Richard F. Heck (1931–2015)

Nobel Laureate in Chemistry 2010

Richard F. Heck

Richard Frederick Heck, who developed the reaction that bears his name, died at the age of 84 on October 10, 2015 in Manila. He shared the 2010 Nobel Prize in Chemistry with Akira Suzuki (Hokkaido University) and Ei-ichi Negishi (Purdue University) in the area of palladium-catalyzed cross-coupling, a class of reactions that has transformed modern organic chemistry.

Heck was born on August 15, 1931 in Springfield, Massachusetts as the only child of Freoff and Lucille Heck, who were professional dancers, although Freoff had to work as a departmental store salesman to supplement the family's income. At the age of seven, Heck's family relocated to Los Angeles, where his hobby of gardening stimulated his interest in chemistry and its role in plant growth. In fact, this childhood memory was vividly echoed in his 2012 speech at De La Salle University, "I had never thought the simple work of planting an empty yard would bloom and peak into an achievement of the noblest honor in the world of science".

Heck received his PhD in chemistry (supervised by Saul Winstein) in 1964 from the University of California, Los Angeles (UCLA), in the area of neighboring-group participation, a subject today found in all organic chemistry textbooks. Two years of postdoctoral study followed at the ETH Zurich with Vladimir Prelog, 1975 Nobel Laureate in Chemistry. In 1956, Heck took a position with the Hercules Corporation (today Ashland Inc.) in Delaware. Although palladium was discovered in 1802, its major industrial application other than hydrogenation came only in the late 1950s for converting ethylene to acetaldehyde (the Wacker Process). Heck's interest in organometallic chemistry, an underdeveloped area in those days, inspired him to have a discussion with Pat Henry, a colleague at Hercules. Henry had experience with the Wacker Process, where the coordination of ethylene to palladium was well utilized. The company's background in polymerization of olefins by Ziegler–Natta catalysis also prompted Heck to investigate a reaction of phenylmercuric acetate with a $Li_2[PdCl_4]$ solution in acetonitrile at 0 °C under an atmosphere of ethylene to produce styrene. These systematic studies resulted in seven back-to-back publications in *J. Am. Chem. Soc.* in 1968.

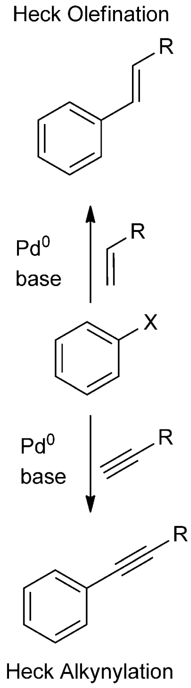
While Heck was concerned about the practical application of his findings due to the high toxicity of mercury, Peter Fitton reported on an oxidative addition product of aryl iodides with Pd(0), which possessed a strong similarity to the intermediates Heck had proposed earlier in his organomercury reactions. With these clues, Heck began to investigate the direct coupling of an aryl iodide with ethylene.

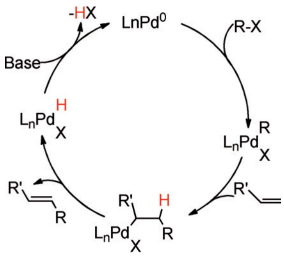
In 1971, he joined the faculty of the Department of Chemistry and Biochemistry at the University of Delaware. During the same year, Tsutomu Mizoroki published a paper in *Bull. Chem. Soc. Jpn.* for making aryl-substituted alkenes by heating aryl iodides with alkenes at 120˚C in the presence of $PdCl_2$. Mizoroki proposed the in situ formation of palladium particles as the active catalyst, but did not provide any further details. In 1972, Heck acknowledged the work of Mizoroki in a publication in *J. Org. Chem.* that explained the benefits of his catalytic version of the reaction (1 mol% loading), while also proposing the currently accepted mechanism for the first time. Important steps include the reduction of Pd(II) to Pd(0), oxidative addition of an aryl halide to Pd(0), olefin coordination, migratory insertion of alkene to the Pd–C bond, and β-H elimination with the formation of PdHX and the subsequent regeneration of Pd(0) in the presence of a suitable base. Heck also commented about the limitations of the reaction, such as stereoisomerization. He concluded the paper with the statement "in spite of some limitations, the organic halide olefinic substitution reaction should prove to be a useful synthetic reaction". He was indeed correct, as today this reaction has become the well-known Mizoroki–Heck reaction.

