

Course Name: Methods in Organic Synthesis

Paper Number: 202

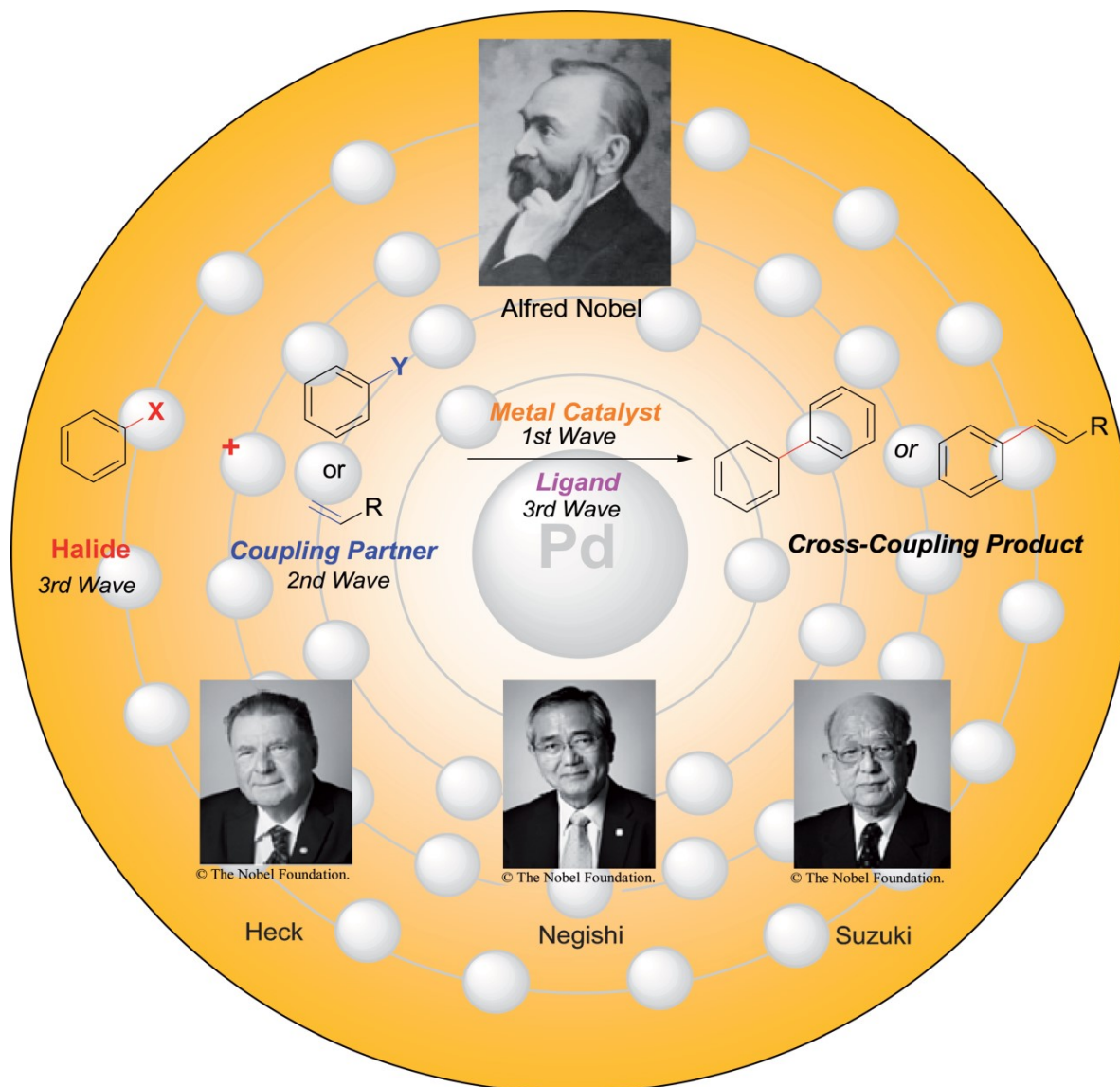
Section: B

Course Instructor: Dr BK Singh

Study Material (Name of Topic/Chapter):

Organosilicone Compounds, Preparation and applications in organic synthesis; Application of Pd(0) and Pd(II) Complexes in Organic Synthesis- Stille, Suzuki and Sonogashira Coupling, Heck reaction and Negishi Coupling.

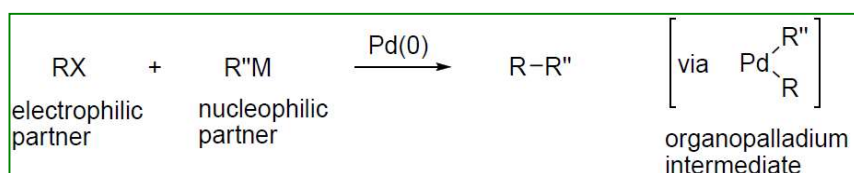
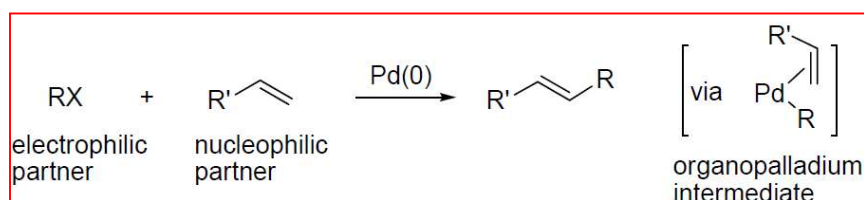
Applications of Pd(0) and Pd(II) complexes in organic synthesis- **Heck, Negishi, Suzuki**, Stille and Sonogashira Coupling



2010 Nobel Prize in Chemistry awarded jointly to Richard F. **Heck**, Ei-ichi **Negishi**, and Akira **Suzuki** "for palladium-catalyzed cross couplings in organic synthesis"

Palladium-catalyzed carbon-carbon bond formation via cross coupling

- ❖ The principle of palladium-catalyzed cross couplings is that two molecules are assembled on the metal via the formation of metal-carbon bonds.
- ❖ In this way the carbon atoms bound to palladium are brought very close to one another.
- ❖ In the next step they couple to one another and this leads to the formation of a new carbon-carbon single bond.
- ❖ There are two types of cross-coupling reactions that have become important in organic synthesis.

