation of black Pd metal. Furthermore we found the reaction of π -allylpalladium chloride (**5**) with the enamine **7** of cyclohexanone, which is regarded as a pseudo-carbanion, to afford 2-allylcyclohexanone (**8**) after hydrolysis of the reaction product. These reactions constitute the basis of the stoichiometric as well as the catalytic π -allylpalladium chemistry, which developed remarkably later. Success of these reactions means the birth of π -allylpalladium chemistry (Scheme 4).



Scheme 4

This reaction of π -allylpalladium chloride with the carbanion is significant in the history of organometallic chemistry by the following reason. It is well known that allyl metal compounds known at that time, typically allylmagnesium halide (**9**), react with electrophiles. At the same time Mg(II) is generated, showing that 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, reduction of Pd(II) to Pd(0) occurs by the reaction of π -allylpalladium **5** with the carbanions. Formation of Pd(0) suggests the possibility of catalytic reaction. These stoichiometric and catalytic reactions are summarized in Scheme 5.

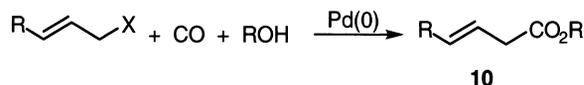


Scheme 5

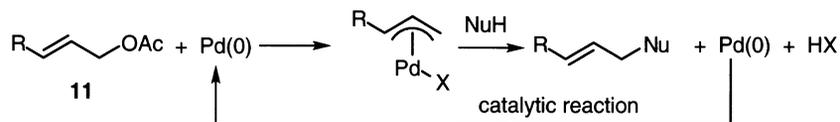
As the catalytic version of π -allylpalladium chemistry, we found Pd-catalyzed carbonylation of allylic esters, alcohols, and chlorides to give β,γ -unsaturated esters **10** using PdCl₂ as a precursor of Pd(0) catalyst. This is the first example of the Pd-catalyzed reactions of allylic compounds (Scheme 6) [6].

Later, based on Pd-catalyzed reversible exchange reaction of allylic esters, catalytic allylation of nucleophiles with allyl acetate (**11**) and allyl phenyl ether shown below was reported by two groups in 1970 (Scheme 7) [7].

During our mechanistic studies on Pd-catalyzed carbonylation described later, we found Pd and Rh-catalyzed decarbonylation of acyl halides and aldehydes [8]. We proposed that the first step of the decarbonylation is the oxidative addition of acyl halides and aldehydes to form the acylpalladiums **12** and **13**. Based on our speculation of the possibility of alkene insertion to the acylpalladium complexes **12** and

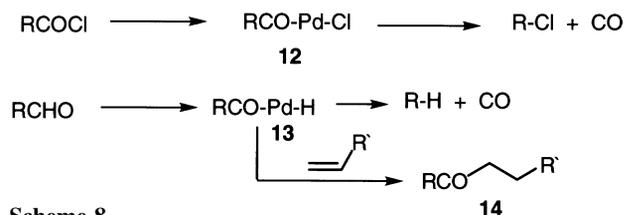


Scheme 6



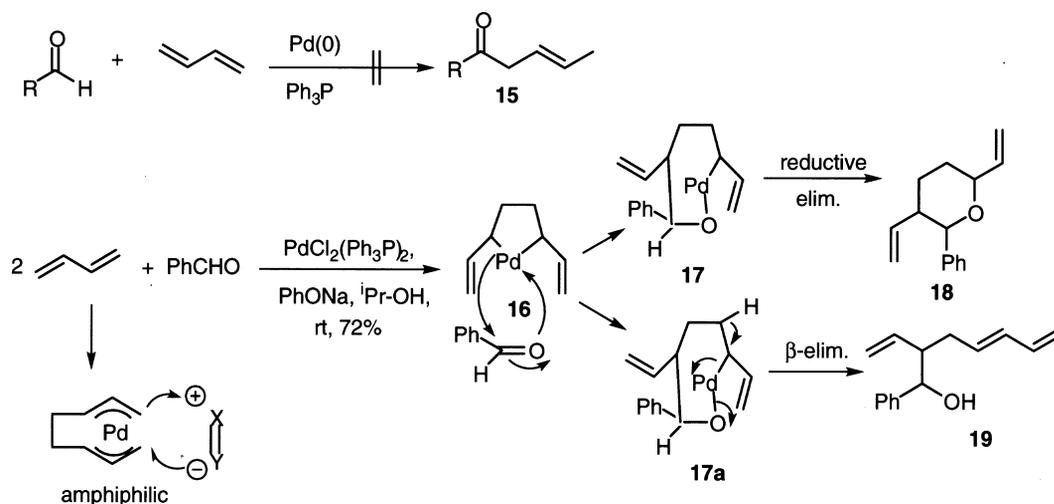
Scheme 7

13, we tried ketone synthesis from aldehyde and alkenes. We expected that the insertion of alkenes to the acylpalladium should give the ketones **14**. But we were not successful (Scheme 8).