The intramolecular version allows the construction of cyclic structures, while the asymmetric versions produce chiral molecules that are essential in natural product and drug synthesis. New reactions such as carboiodination, and carbonylative and oxidative Heck reactions have been emerging as the new trends in cross-coupling reactions.

In 1975, Heck was also able to couple an acetylene moiety to an aryl halide; Sonogashira's subsequent improvement on the process by adding CuI led to a very popular class of coupling reactions that bear his name. However, the Heck alkynylation has recently gained substantial momentum as Cu(I) has been identified to be detrimental, since it can oxidize Pd(0) catalysts containing bulky, electron-rich ligands in the catalytic cycle. However, for challenging substrates such as aryl chlorides, catalysts containing bulky, electron-rich ligands are required for oxidative addition. In fact one of the new trends in modern cross-coupling reactions is the identification of the role of ligands. Heck's observation in 1982 on the higher activity of relatively bulky and electron-rich $(o\text{-Tol})_3P$ ligand in comparison to Ph_3P was also an important milestone in this area.

The major commercial applications of the Heck reaction are in the pharmaceutical industry. To the best of the author's knowledge, montelukast from Merck & Co (launched in 1997) for asthma was the





Heck's original mechanism

first commercialized drug that involved the Heck reaction in its development. Subsequently, the reaction has been used in making active pharmaceutical ingredients (APIs) for AIDS, migraines, leukaemia, cancer, and diabetes, among other conditions. Other important applications include the synthesis of liquid crystals and OLEDs (for display screens in TVs, computers and smart phones), thin circuit boards, and for fluorescent probes for sequencing the human genome.

In addition to the Nobel Prize, Heck was awarded the 2005 Carothers Lecture Award, from the Delaware Section of the American Chemical Society (ACS), in recognition of creative applications of chemistry that have had subsequent commercial impact, the 2006 Herbert C. Brown Award for Creative Research in Synthetic Methods (ACS), and the 2011 Glenn T. Seaborg Medal (UCLA) for his work on palladium-catalyzed cross coupling reactions.

After his early retirement from the University of Delaware in 1989, Heck and his wife Socorro, whom he had met in 1979 at a restaurant in Manila, eventually fully relocated to the Philippines in 2007. In the previous year, Heck moved from Florida to spend a six-month sabbatical with Victor Snieckus at Queens University, Ontario, to reinvestigate the cobalt carbonyl chemistry he had started with David Breslow at Hercules prior to his work on palladium. With Breslow, he had proposed the well-known textbook mechanism for hydroformylation. In Manila, Heck returned to his childhood hobby of growing orchids and vegetables. Sadly his wife died two years after he was awarded the Nobel Prize. The couple did not have any children.

Heck was a true scientist, who inspired students by saying that "it is important that science must be done, because you love it, not because you make a lot of money". In a BBC interview after winning the Nobel Prize he said: "I did not make a single dime out of this technology". Unassuming, quiet, humble, and somewhat shy, he neither attempted to profit from his chemistry nor from his fame before or after the award of the Nobel Prize. In one of his last public events, where De La Salle University in the Philippines awarded him an honorary doctorate in 2012, he expressed his humility through these words "I find my meaning in what I can bequeath to this world, when the glory and splendor of a celebrated achievement begins to wane, when I would have to finally desert this earthly habitat, and leave myself to the creator".

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