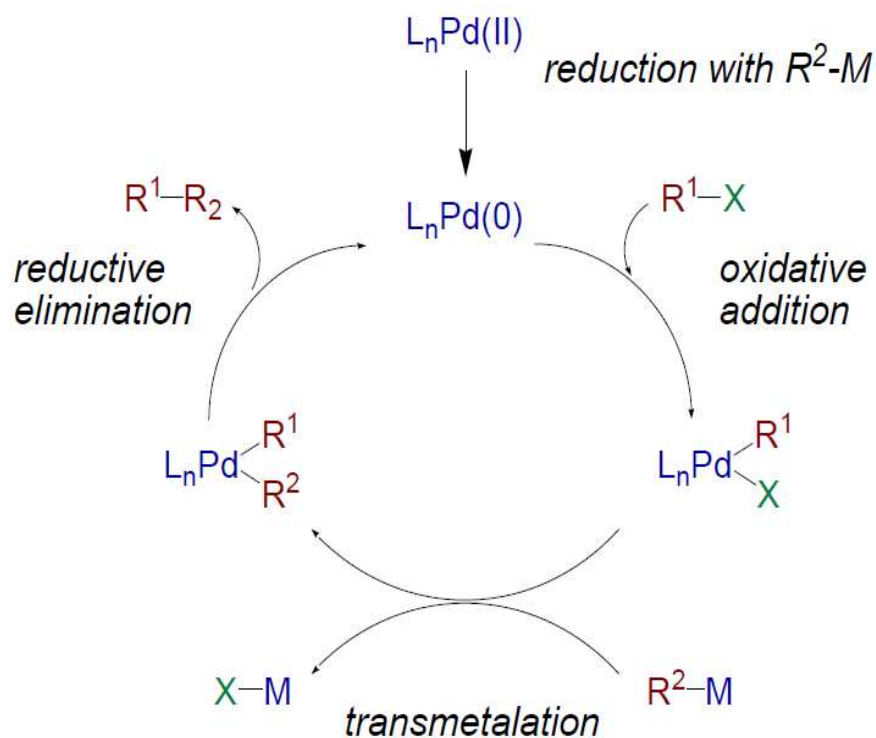
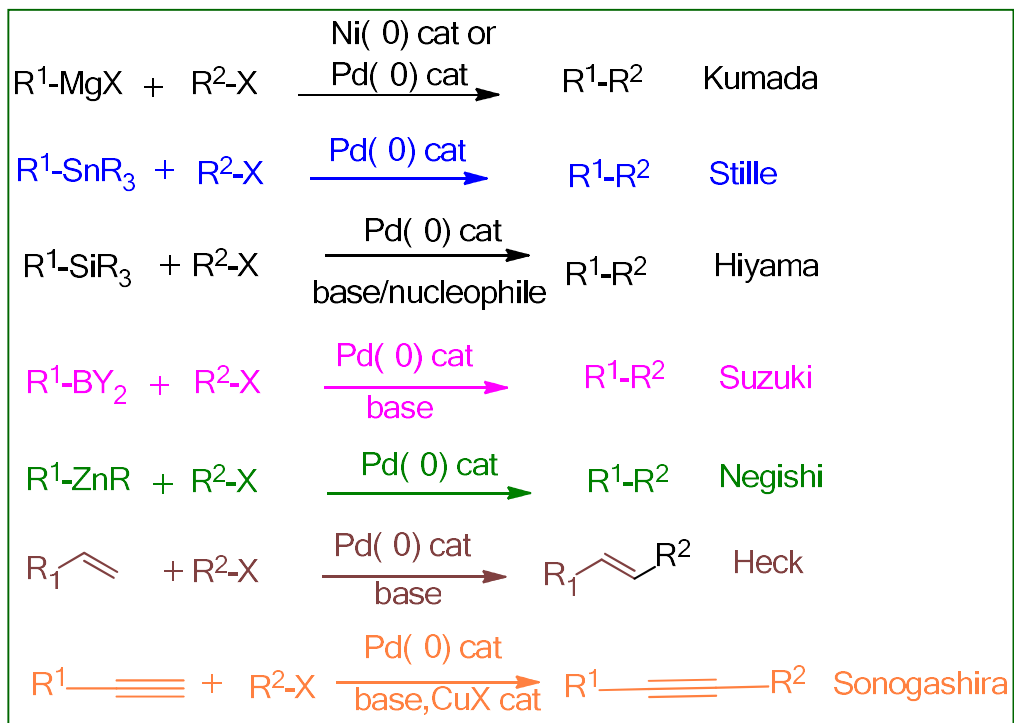


Both reactions are catalyzed by zero valent Pd and both reactions employ an organohalide RX (or analogous compound) as the electrophilic coupling partner.

The nucleophilic coupling partner differs in these two reactions.

In the first type it is an **olefin** whereas in the second type it is an **organometallic** compound R''M where, M is typically zinc, boron, or tin.

- ❖ Both reactions begin by generating an organopalladium complex RPdX from the reaction of the organic halide with Pd(0). The RPdX will subsequently react with the nucleophilic coupling partner.



- ❖ The chemistry of palladium is dominated by two stable oxidation states: the zerovalent state [Pd(0), d10] and the +2 state [Pd(II), d8].
- ❖ Palladium(0) complexes are readily accessible, easily prepared, and easily handled.
- ❖ The nature of the ligand plays an important role in palladium-catalyzed coupling reactions.
- ❖ Pd(0) complexes are electron-rich nucleophilic species, and are prone to oxidation, ligand dissociation, insertion, and oxidative-coupling reactions.
- ❖ Pd(II) complexes are electrophilic and undergo ligand association and reductive-coupling reactions.
- ❖ Phosphine ligands provide a high electron density on the metal, making it a good nucleophile, thereby favoring oxidative additions with suitable substrates.
- ❖ Also, high electron density on the metal favours dissociation of the ligands to a coordinatively unsaturated complex.

Palladium-Catalyzed Cross Couplings in Organic Synthesis

*Three researchers share this year's Nobel Prize in Chemistry, Professor **Richard F. Heck**, who has been working at University of Delaware, Newark, Delaware, USA, Professor **Ei-ichi Negishi**, Purdue University, West Lafayette, Indiana, USA, and Professor (emeritus) **Akira Suzuki**, Hokkaido University, Sapporo, Japan. The Royal Swedish Academy of Sciences is rewarding the three chemists for: "palladium-catalyzed cross couplings in organic synthesis". The discoveries by the three organic chemists have had a great impact on academic research, the development of new drugs and materials, and are used in many industrial chemical processes for the synthesis of pharmaceuticals and other biologically active compounds. A background and description of their discoveries are given below.*

Introduction

This year's Nobel Prize in Chemistry concerns the development of methods for palladium-catalyzed formation of carbon-carbon bonds via so-called cross-coupling reactions. The formation of new carbon-carbon bonds is of central importance in organic chemistry and a prerequisite for all life on earth. Through the assembly of carbon atoms into chains, complex molecules, e.g. molecules of life, can be created. The importance of the synthesis of carbon-carbon bonds is reflected by the fact that Nobel Prizes in Chemistry have previously been given to this area: The Grignard reaction (1912), the Diels-Alder reaction (1950), the Wittig reaction (1979), and olefin metathesis to Y. Chauvin, R. H. Grubbs, and R. R. Schrock (2005).

