

# The 2010 Nobel Prize in Chemistry: Palladium-Catalysed Cross-Coupling

The importance of carbon–carbon coupling for real world applications

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*The 2010 Nobel Prize in Chemistry was awarded jointly to Professor Richard F. Heck (University of Delaware, USA), Professor Ei-ichi Negishi (Purdue University, USA) and Professor Akira Suzuki (Hokkaido University, Japan) for their work on palladium-catalysed cross-coupling in organic synthesis. This article presents a brief history of the development of the protocols for palladium-catalysed coupling in the context of Heck, Negishi and Suzuki coupling. Further developments in the area of palladium-catalysed cross-coupling are also briefly discussed, and the importance of these reactions for real world applications is highlighted.*

The 2010 Nobel Prize in chemistry was the third awarded during the last ten years in the area of platinum group metal (pgm)-based homogeneous catalysis for organic synthesis. Previous prizes had been awarded to Dr William S. Knowles (Monsanto, USA), Professor Ryoji Noyori (Nagoya University, Japan) and Professor K. Barry Sharpless (The Scripps Research Institute, USA) in 2001, for their development of asymmetric synthesis reactions catalysed by rhodium, ruthenium and osmium complexes, and to Dr Yves Chauvin (Institut Français du Pétrole, France), Professor Robert H. Grubbs (California Institute of Technology (Caltech), USA) and Professor Richard R. Schrock (Massachusetts Institute of Technology (MIT), USA) in 2005 for the development of the ruthenium- and molybdenum-catalysed olefin metathesis method in organic synthesis.

Figure 1 shows some of the researchers who have made significant contributions in the area of palladium-catalysed cross-coupling, including 2010 Nobel laureate, Professor Akira Suzuki, during a cross-coupling conference at the University of Lyon, France, in 2007 (1).

## Palladium-Catalysed Reactions

Organometallic compounds of pgms are vitally important as catalysts for real world applications in



Fig. 1. From left: Professor Kohei Tamao (a significant contributor in Kumada coupling), Professor Gregory C. Fu (a significant contributor in promoting the bulky electron-rich tert-butyl phosphine for challenging cross-coupling), Professor Akira Suzuki (2010 Nobel Prize in Chemistry Laureate), Dr Thomas J. Colacot (author of this article) and Professor Tamejiro Hiyama (who first reported Hiyama coupling) in front of a photograph of Professor Victor Grignard (who initiated the new method of carbon-carbon coupling) in the library of the University of Lyon, France

synthetic organic chemistry. Chemists are continually striving to improve the efficiency of industrial processes by maximising their yield, selectivity and safety. Process economics are also important, and chemists work to minimise the number of steps required and thereby reduce the potential for waste and improve the sustainability of the process. Homogeneous catalysis is a powerful tool which can help to achieve these goals. Of the three Nobel Prizes in pgm-based homogeneous catalysis, perhaps the most impact in practical terms has been made by palladium-catalysed cross-coupling (2).

In order for an area to be recognised for the Nobel Prize, its real world application has to be demonstrated within 20 to 30 years of its discovery. Although the area of metal-catalysed cross-coupling was initiated in the early 1970s, there were a very limited number of publications and patents in this area before the 1990s (see Figure 2). However, the area has grown rapidly from 1990 onwards, especially since 2000.

In terms of the number of scientific publications, patents and industrial applications, Suzuki coupling is by far the largest area, followed by Heck, Sonogashira and Stille coupling (Figure 2). Negishi

coupling is smaller in terms of the number of publications, but its popularity is growing due to the functional group tolerance of the zinc reagent in comparison to magnesium, in addition to its significant potential in  $sp^3$ - $sp^2$  coupling, natural product synthesis and asymmetric carbon-carbon bond forming reactions (1).

The history and development of the various types of palladium-catalysed coupling reactions have been covered in detail elsewhere (3, 4). This short article will focus on the practical applications of palladium-catalysed coupling reactions.

### Heck Coupling



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Between 1968 and 1972, Mizoroki and coworkers (5, 6) and Heck and coworkers (7–9) independently discovered the use of Pd(0) catalysts for coupling of aryl, benzyl and styryl halides with olefinic com-

