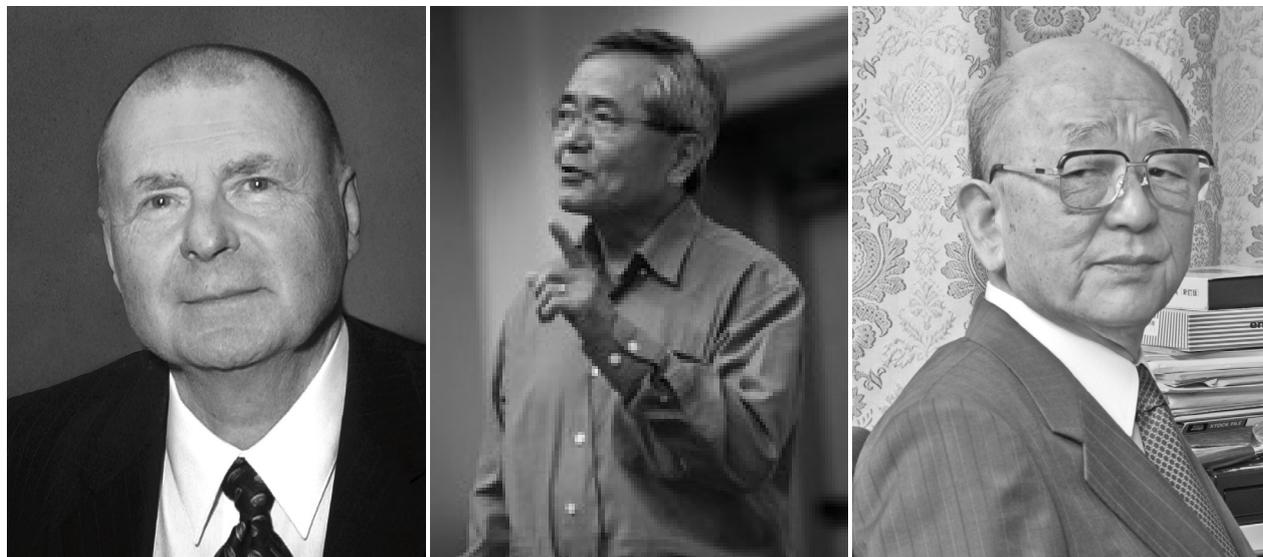# The 2010 Nobel Prize in Chemistry

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**L-R**: Richard Heck (courtesy Delaware University/Kathy Atkinson), Ei-ichi Negishi (courtesy Purdue University/Mark Simons) and Akira Suzuki (courtesy International Relations/Hokkaidō University)

The 2010 Nobel Prize in Chemistry was awarded jointly to three stalwarts of organic chemistry: **Richard F. Heck** (University of Delaware, USA**), Ei-ichi Negishi** (Purdue University, USA) and **Akira Suzuki** (Hokkaidō University, Japan), by the Swedish Academy of Sciences *for palladium-catalyzed cross couplings in organic synthesis*.

The prize recognises the work of these three chemists, who have developed reactions that enable more efficient ways of linking carbon atoms together to build the complex molecules that are improving our everyday lives. The Heck, Suzuki and Negishi reactions, examples of palladium-catalyzed cross coupling reactions, stem from separate work in the 1960s and 1970s that developed reactions using palladium to construct whole molecules at lower temperatures and with less waste than before. They provide a marvellous example of great work carried out in parallel. The painkiller naproxen, a generic sold in the US under the brand name Aleve, Merck & Co.'s allergy treatment Singulair, and Boscalid, a fungicide made by BASF SE, are among the chemicals made possible by their work.

## Introduction

The 2010 Nobel Laureates have received the customary medals minted in gold, but it is their work with another noble metal—palladium—that earned Heck, Negishi, and Suzuki their 2010 award. Palladium-catalyzed cross coupling reactions, in which palladium is used to catalyze the formation of carbon-carbon bonds, are widely used to make complex molecular structures. It is a well deserved and long overdue honour, and it is hard to overstate the importance of their processes in modern day synthetic chemistry; they have been employed to make materials, pharmaceuticals, and other biologically active compounds. Although chemistry bookmakers had been expecting that Pd-catalyzed cross-coupling chemistry would earn the Nobel Prize for many years, Heck, who is now 79 and living in the Philippines, told *Chemistry & Engineering News* that his win was *totally unexpected*.

The pioneering chemistry discovered by Heck in 1968 uses Pd to wed an aryl halide with an olefin; it has been, and continues to be, of great use. Negishi, who is now 75 and the H. C. Brown Distinguished Professor of Organic Chemistry at Purdue University, used Pd to catalyze couplings of organozinc reagents with organohalides in 1977. Negishi likened the Pd-catalyzed cross-couplings to the Grignard reaction, which earned 31 year old Viktor Grignard the 1912 Nobel Prize. He told reporters that the cross coupling methods not only complement but surpass the versatility of the Grignard. Akira Suzuki was born in 1930 in Hokkaidō, studied at the university there, gaining his PhD, and then became assistant professor. For two years he was a postdoctoral fellow (1963–65) with H. C. Brown at Purdue and after returning to the University of Hokkaidō he became a full professor there. It was a little while after Negishi that Suzuki began developing a Pd-catalyzed coupling of organoboron compounds with organohalides. With his retirement from the University of Hokkaidō in 1994, he took several positions in other Universities: 1994–1995 at Okayama University of Science and 1995–2002 in Kurashiki University of Science and the Arts, but is now back at his *alma mater*.