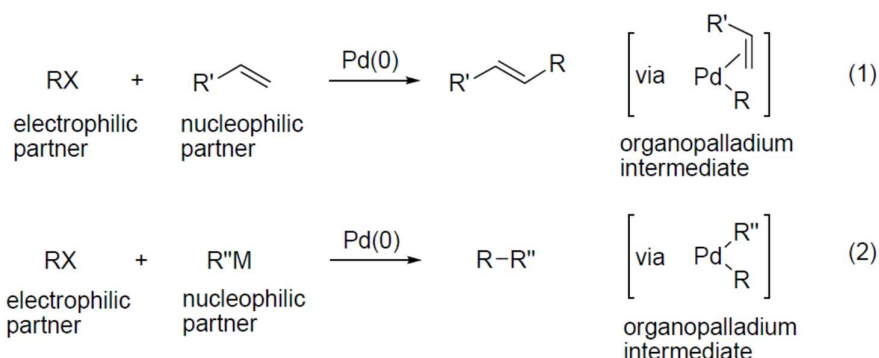
Transition metals in synthetic organic chemistry

During the second half of the 20th century, transition metals have come to play an important role in organic chemistry and this has led to the development of a large number of transition metal-catalyzed reactions for creating organic molecules. Transition metals have a unique ability to activate various organic compounds and through this activation they can catalyze the formation of new bonds. One metal that was used early on for catalytic organic transformations was palladium. One event that stimulated research into the use of palladium in organic chemistry was the discovery that ethylene is oxidized to acetaldehyde by air in a palladium-catalyzed reaction and this became the industrially important Wacker process.¹ Subsequent research on palladium-catalyzed carbonylation led to new reactions for the formation of carbon-carbon bonds. In general, transition metals, and in particular palladium, have been of importance for the development of reactions for the formation of carbon-carbon bonds. In 2005 the Nobel Prize in chemistry was awarded to metal-catalyzed reactions for the formation of carbon-carbon double bonds. This year the Nobel Prize in chemistry is awarded to the formation of carbon-carbon single bonds through palladium-catalyzed cross-coupling reactions.

Palladium-catalyzed carbon-carbon bond formation via cross coupling

The principle of palladium-catalyzed cross couplings is that two molecules are assembled on the metal via the formation of metal-carbon bonds. In this way the carbon atoms bound to palladium are brought very close to one another. In the next step they couple to one another and this leads to the formation of a new carbon-carbon single bond. There are two types of cross-

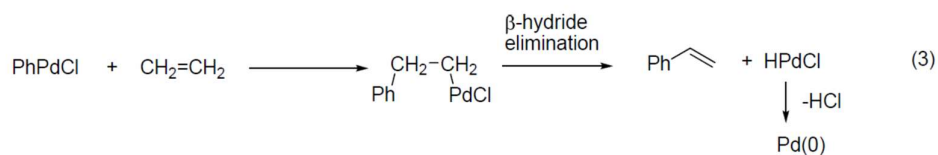
coupling reactions according to this principle that have become important in organic synthesis. These two types of reactions are shown in equations 1 and 2.



Both reactions are catalyzed by zerovalent palladium and both reactions employ an organohalide RX (or analogous compound) as the electrophilic coupling partner. However, the nucleophilic coupling partner differs in the two reactions. In the first type (eq. 1) it is an olefin whereas in the second type (eq. 2) it is an organometallic compound R''M. In this way the palladium-catalyzed cross-coupling reactions in equations 1 and 2 complement one another as regards the nucleophilic coupling partner. A common feature of the two types of cross couplings is that the organic groups from the reagents are assembled on palladium. Furthermore, both reactions begin by generating an organopalladium complex RPdX from the reaction of the organic halide with Pd(0). The organopalladium species RPdX will subsequently react with the nucleophilic coupling partner (see detailed mechanisms below). The reactions are very mild since they utilize organic halides (or analogous compounds) and olefins or organometallic compounds R''M of low reactivity, where M is typically zinc, boron, or tin.

Heck's pioneering work on cross couplings involving olefins

In 1968 Heck reported in a series of papers² that in situ-generated methyl- and phenylpalladium halides (RPdX; R = Me, Ph; X = halide) are added to olefins at room temperature. The addition of phenylpalladium chloride (PhPdCl) to ethylene followed by elimination of palladium gave styrene (eq. 3).

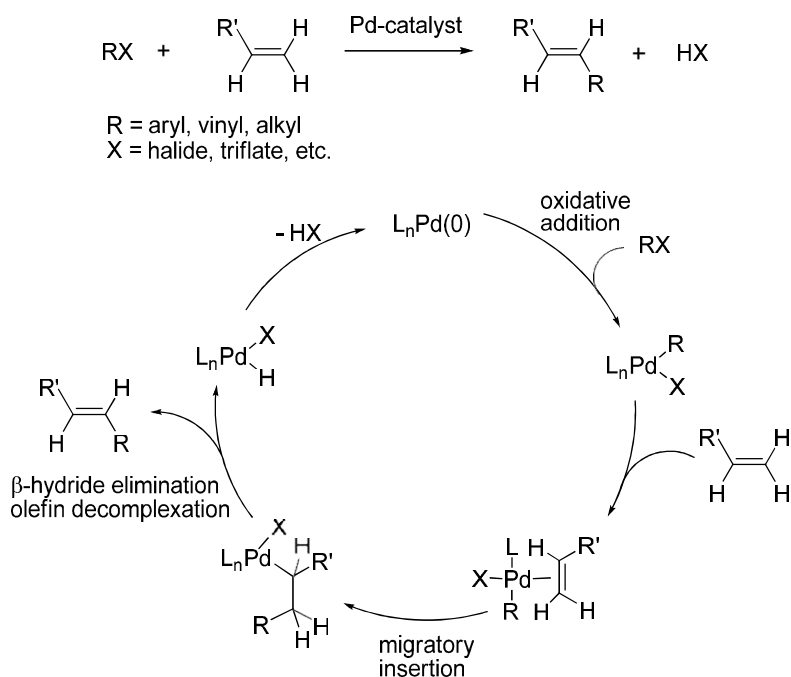


Through this discovery Heck had designed an unprecedented reaction – an arylation (or alkylation) of an olefin. This reaction was to become one of the most important reactions for making carbon-carbon single bonds. In these early examples the organopalladium compound, RPdX (R = aryl or alkyl), was generated from an organomercury compound, RHgX, and a palladium(II) salt. Since palladium(0) is formed at the end of the reaction shown in equation 3, the overall reaction is not catalytic if it is run without any additives. In one of the papers published in 1968 Heck demonstrated that the reaction can be made catalytic with respect to palladium by the use of CuCl₂ as a reoxidant for Pd(0) that is formed at the end of the reaction.

Heck gave a correct mechanism for the arylation of olefins,² and in more detailed studies in 1969 he also provided an explanation for the stereochemical course of the reaction.³

In 1972, Heck made an important modification of his reaction that increased its synthetic utility.⁴ In this new version, which became the standard protocol for carrying out the Heck reaction, the organopalladium complex RPdX is generated from an organohalide, RX , and $\text{Pd}(0)$ in a so-called oxidative addition. Such oxidative additions to $\text{Pd}(0)$ had been previously reported by Fitton,⁵ who in 1968 found that aryl halides react with $\text{Pd}(0)$ to give arylpalladium halides.

Heck was aware of Fitton's work and used it for generating the organopalladium complex for the coupling reaction. Thus, with this new modification an arylation of an olefin was achieved from the reaction of an aryl halide and an olefin in the presence of a palladium catalyst. The mechanism of the Heck reaction is shown in Scheme 1.