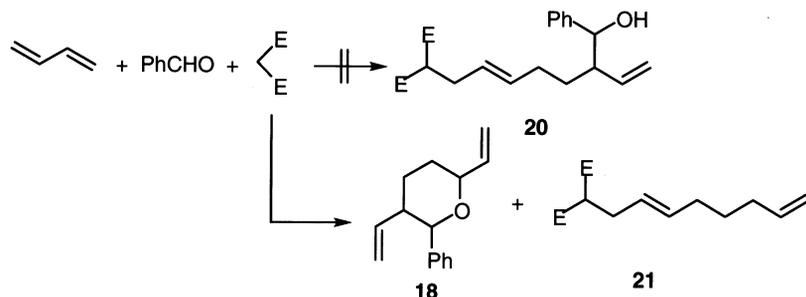
Scheme 8

In 1971 when we attempted preparation of the ketone **15** by the reaction of butadiene with aldehyde, the completely unexpected products, namely divinyltetrahydropyran **18** and the unsaturated alcohol **19**, were obtained [9]. Formation of the pyran **18** is interesting, because benzaldehyde, an electrophile, attacks the bis- π -allylpalladium intermediate **16**. This was unknown reaction, which can be explained by the following mechanism. The first step of the Pd-catalyzed reaction of butadiene is the formation of the bis- π -allylpalladium **16**, which is amphiphilic, and nucleophilic attack of the bis- π -allylpalladium to aldehyde generates the intermediate **17**. Reductive elimination of **17** affords the pyran **18**, which is expected to be favored by a higher ratio of Ph_3P to Pd. Elimination of β -hydrogen from C-6 in **17a** gives the trienyl alcohol **19**, formation of which is favored when the ratio of Ph_3P is small. Actually the unsaturated alcohol **19** was obtained as a main product when a ratio of Ph_3P to Pd was 1~2, and the pyran **18** was formed as the main product by reductive elimination when the ratio was larger than 3. It is reasonably expected that the coordinative saturation accelerated the reductive elimination. The same reaction was reported by Haynes and Manyik *et al.* independently (Scheme 9) [10].



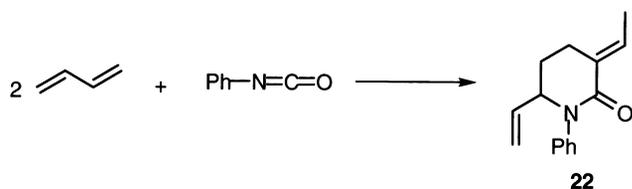
Scheme 9

In addition, it was reported that Pd-catalyzed telomerization with pronucleophiles such as amines, acids, and malonate proceeds smoothly [11]. Formation of the pyran **18** by the reaction of aldehydes showed for the first time that bis- π -allylpalladium system **16** generated from butadiene has amphiphilic nature. We attempted the three component reaction of butadiene, aldehyde, and acetoacetate or cyanoacetate in the absence of a base, expecting the formation of **20** without success. Instead, the aldehyde and cyanoacetate reacted with butadiene separately to afford **18** and **21** (Scheme 10) [12].



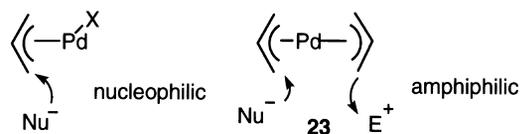
Scheme 10

In addition to aldehydes, isocyanates as another electrophile underwent the cyclization with butadiene to give the piperidone **22** (Scheme 11) [13].



Scheme 11

Recently Yamamoto and co-workers showed amphiphilic nature of a simple bis- π -allylpalladium system **23** generated *in situ* (Scheme 12) [14].