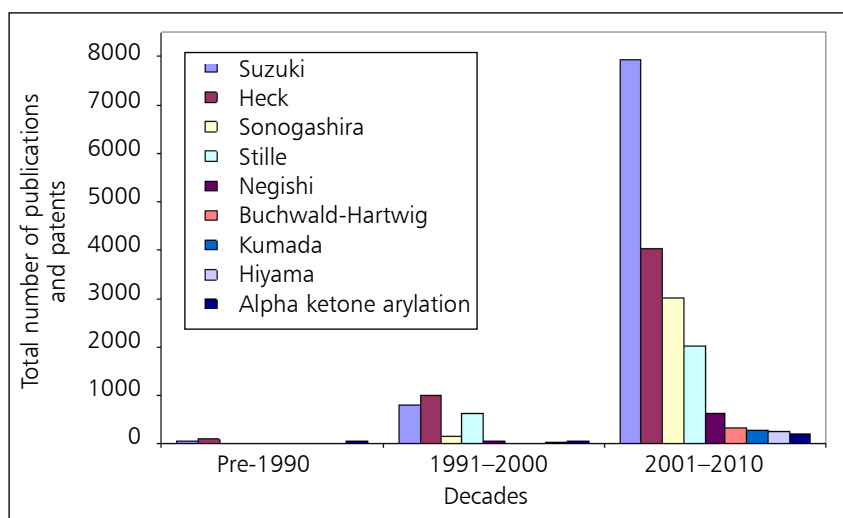
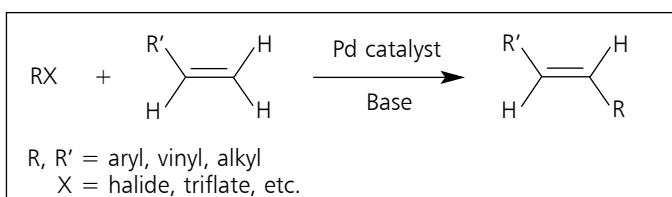


Fig. 2. Growth in the number of scientific publications and patents on platinum group metal-catalysed coupling reactions



Scheme 1. The Heck coupling reaction

pounds, now known as the Heck coupling reaction (Scheme 1) as Heck was the first to uncover the mechanism of the reaction.

The applications of this chemistry include the synthesis of hydrocarbons, conducting polymers, light-emitting electrodes, active pharmaceutical ingredients and dyes. It can also be used for the enantioselective synthesis of natural products.

Heck coupling has a broader range of uses than the other coupling reactions as it can produce products of different regio (linear and branched) and stereo (*cis* and *trans*) isomers. Typically, olefins possessing electron-withdrawing groups favour linear products while electron-rich groups give a mixture of branched and linear products. The selectivity is also influenced by the nature of ligands, halides, additives and solvents, and by the nature of the palladium source. The reaction has recently been extended to include direct arylation and hydroarylation, which may have future potential in terms of practical applications. Heck coupling also has the unique advantage of making chiral C–C bonds, with the exception of  $\alpha$ -arylation reactions.

### The Negishi Reaction



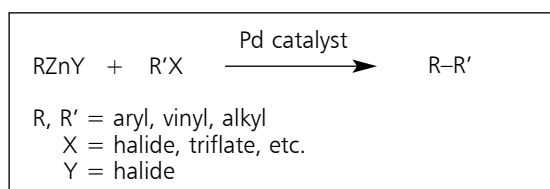
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During 1976–1977, Negishi and co-workers (10–12) and Fauvarque and Jutand (13) reported the use of zinc reagents in cross-coupling reactions. During the same period Kumada *et al.* (14–17) and Corriu *et al.* (18) independ-

ently reported that nickel–phosphine complexes were able to catalyse the coupling of aryl and alkenyl halides with Grignard reagents. Kumada and coworkers later reported (in 1979) the use of dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) (PdCl<sub>2</sub>(dppf)) as an effective catalyst for the cross-coupling of secondary alkyl Grignard reagents with organic halides (19). One common limitation to both Ni- and Pd-catalysed Kumada coupling is that coupling partners bearing base sensitive functionalities

are not tolerated due to the nature of the organomagnesium reagents.

In 1982 Negishi and coworkers therefore carried out a metal screening in order to identify other possible organometallic reagents as coupling partners (20). Several metals were screened in the coupling of an aryl iodide with an acetylene organometallic reagent, catalysed by bis(triphenylphosphine)palladium(II) dichloride ( $\text{PdCl}_2(\text{PPh}_3)_2$ ). In this study, the use of zinc, boron and tin were identified as viable counterions, and provided the desired alkyne product in good yields. The use of organozinc reagents as coupling partners for palladium-catalysed cross-coupling to form a C–C single bond is now known as the Negishi reaction (**Scheme II**).



*Scheme II. The Negishi coupling reaction*

The Negishi reaction has been used as an essential step in the synthesis of natural products and fine chemicals (21–23).

### Suzuki Coupling

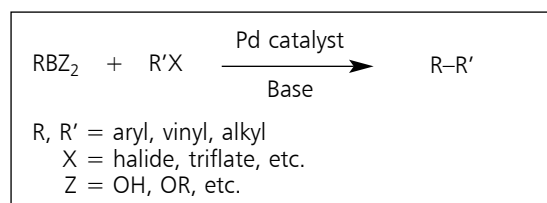


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During the same period as the initial reports of the use of palladium–phosphine complexes in Kumada couplings, the palladium-catalysed coupling of acetylenes with aryl or vinyl halides was concurrently disclosed by

three independent research groups, led by Sonogashira (24), Cassar (25) and Heck (26).