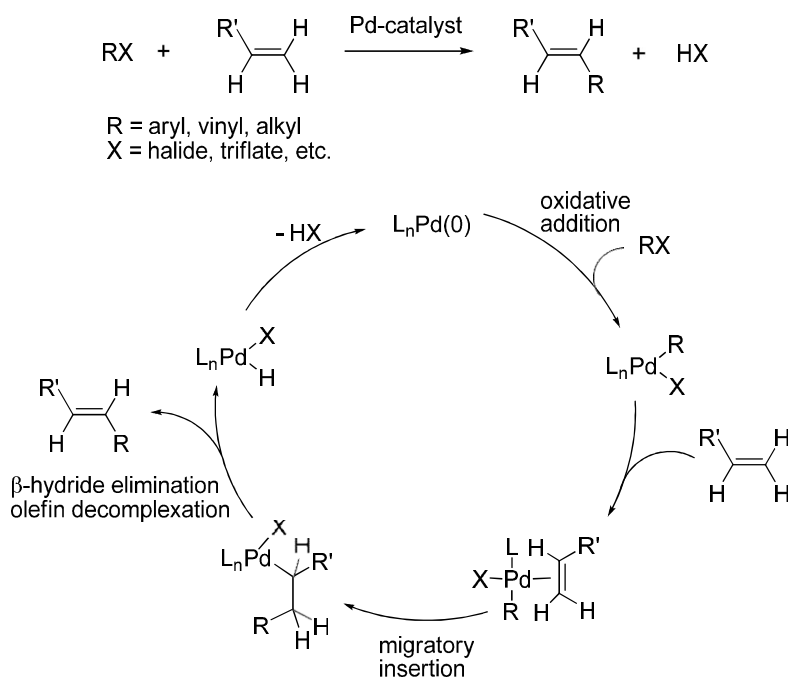
Scheme 1. Mechanism of the Heck reaction.

The reaction begins when the active $\text{Pd}(0)$ catalyst reacts with the organohalide RX in a so-called oxidative addition. In this reaction the oxidation state of palladium formally changes from $\text{Pd}(0)$ to $\text{Pd}(\text{II})$ with the formation of an organopalladium compound RPdX . In this process a new palladium-carbon bond is formed. In the next step the olefin co-ordinates to palladium, and the olefin and the R group are now assembled on the metal and can react with one another. In the next step the R group on palladium migrates to one of the carbons of the co-ordinated olefin and palladium will shift to the other carbon of the olefin. This process is called a migratory insertion and generates the carbon-carbon bond. Finally, the release of the organic group occurs via a β -hydride elimination which forms the new olefin in which the R group from the organohalide RX has replaced a hydrogen atom on the substrate olefin. In this step a short-lived HPdX species is formed, which loses HX to give $\text{Pd}(0)$. The $\text{Pd}(0)$ species formed is now ready to enter another catalytic cycle.

Heck gave a correct mechanism for the arylation of olefins,² and in more detailed studies in 1969 he also provided an explanation for the stereochemical course of the reaction.³

In 1972, Heck made an important modification of his reaction that increased its synthetic utility.⁴ In this new version, which became the standard protocol for carrying out the Heck reaction, the organopalladium complex RPdX is generated from an organohalide, RX , and $\text{Pd}(0)$ in a so-called oxidative addition. Such oxidative additions to $\text{Pd}(0)$ had been previously reported by Fitton,⁵ who in 1968 found that aryl halides react with $\text{Pd}(0)$ to give arylpalladium halides.

Heck was aware of Fitton's work and used it for generating the organopalladium complex for the coupling reaction. Thus, with this new modification an arylation of an olefin was achieved from the reaction of an aryl halide and an olefin in the presence of a palladium catalyst. The mechanism of the Heck reaction is shown in Scheme 1.



Scheme 1. Mechanism of the Heck reaction.

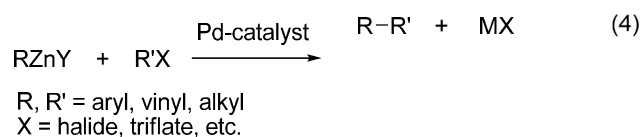
The reaction begins when the active $\text{Pd}(0)$ catalyst reacts with the organohalide RX in a so-called oxidative addition. In this reaction the oxidation state of palladium formally changes from $\text{Pd}(0)$ to $\text{Pd}(\text{II})$ with the formation of an organopalladium compound RPdX . In this process a new palladium-carbon bond is formed. In the next step the olefin co-ordinates to palladium, and the olefin and the R group are now assembled on the metal and can react with one another. In the next step the R group on palladium migrates to one of the carbons of the co-ordinated olefin and palladium will shift to the other carbon of the olefin. This process is called a migratory insertion and generates the carbon-carbon bond. Finally, the release of the organic group occurs via a β -hydride elimination which forms the new olefin in which the R group from the organohalide RX has replaced a hydrogen atom on the substrate olefin. In this step a short-lived HPdX species is formed, which loses HX to give $\text{Pd}(0)$. The $\text{Pd}(0)$ species formed is now ready to enter another catalytic cycle.

Other researchers have also contributed to the development of this reaction. I. Moritani and Y. Fujiwara⁶ observed in 1967 that benzene reacts with olefins to give styrenes. After Heck's papers in 1968 and 1969 they realized⁷ that the reaction occurs via arylpalladium species. In 1971, T. Mizoroki, stimulated by the earlier studies by Heck and Fujiwara, reported that iodobenzene arylates alkenes in the presence of a palladium catalyst to give styrenes.⁸

Negishi's development of a mild cross coupling

Transition metal-catalyzed reactions of Grignard reagents (as arylmagnesium bromides) and organohalides in the presence of catalytic amounts of salts of cobalt, nickel and iron were reported by Kharasch in 1941 to give high yields of biaryls, this was however, via homocoupling of the Grignard reagent.⁹ Carbon-carbon bond formation via copper-catalyzed coupling between methylmagnesium bromide and methyl iodide was also reported by Gilman in 1952.¹⁰ These cross couplings with the aid of copper were further studied in the 60's. Also, Kochi's work on iron-catalyzed cross coupling from 1971 should be mentioned.¹¹ In 1972 the teams of Corriu (using nickel acetylacetonate)¹² and Kumada (using nickel phosphine complexes)¹³ independently reported nickel-catalyzed cross couplings between Grignard reagents and aryl or vinyl halides. This reaction was extended to palladium by Murahashi in 1975.¹⁴ The highly reactive organometallic species, RM, such as Grignard reagents, RMgX, or organolithium compounds, RLi, which had been employed in these early cross-coupling reactions do not tolerate certain functional groups and are associated with low chemoselectivity. Therefore, the use of these reagents in cross-coupling reactions was not optimal for synthetic applications.

In 1976, Negishi initiated a series of studies to explore more chemoselective organometallic species in the palladium-catalyzed couplings with organohalides.¹⁵ In the first studies Negishi employed organozirconium or organoaluminium compounds as coupling partners.¹⁵ The positive results obtained from these studies stimulated him to try even less reactive organometallic species. The breakthrough came in 1977 when Negishi introduced organozinc compounds as the nucleophilic coupling partners in palladium-catalyzed cross coupling.¹⁶ The organozinc compounds gave superior yields compared to other organometallic compounds, and furthermore, they were very mild and highly selective. The use of organozinc compounds in the palladium-catalyzed cross-coupling reaction allowed for the presence of a wide range of functional groups; this was in contrast to previous methods employing a Grignard reagent or an organolithium compound as the nucleophilic coupling partner. The new coupling reaction became a very important method for making carbon-carbon single bonds and it is called the Negishi reaction (eq. 4).