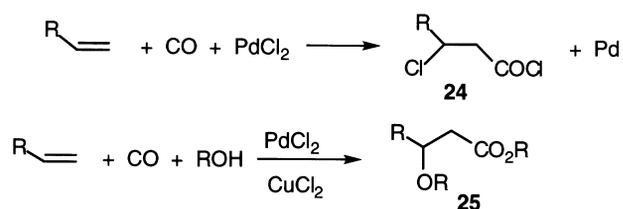
Scheme 12

CARBONYLATION REACTIONS

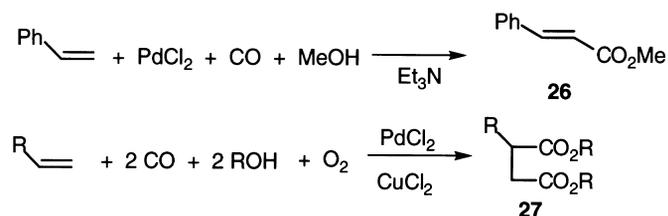
Since CO behaves as a nucleophile, we expected that CO should attack alkenes in the presence of PdCl₂. Based on this expectation, we tried the reaction of alkenes with CO in benzene in the presence of PdCl₂ under CO pressure, and obtained β -chloroacyl chloride **24** [15]. This is a unique oxidative carbonylation of alkenes with Pd(II) salts, which is mechanistically different from the hydrocarbonylation of alkenes catalyzed by Pd(0). The oxidative carbonylation of alkene in alcohol gave β -alkoxy ester **25**. These reactions are the first example of the oxidative carbonylation of alkenes mediated by Pd(II). The oxidative carbonylation is specific to Pd(II), which is impossible by other metal carbonyls (Scheme 13).

Later Yukawa and other groups expanded the oxidative carbonylation to produce the α,β -unsaturated ester **26** and the succinate **27** depending on reaction conditions (Scheme 14) [16].

Then we found two types of the oxidative carbonylation of alkynes. Reaction of acetylene in the presence of PdCl₂ under CO pressure afforded maleic and fumaric chlorides **28** [17]. In addition, we observed the dimerization and carbonylation to afford muconic chloride (**29**). Later as another type of the oxidative carbonylation of alkynes, we found a useful synthetic method of alkynoates **30** by the

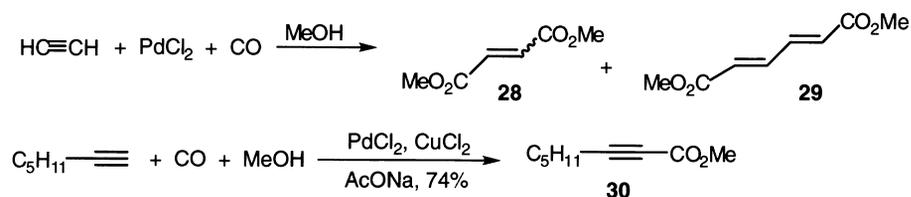


Scheme 13



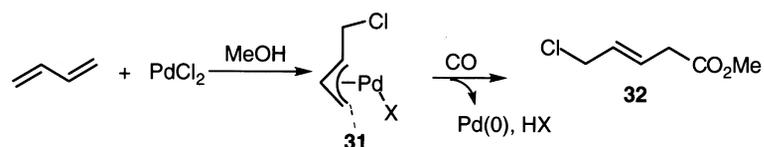
Scheme 14

carbonylation of terminal alkynes using a catalytic amount of PdCl_2 and an excess of CuCl_2 in the presence of a base (Scheme 15) [18].



Scheme 15

Reaction of butadiene with PdCl_2 under CO afforded 5-chloro-3-pentenoate (**32**) via the complex **31** [19]. This is the first example of 1,4-difunctionalization of conjugated dienes (Scheme 16).