A year after the seminal report on the Stille coupling (27, 28), Suzuki picked up on boron as the last remaining element out of the three (Zn, Sn and B) identified by Negishi as suitable counterions in cross-coupling reactions, and reported the palladium-catalysed coupling between 1-alkenylboranes and aryl halides (29) that is now known as Suzuki coupling (**Scheme III**).



*Scheme III. The Suzuki coupling reaction*

It should be noted that Heck had already demonstrated in 1975 the transmetallation of a vinyl boronic acid reagent (30). Perhaps the greatest accomplishment of Suzuki was that he identified  $\text{PdCl}_2(\text{PPh}_3)_2$  as an efficient cross-coupling catalyst, thereby demonstrating the relatively easy reduction of Pd(II) to Pd(0) during catalysis.

The Suzuki coupling reaction is widely used in the synthesis of pharmaceutical ingredients such as losartan. Its use has been extended to include coupling with alkyl groups and aryl chlorides through the work of other groups including Fu and coworkers (31). Subsequent work from Buchwald, Hartwig, Nolan, Beller and others, including Johnson Matthey, has expanded the scope of this reaction.

### Other Name Reactions in Carbon–Carbon Coupling

In 1976, Eaborn *et al.* published the first palladium-catalysed reaction of organotin reagents (32), followed by Kosugi *et al.* in 1977 on the use of organotin reagents (33, 34). Stille and Milstein disclosed in 1978 the synthesis of ketones (27) under significantly milder reaction conditions than Kosugi. At the beginning of the 1980s, Stille further explored and improved this reaction protocol, to develop it into a highly versatile methodology displaying very broad functional group compatibility (28).

In 1988, Hiyama and Hatanaka published their work on the Pd- or Ni-catalysed coupling of organosilanes with aryl halides or trifluoromethanesulfonates (triflates) (35). Although silicon is less toxic than tin, a fluoride source, such as tris(dimethylamino)-sulfonium difluorotrimethylsilicate (TASF) (35) or caesium fluoride (CsF) (36), is required to activate the organosilane towards transmetallation. Professor S. E. Denmark has also contributed significantly to this area.

### Industrial Applications

In the early 1990s the Merck Corporation was able to develop two significant drug molecules, losartan, 1,

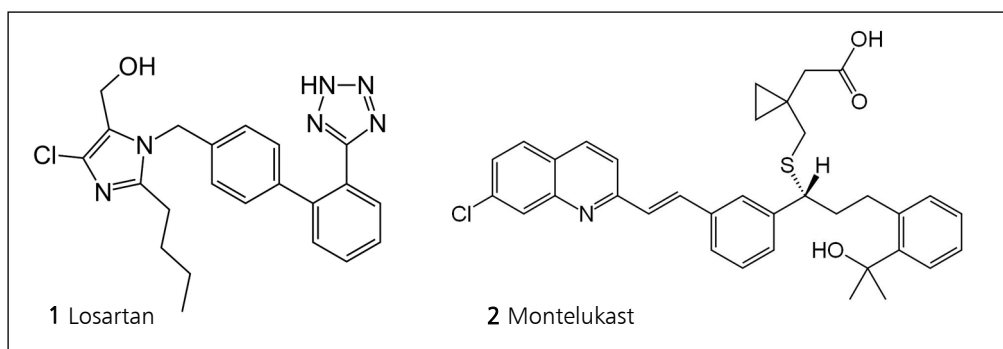


Fig. 3. Structures of losartan and montelukast

(also known as Cozaar™, for the treatment of hypertension) (37) and montelukast, **2**, (also known as Singulair™, for the treatment of asthma) (38, 39), (Figure 3) using Suzuki and Heck coupling processes respectively. This also increased awareness among related industries to look into similar processes. Today, coupling reactions are essential steps in the preparation of many drugs. Recent reviews by Beller (40) and by Sigman (41) summarise the applications of Pd-catalysed coupling in the pharmaceutical, agrochemical and fine chemicals industries. Apart from the major applications in the pharmaceutical and agrochemical industries (the boscalid process is the world's largest commercial Suzuki process), cross-coupling is also being practiced in the electronics industry for liquid crystal and organic light-emitting

diode (OLED) applications in display screens (42, 43).