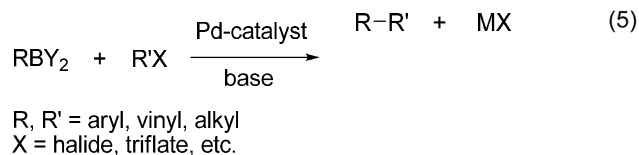


Negishi also noted in 1978 that an alkynylboron compound coupled with an organic halide in the presence of a palladium catalyst. He did not pursue the use of organoboron compounds as nucleophilic coupling partners and there is only a single example reported in a book chapter.¹⁷ The use of organoboron compounds in cross-coupling reactions with organohalides is discussed below (Suzuki reaction).

Other researchers have also made important contributions to the use of organozinc reagents in palladium-catalyzed cross coupling. J. F. Fauvarque and A. Jutand reported in 1977 that zinc enolates in the form of Reformatzky reagents couple with aryl halides in the presence of a Pd(0) catalyst to give a new carbon-carbon bond.¹⁸ P. Knochel has widened the scope of oligo- functional organozinc derivatives and thus enhanced the synthetic utility of the Negishi reaction.¹⁹

Suzuki's discovery of a practical process

In 1979 Suzuki and co-workers reported in two papers that organoboron compounds in the presence of a base can be used as coupling partners in palladium-catalyzed cross coupling with vinyl and aryl halides (eq. 5).²⁰ Thus, base activation of organoboron reagents as boronate intermediates facilitated the transfer of the organic group from boron to palladium (transmetallation). The reaction has later been extended to also include couplings with alkyl groups.

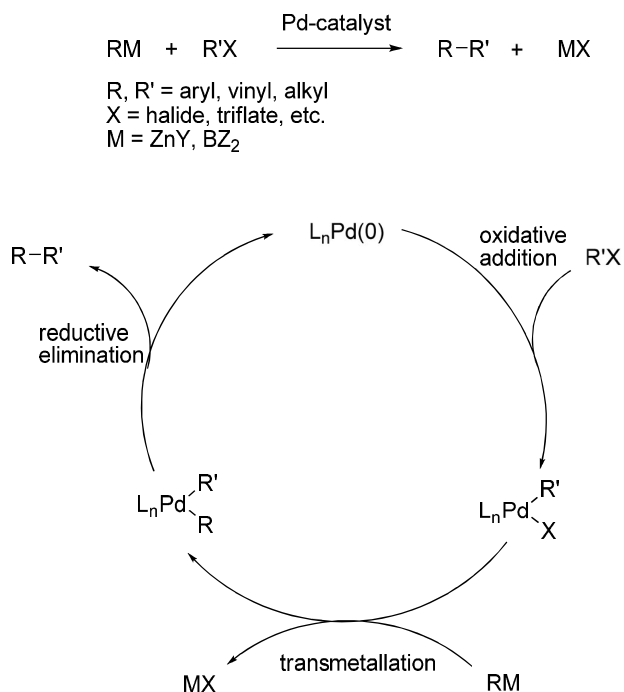


A further significant development came from the observation that arylboronic acids are able to participate as coupling partners in the palladium-catalyzed cross-coupling reaction. In the latter case the reaction was even more efficient and weaker bases could be employed. The stability and weak nucleophilic nature of organoboron compounds has made this reaction very practical. It tolerates a wide range of functional groups and it is highly chemoselective. Furthermore, boron compounds are generally non-toxic and the reaction can be run under very mild conditions. This has made the reaction popular in the pharmaceutical industry. The reaction is called the Suzuki reaction.

Other researchers have contributed to the development of using organoboron compounds as coupling partners and in 1975, H. A. Dieck and Heck employed vinyl boronic acids as coupling partners with olefins in stoichiometric Heck reactions.²¹ As mentioned above, Negishi showed one example of coupling with an alkynylboron compound. Also, N. Miyaura (who was Suzuki's associate professor at the time) later made several important improvements on boron couplings.²² The Suzuki reaction has been extended to aryl chlorides by G. C. Fu by the use of sterically hindered phosphine ligands.²³

The mechanism of the Negishi and Suzuki cross-coupling reactions

In the Negishi and Suzuki cross-coupling reactions an organozinc or organoboron compound, respectively, couples with an organohalide (or an analogous compound such as an organotriflate or a diazo compound) in the presence of a catalytic amount of a palladium(0) complex. The reaction leads to the formation of a new carbon-carbon single bond. The mechanism of these palladium-catalyzed cross-coupling reactions is given in Scheme 2.



Scheme 2. Mechanism of the Negishi and Suzuki palladium-catalyzed cross-coupling reactions.

The first step in the Negishi and Suzuki cross-coupling reactions is identical to that of the Heck reaction. This step is an oxidative addition of $\text{R}'\text{X}$ to $\text{Pd}(0)$ to give an organopalladium compound. In the second step the organic group, R on zinc or boron, is transferred to palladium in a process called transmetalation. In this way the two organic groups are assembled on the same palladium atom via palladium-carbon bonds. In the final step the R' and R groups couple with one another to give a new carbon-carbon single bond and $\text{R-R}'$ is released from palladium. In this process Pd(II) is reduced to Pd(0) and therefore the final step is called a reductive elimination. Such a reductive elimination was demonstrated by A. Yamamoto in 1970 with the use of a diethylnickel complex.²⁴ The nickel complex employed is electronically analogous to the diaorganopalladium complex formed in the catalytic cycle. Yamamoto found that by heating or adding an electron-withdrawing ligand to these diethylnickel complexes they underwent a reductive elimination to give butane and a nickel(0) complex.

Contributions to the understanding of the mechanism of metal-catalyzed cross-coupling reactions have also been made by M. Kumada and K. Tamao.¹³ These researchers reported on a related nickel-catalyzed cross coupling in 1972 and they proposed a mechanism via oxidative addition, transmetalation, and reductive elimination (cf. Scheme 2). S.-I. Murahashi¹⁴ reported a palladium-catalyzed cross coupling between Grignard reagents and organohalides in 1975.

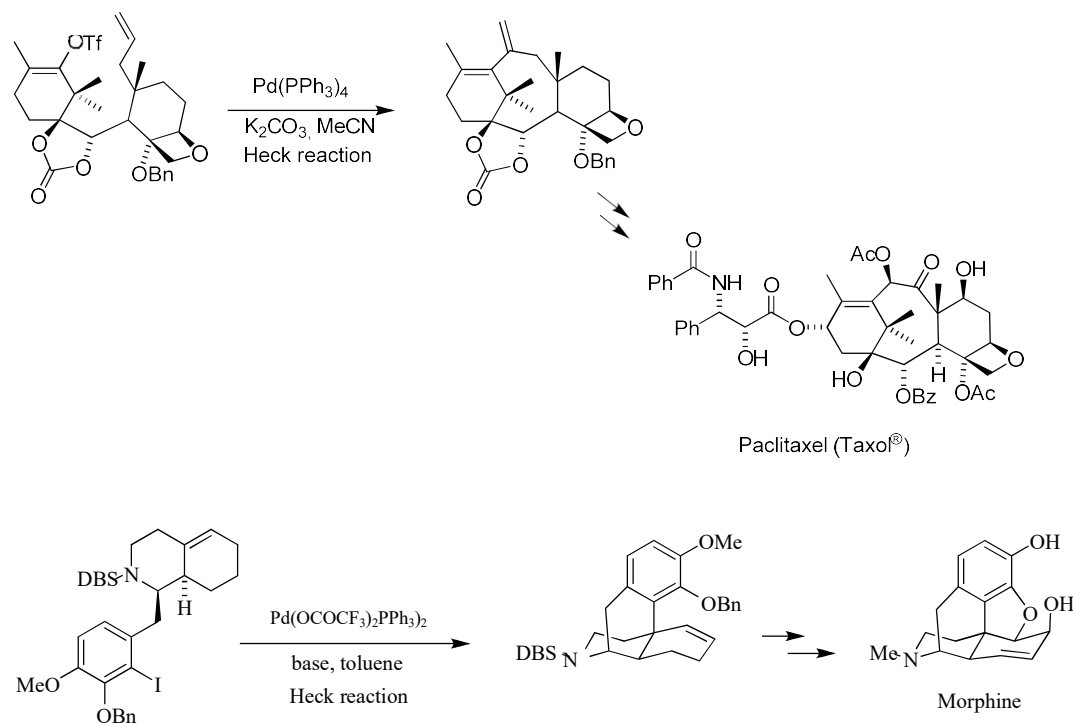
Important contributions for the synthetic development of palladium-catalyzed cross coupling have also been made by the groups of T. Migita²⁵ and J. K. Stille²⁶, who in 1977 and 1978, respectively, developed palladium-catalyzed cross couplings using an organotin compound as the nucleophilic coupling partner. Organotin compounds are stable organometallic compounds with low reactivity and give mild reaction conditions. The reaction developed became known as the Stille reaction and is used as an alternative to the Negishi and Suzuki reactions for