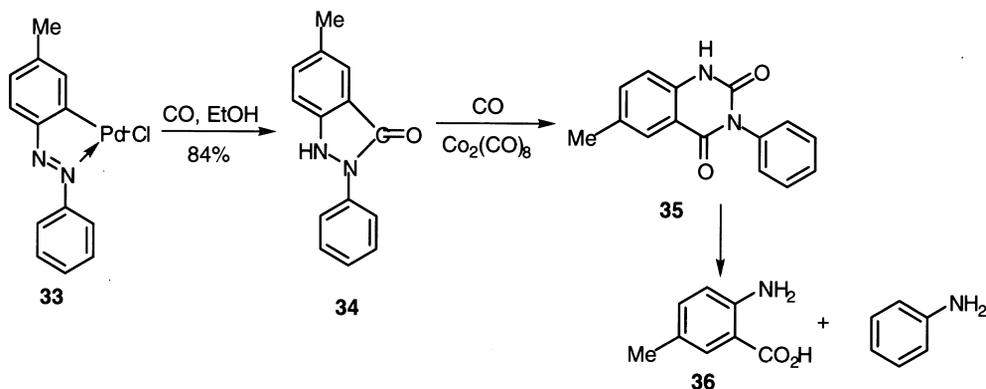


Scheme 16

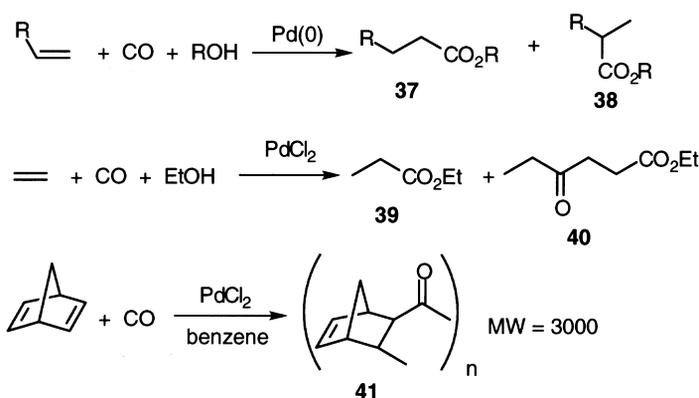
We found facile insertion of CO to ortho-palladated complexes. 2-Aryl-3-indazolone **34** was produced in high yield by the carbonylation of the azobenene complex **33**. Further carbonylation of **34** catalyzed by $\text{Co}_2(\text{CO})_8$ afforded quinazolinodione **35**, which was hydrolyzed to afford anthranilic acid (**36**) (Scheme 17) [20].

During our studies on the oxidative carbonylation, we discovered alkenes are carbonylated in alcohol to give saturated esters **37** and **38**. We soon realized that these esters are formed with a catalytic amount of PdCl_2 , which is reduced *in situ* to Pd(0) and catalyzes the carbonylation. Thus the Pd(0)-catalyzed hydrocarbonylation of alkenes as well as alkynes was discovered [21,22]. The carbonylation of ethylene in ethanol afforded ethyl propionate (**39**) and γ -keto ester **40** as a byproduct. Formation of the keto ester **40** suggests the possibility of polyketone formation. Actually, the polyketone **41** was obtained by the carbonylation of norbornadiene in benzene (Scheme 18) [23].

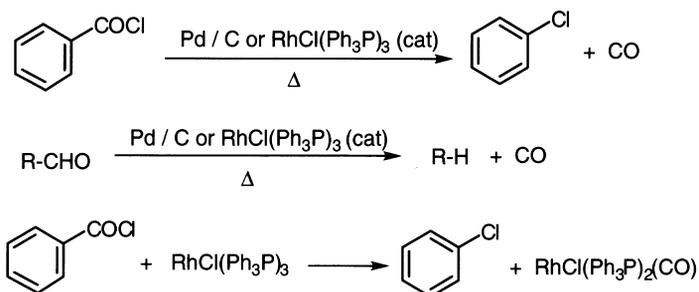
Based on the assumption that CO insertion is reversible, we found Pd-catalyzed decarbonylation of acyl halides and aldehydes at high temperature to give alkanes and alkenes. Also the Rh-catalyzed or promoted decarbonylation of acyl halides and aldehydes proceeds more smoothly. Stoichiometric decarbonylation of acyl halides and aldehydes with Wilkinson complex took place at room temperature, and catalytic decarbonylation at high temperature (Scheme 19) [8].



Scheme 17



Scheme 18

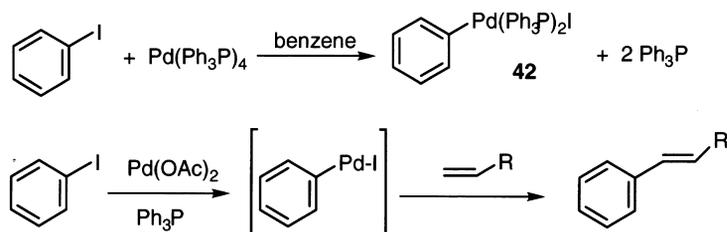


Scheme 19

DISCOVERY OF THE MIZOROKI–HECK REACTION

Another important event in Pd-catalyzed reaction is the discovery of the Mizoroki–Heck reaction, which is the reaction of aryl and alkenyl halides with alkenes to afford aryl alkenes and conjugated dienes. At first stoichiometric versions were discovered by Fujiwara [24] and Heck [25].

In 1968, Fitton *et al.* showed experimentally the oxidative addition of iodobenzene to Pd(0) to form phenylpalladium iodide complex **42** [26]. This report led Heck to try the reaction of iodobenzene and alkenes in the presence of a catalytic amount of Pd(OAc)₂ without phosphine, and he discovered the Heck reaction in 1972 [27]. Also one year before in 1971, Mizoroki *et al.* reported independently the coupling of iodobenzene with acrylate catalyzed by Pd on carbon to afford methyl cinnamate [28]. In this way the catalytic Mizoroki–Heck reaction was discovered (Scheme 20).



Scheme 20

CONCLUSION AND ACKNOWLEDGEMENT

Development of organopalladium chemistry in 1960s mainly in our laboratory is described. The account of our research on carbon–carbon bond formation was given in *Acc. Chem. Res* [3]. The author wishes to express his sincere thanks to many co-workers for their important contributions to the research.

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