## The Chemistry of Palladium-Catalyzed Cross-Coupling Reactions

The formation of carbon–carbon bonds is the Holy Grail of organic chemistry because it enables the construction of complex organic molecules from simpler precursors. Palladium-catalyzed cross couplings, as honoured by the 2010 Nobel Prize, provide the cornerstone of this effort by allowing the connection, at carbon, of two compounds with virtually any hybridization. These reactions involve coupling of an organic halide (often a haloalkene or aromatic halide) with either an alkene (the Heck reaction), an organozinc reagent (the Negishi reaction), or an organoboron reagent (the Suzuki reaction).

### The Heck Reaction

In 1968, Heck began studying the palladium-catalyzed alkylation and arylation of unsaturated molecules using organomercury reagents as the source of the transferred alkyl or aryl group.[1,2] At that time, the addition of metal alkyls and aryls to alkenes was known, but very few examples involved the transition metals other than for polymerization. The original Heck procedure was soon improved by Mizoroki (1971) and Heck (1972) through the use of organic halides in place of the toxic mercury reagents.[3,4] The 1974 modification by Heck to involve palladium in truly catalytic amounts was achieved by use of an amine base [which reduces the spent catalyst to the active Pd(0) species] and a phosphine ligand, representing the Heck reaction as we know it today (Scheme 1).[5] The preferred stereoisomer tends to be the *trans*-olefin, for steric reasons, and the transferred organic group ends up attached to the less electron-rich terminus of the alkene.
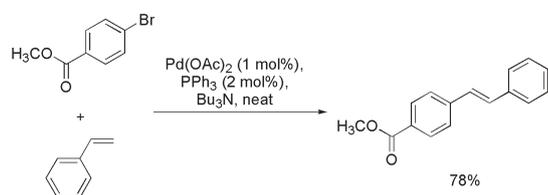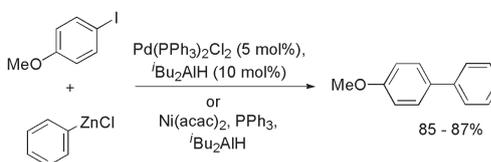


**Scheme 1**

The Heck reaction has been widely used industrially, including in the synthesis of octyl methoxycinnamate, the active component of most sunscreens. Scheme 2 shows an example of this reaction in water, at very low catalyst loadings, demonstrating the convenience and power of this reaction.[6]
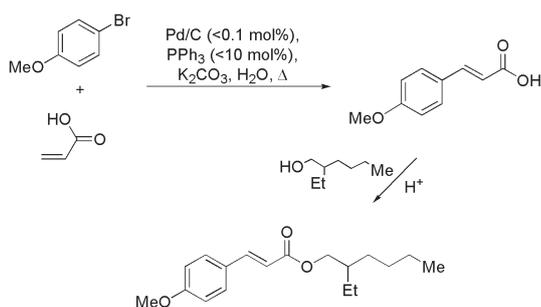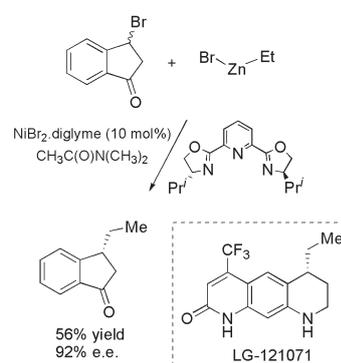


**Scheme 2**

### The Negishi Reaction

The 1977 report, by Negishi and co-workers, of the cross coupling between organic halides and organozinc reagents heralded the advent of a very mild procedure for reliably constructing C–C bonds.[7] Catalysis with either nickel(0) or palladium(0) effects the transformation as illustrated by Scheme 3.
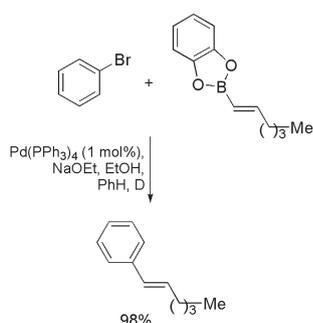


**Scheme 3**

The mildness of the reaction conditions renders them suitable for use with many substrates, including $sp^3$-hybridized organic halides with β-hydrogens – often a challenge in cross-coupling reactions. Extension of the Negishi cross coupling into the arena of asymmetric synthesis is elegantly demonstrated by Fu's enantioselective preparation of a key intermediate *en route* to the first orally active, non-steroidal androgen receptor agonist, LG-121071 (Scheme 4).[8] A chiral ligand for the metal catalyst produces the observed stereoselectivity. It is noteworthy that the reaction can be performed in air and that both enantiomers of the racemic starting material are transformed into the highly enantiomerically enriched product.