substrates with sensitive functional groups. However, the toxicity of organotin compounds has limited their industrial use.

Application of palladium-catalyzed cross couplings

The palladium-catalyzed carbon-carbon bond forming reactions developed by Heck, Negishi and Suzuki have had a large impact on synthetic organic chemistry and have found many applications in target oriented synthesis. Their widespread use in organic synthetic applications is due to the mild conditions associated with the reactions together with their tolerance of a wide range of functional groups. These three cross-coupling reactions have been applied to the synthesis of a large number of natural products and biologically active compounds of complex molecular structures. They have also found applications in the fine chemical and pharmaceutical industries. Some examples of the use of the Heck, Negishi, and Suzuki reactions in natural product synthesis and industrial applications are given below.

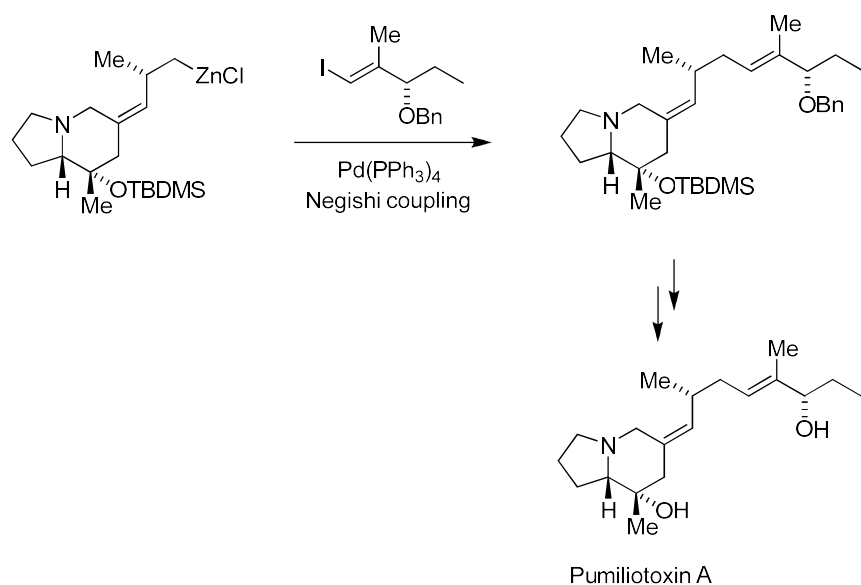
The Heck reaction has been used in more than 100 different syntheses of natural products and biologically active compounds. Two examples are given in Scheme 3. The first example is for the synthesis of Taxol[®], where the Heck reaction was employed for creating the eight-membered ring.²⁷ The ring closure to complete the rigid tricyclic system is not trivial. In the other example an intramolecular Heck-type coupling provides the morphine skeleton and the product is transformed to morphine in a few steps.²⁸



Scheme 3. Examples of the use of the Heck reaction in natural product synthesis (refs. 27 and 28)

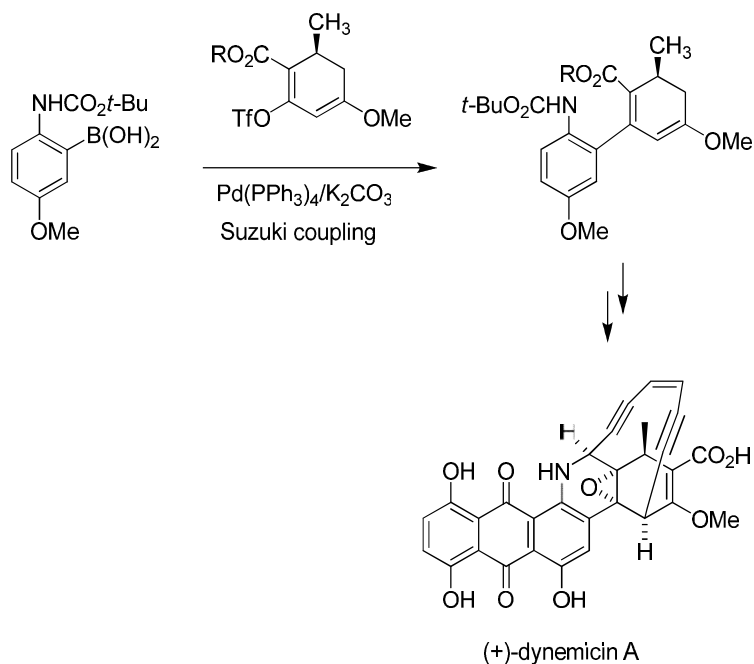
The Heck reaction has also been used as an important carbon-carbon bond-forming step in the synthesis of other complex organic molecules such as steroids,²⁹ strychnine,³⁰ and the diterpenoid scopadulcic acid B³¹ WITH cytotoxic and antitumor activity.

The Negishi and Suzuki reactions have also been frequently employed in natural product synthesis. Pumiliotoxin A is a toxic alkaloid found in the skin of frogs from the Dendrobatidae family that the frog uses for its defence. The total synthesis of pumiliotoxin A was performed via the use of a Negishi coupling in one of the key steps (Scheme 4).³² It is interesting to note that an alkylzinc compound with α -hydrogens is used in this reaction.



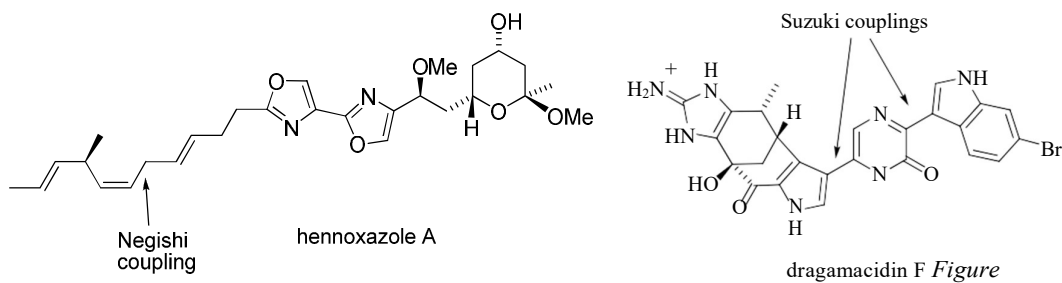
Scheme 4. The use of the Negishi coupling in the synthesis of Pumiliotoxin A (ref. 32).