The research and development group at Johnson Matthey's Catalysis and Chiral Technologies has developed commercial processes for preformed catalysts such as PdCl<sub>2</sub>(dtbpf) (Pd-118), **3**, (44–46), L<sub>2</sub>Pd(0) complexes, **4**, (47) and precursors to twelve-electron species such as [Pd(μ-Br)<sup>t</sup>Bu<sub>3</sub>P]<sub>2</sub> (Pd-113), **5**, (48) and LPd(η<sup>3</sup>-allyl)Cl, **6**, (49, 50) (Figure 4). These catalysts are all highly active for various cross-coupling reactions which are used for real world applications. More details on the applications of these catalysts are given elsewhere (48, 51, 52). A special issue of *Accounts of Chemical Research* also covered recent updates of these coupling reactions from academia in detail (53).

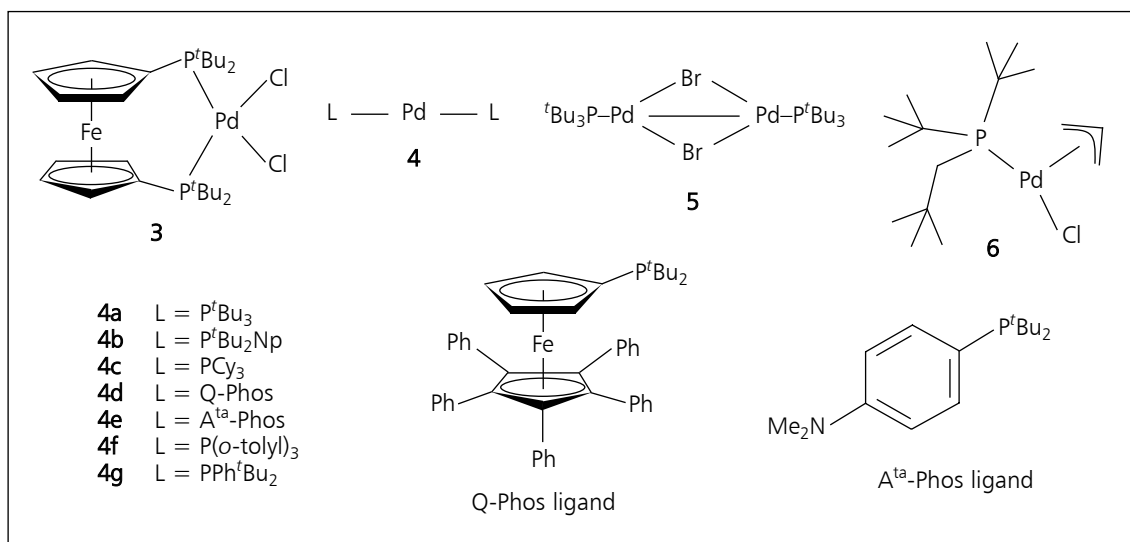


Fig. 4. Examples of highly active Pd cross-coupling catalysts developed and commercialised by Johnson Matthey

In order to address the issue of residual palladium in the final product, several solid-supported preformed palladium complexes have been developed and launched onto the catalyst market (54–56).

### Conclusions

Palladium-catalysed cross-coupling is of great importance to real world applications in the pharmaceutical, agrochemicals, fine chemicals and electronics industries. The area has developed quite rapidly beyond the work of Heck, Negishi and Suzuki, though all three reactions are widely used. Academic groups such as those of Beller, Buchwald, Fu, Hartwig and Nolan as well as industrial groups such as that at Johnson Matthey, are now developing the field even further. Buchwald-Hartwig coupling has become par-

ticularly important for developing compounds containing carbon–nitrogen bonds for applications in industry, as well as  $\alpha$ -arylation of carbonyl compounds such as ketones, esters, amides, aldehydes etc., and nitriles (57). The significant growth of cross-coupling reactions can be summarised in Professor K. C. Nicolaou's words:

“In the last quarter of the 20th century, a new paradigm for carbon–carbon bond formation has emerged that has enabled considerably the prowess of synthetic organic chemists to assemble complex molecular frameworks and has changed the way we think about synthesis” (58).

More detailed articles summarising the history of cross-coupling in the context of the 2010 Nobel Prize in Chemistry with an outlook on the future of cross-coupling will be published elsewhere (59, 60).

### Glossary

Ligand	Name
A <sup>ta</sup> -Phos	<i>p</i> -dimethylaminophenyl(di- <i>tert</i> -butyl)phosphine
Cy	cyclohexyl
dppf	1,1'-bis(diphenylphosphino)ferrocene
dtbpf	1,1'-bis(di- <i>tert</i> -butylphosphino)ferrocene
Np	neopentyl
Ph	phenyl
Q-Phos	1,2,3,4,5-pentaphenyl-1'-(di- <i>tert</i> -butylphosphino)ferrocene
<sup>t</sup> Bu	<i>tert</i> -butyl

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