**Scheme 4**

### The Suzuki Reaction

The Suzuki cross coupling, also known as the Suzuki-Miyaura reaction, was first reported in 1979. The two seminal papers[9,10] describe the reactions of alkenylboron reagents with alkenyl and aryl halides (Scheme 5). The low toxicity and cost of boron reagents and the fact they may be readily accessible by hydroboration of an alkyne has led to increasing applications.[11] It is now possible to perform Suzuki reactions with boranes (R–BR′$_2$), boronic acids [R–B(OH)$_2$], boronates [R–B(OR′)$_2$] or organotrifluoroborates [(R–BF$_3$$^+$] as the boron reagent. The transfer of the organic fragment R from boron to palladium as part of the mechanism (*vide infra*) is greatly facilitated by base, through formation of a four-coordinate 'ate'-complex. The versatility of the Suzuki reaction has recently been extended to encompass alkyl halide and alkyl boron partners,[12] and aqueous reaction conditions.[13]
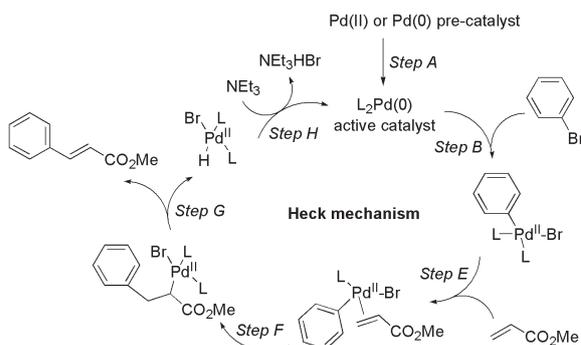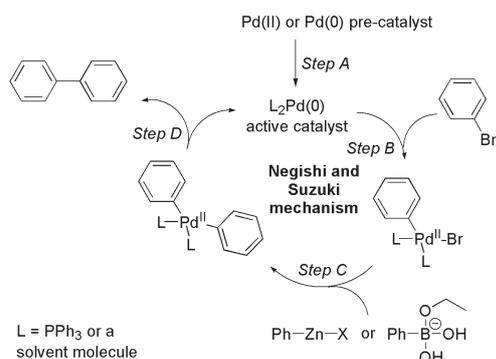
**Scheme 5**

## Mechanistic and Experimental Details

The cross-coupling mechanism (Scheme 6) involves, initially, *in situ* generation of the active Pd(0) catalyst from a less reactive, storable and often commercially available precursor, a *pre-catalyst*, through either reduction or ligand substitution (Step A). The first step of the catalytic cycle is oxidative addition (Step B), wherein the Pd(0) catalyst inserts into the C–X bond of the organic halide and is oxidized in the process. The mechanism then proceeds through transmetallation (Step C), in which an organic group is transferred from the organometallic precursor (a zinc or boron species for Negishi and Suzuki, respectively) to the Pd(II) complex. The resultant bis-organopalladium complex then undergoes reductive elimination (Step D) to produce the new C–C bond of the product and regenerate the catalyst. Technically, the Heck reaction is not a cross coupling, as it follows a different mechanistic pathway beyond the oxidative addition (Step B). Specifically, alkene complexation to the oxidized palladium (Step E) is followed by migratory insertion of the alkene π-bond into the Pd–C bond (Step F). The ensuing process is β-hydride elimination (Step G), producing the substituted alkene product and a palladium hydride. Because the migratory insertion produces a *syn*-relationship between the Pd and the organic substituent, and the β-hydride elimination requires a *syn*-relationship between the Pd and the removed hydrogen, there are stereochemical (and sometimes regiochemical) consequences of this sequence. However, in acyclic cases with two geminal β-hydrogen atoms, the *trans*-alkene is favoured. The active catalyst is regenerated by reduction of the palladium hydride by way of a base-promoted elimination of hydrogen halide, *e.g.* HBr (Step H).

Together with the Nobel Prize winning methods, the Stille reaction (using an organostannane), the Hiyama coupling (using an organosilicon) and the Sonogashira reaction (using an alkyne) represent the main (named) metal-catalyzed cross couplings. The versatility and reliability of the Stille reaction has made it one of the most heavily used couplings, despite its involvement of highly toxic organotin reagents. It seems likely that, if John Stille was still alive, he would have shared in the 2010 Nobel Prize. Tragically, he was killed in the crash landing of United Airlines Flight 232 in 1989 at Sioux City, Iowa.

It will come as no surprise to those working in the field of synthetic organic chemistry that three of the past ten Nobel Prizes (2010, 2005, 2001) have been awarded for

**Scheme 6**

transition metal-catalyzed reactions. The very nature of transition metals lends their ability to wed organic chemical functionalities that would otherwise be unreactive. Heck, Negishi and Suzuki together pioneered some of the most industrially useful, reliable and mechanistically interesting reactions of all time, so this Nobel Prize award is entirely appropriate and timely. No doubt, the future will bring further improvements and new procedures.

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