An efficient synthesis of the potent natural antitumor agent (+)-dynemicin A involved a Suzuki coupling in one of the key carbon-carbon bond forming steps (Scheme 5).³³



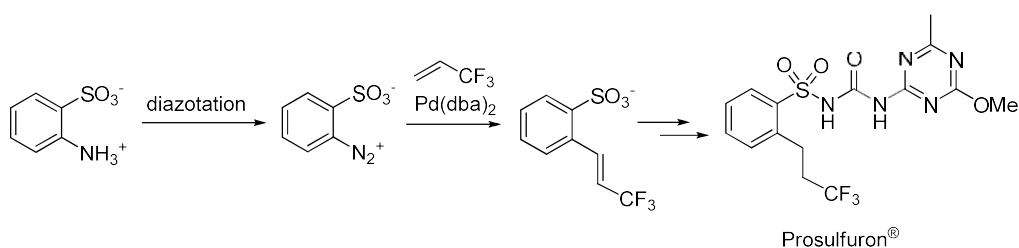
Scheme 5. An efficient Suzuki coupling in the synthesis of (+)-dynemicin A (ref. 33).

There are a number of natural product syntheses reported in the literature that rely on the Negishi and Suzuki couplings for carbon-carbon bond formation. Two more examples are given in Figure 1. The Negishi coupling was employed in the synthesis of the natural marine antiviral product hennoxazole A³⁴ and the Suzuki reaction was used for preparing the antiviral bromoindole alkaloid dragmacidin F.³⁵ At the cross coupling stage there were several sensitive functional groups present, and therefore mild reagents such as an organoboron or organozinc reagent are required.



1. Synthesis of hennoxazole A (ref 34) and dragmacidin F (ref 35) via palladium- catalyzed cross coupling.

The palladium-catalyzed cross-coupling reactions are suitable for carrying out on a large scale and the Heck reaction has been used for a number of large scale industrial applications. Several of these processes are run on a multiton scale per year. The sulfonyl urea herbicide Prosulfuron® is produced on a large scale with a process developed by Ciba-Geigy (Scheme 6). The key step is a Heck reaction, where a diazonium salt generates an arylpalladium intermediate, which couples with the olefin.



Scheme 6. An industrial process for the synthesis of Prosulfuron® (Ciba-Geigy 1994, ref 36)

The anti-inflammatory drug Naproxen (Albermarle, Hoechst AG, 1994) and the asthma drug Singulair (Merck, 1993) are other examples of industrial manufacturing of pharmaceuticals via the Heck reaction.

Some examples of the use of the Heck, Negishi, and Suzuki reactions in the industrial preparation of fine chemicals are given in Figure 2.

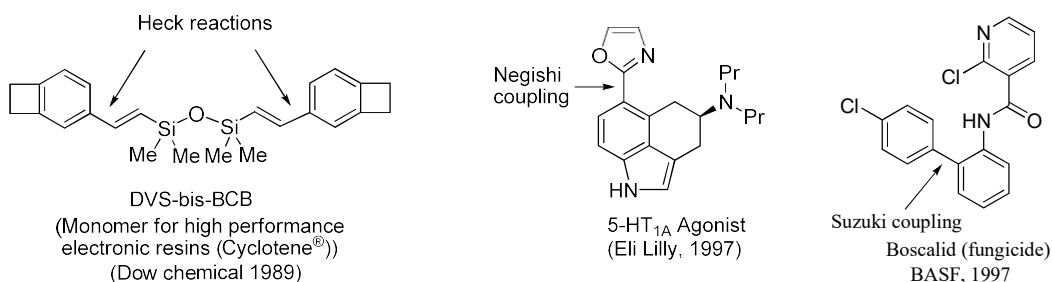
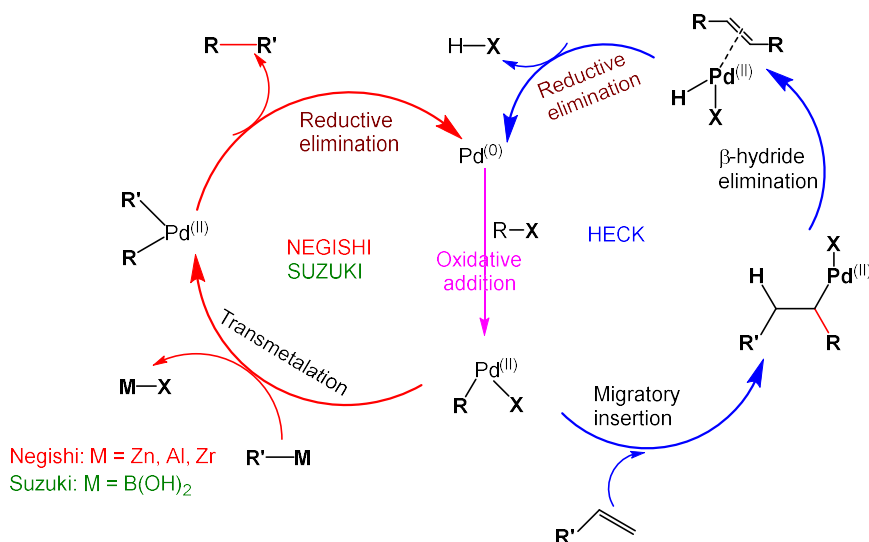


Figure 2. Palladium-catalyzed cross-coupling reactions in industrial preparation of fine chemicals: DVS-bis-BCB (Cyclotene®) (ref. 37), 5-HT_{1A} Agonist (ref. 38), and Boscalid (ref 39)

Mechanism summary of Pd catalyzed coupling reactions.



Consequences and applications:

Some of the applications of the Laureates' pioneering work on carbon-carbon bond formation have already been discussed. It is important to emphasize the great significance their discoveries have for both academic and industrial research and in the production of fine chemicals – including pharmaceuticals, agricultural chemicals, and high tech materials – that benefit society. Few reactions have contributed to enhancing the efficiency of organic synthesis as much as the palladium-catalyzed cross-coupling reactions. These reactions have changed the practice of the science of synthesis and they are used for making complex molecules producing both natural products and biologically active compounds.

References

- ¹ J. Smidt, W. Hafner, R. Jira, J. Sedlmeier, R. Sieber, R. Rüttinger, and H. Kojer, *Angew. Chem.* **1959**, *71*, 176.
- ² (a) R. F. Heck, *J. Am. Chem. Soc.* **1968**, *90*, 5518. (b) R. F. Heck, *J. Am. Chem. Soc.* **1968**, *90*, 5526. (c) R. F. Heck, *J. Am. Chem. Soc.* **1968**, *90*, 5531. (d) R. F. Heck, *J. Am. Chem. Soc.* **1968**, *90*, 5538. (e) R. F. Heck, *J. Am. Chem. Soc.* **1968**, *90*, 5542.
- ³ R. F. Heck, *J. Am. Chem. Soc.* **1969**, *91*, 6707.
- ⁴ R. F. Heck and J. P. Nolley, *J. Org. Chem.* **1972**, *37*, 2320
- ⁵ (a) P. Fitton and J. E. McKeon, *Chem. Commun.* **1968**, 4. (b) P. Fitton, M. P. Johnson, and J. E. McKeon, *Chem. Commun.* **1968**, 6
- ⁶ I. Moritani and Y. Fujiwara, *Tetrahedron Lett.* **1967**, 1119.
- ⁷ Y. Fujiwara, I. Moritani, S. Danno, R. Asano, and S. Teranishi, *J. Am. Chem. Soc.* **1969**, *91*, 7166.
- ⁸ T. Mizoroki, K. Mori, and A. Ozaki, *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581.
- ⁹ M. S. Kharasch and E. K. Fields, *J. Am. Chem. Soc.* **1941**, *63*, 2316.
- ¹⁰ H. Gilman, R. G. Jones, and L. A. Woods, *J. Org. Chem.* **1952**, *17*, 1630
- ¹¹ M. Tamura and J. K. Kochi, *J. Am. Chem. Soc.* **1971**, *93*, 1487.
- ¹² R. J. P. Corriu and J. P. Masse, *Chem. Commun.* **1972**, 144
- ¹³ K. Tamao, K. Sumitani, M. Kumada, *J. Am. Chem. Soc.* **1972**, *94*, 4374.
- ¹⁴ M. Yamamura, I. Moritani, and S.-I. Murahashi, *J. Organometal. Chem.* **1975**, *91*, C39.
- ¹⁵ (a) E.-I. Negishi and S. Baba, *Chem. Commun.* **1976**, 596. (b) S. Baba and E.-I. Negishi, *J. Am. Chem. Soc.* **1976**, *98*, 6729.
- ¹⁶ (a) E.-I. Negishi, A. O. King, and N. Okukado, *J. Org. Chem.* **1977**, *42*, 1821. (b) A. O. King, N. Okukado, and E.-I. Negishi, *Chem. Commun.* **1977**, 683.
- ¹⁷ E.-I. Negishi, "Selective Carbon-Carbon Bond Formation via Transition Metal Catalysis: Is Nickel or Palladium Better than Copper" in "Aspects of Mechanism and Organometallic Chemistry", Ed. J. H. Brewster, Plenum Press, New York, 1978, pp. 285-317.
- ¹⁸ J. F. Fauvarque and A. Jutand, *J. Organometal. Chem.* **1977**, *132*, C17.
- ¹⁹ (a) P. Knochel, M. I. Calaza, and E. Hupe, "Carbon-Carbon Bond Forming Reactions Mediated by Organozinc Reagents" in "Metal-Catalyzed Cross-Coupling Reactions", Eds A. de Meijere and F. Diederich, Wiley-VCH, Weinheim, 2004, pp. 619-670. (b) G. Manolikakes, M. A. Schade, C. Muñoz Hernandez, H. Mayr, and P. Knochel, *Org. Lett.* **2008**, *10*, 2765.
- ²⁰ (a) N. Miyaura, K. Yamada, and A. Suzuki, *Tetrahedron Lett.* **1979**, *20*, 3437. (b) N. Miyaura and A. Suzuki, *J. Chem. Soc. Chem. Commun.* **1979**, 866.
- ²¹ H. A. Dieck and R. F. Heck, *J. Org. Chem.* **1975**, *40*, 1083.
- ²² N. Miyara "Metal-Catalyzed Cross-Coupling Reactions of Organoboron Compounds with Organic Halides" in "Metal-Catalyzed Cross-Coupling Reactions", Eds A. de Meijere and F. Diederich, Wiley-VCH, Weinheim, 2004, pp. 41-123.
- ²³ A. F. Littke and G. C. Fu, *Angew. Chem. Int. Ed.* **1998**, *37*, 3387.
- ²⁴ M. Uchino, A. Yamamoto, S. Ikeda, *J. Organometal. Chem.* **1970**, *24*, C63.
- ²⁵ M. Kosugi, Y. Shimizu, and T. Migita, *Chem. Lett.* **1977**, 1423.
- ²⁶ (a) D. Milstein and J. K. Stille, *J. Am. Chem. Soc.* **1978**, *100*, 3636. (b) D. Milstein and J. K. Stille, *J. Am. Chem. Soc.* **1979**, *101*, 4992.

-
- ²⁷ S. J. Danishefsky, J. J. Masters, W. B. Young, J. T. Link, L. B. Snyder, T. V. Magee, D. K. Jung, R. C. A. Isaacs, W. G. Bornmann, C. A. Alaimo, C. A. Coburn, and M. J. Di Grandi, *J. Am. Chem. Soc.* **1996**, *118*, 2843.
- ²⁸ C. Y. Hong, N. Kado, and L. E. Overman, *J. Am. Chem. Soc.* **1993**, *115*, 11028. ²⁹ Y. Chang, G. Wu, G. Agnel, E.-I. Negishi, *J. Am. Chem. Soc.* **1990**, *112*, 8590. ³⁰ V. H. Rawal and S. Iwasa, *J. Org. Chem.* **1994**, *59*, 2685.
- ³¹ (a) L. E. Overman, D. J. Ricca, and V. D. Tran, *J. Am. Chem. Soc.* **1993**, *115*, 2042. (b) D. J. Kucera, S. J. O'Connor, and L. E. Overman, *J. Org. Chem.* **1993**, *58*, 5304.
- ³² S. Hirashima, S. Aoyagi, and C. Kibayashi, *J. Am. Chem. Soc.* **1999**, *121*, 9873.
- ³³ A. G. Myers, N. J. Tom, M. E. Fraley, S. B. Cohen, and D. J. Madar, *J. Am. Chem. Soc.* **1997**, *119*, 6072.
- ³⁴ P. Wipf and S. Lim, *J. Am. Chem. Soc.* **1995**, *117*, 558.
- ³⁵ N. K. Garg, D. D. Caspi, and B. M. Stoltz, *J. Am. Chem. Soc.* **2004**, *126*, 9552.
- ³⁶ P. Baumeister, G. Seifert, H. Steiner, European Patent EP584043, **1994**.
- ³⁷ A. K. Schrock, U.S. Patent US4812588, **1989**.
- ³⁸ B. A. Anderson, L. M. Becke, R. N. Booher, M. E. Flaugh, N. K. Ham, T. J. Kress, D. L. Varie, J. P. Wepsiec, *J. Org. Chem.* **1997**, *62*, 8634.
- ³⁹ (a) K. Eicken, H. Rang, A. Harreus, N. Götz, E. Ammermann, G. Lorentz, and S. Strathmann, German Patent DE19531813, **1997**. (b) K. Eicken, M. Rack, F. Wetterich, E. Ammermann, G. Lorentz, and S. Strathmann, German Patent DE19735224, **1999**. (c) A. M. Rouhi, *Chem. & Eng. News* **2004**, *82* (36), Sept. 6, pp 49-58.

Further reading

“Metal-Catalyzed Cross-Coupling Reactions”, Eds A. de Meijere and F. Diederich, Wiley-VCH, Weinheim, 2004, vols 1 and 2.

Accounts of Chemical Research, November Issue 2008, Special Issue on Cross Coupling.