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From Noble Metal to Nobel Prize: Palladium-Catalyzed Coupling Reactions as Key Methods in Organic Synthesis

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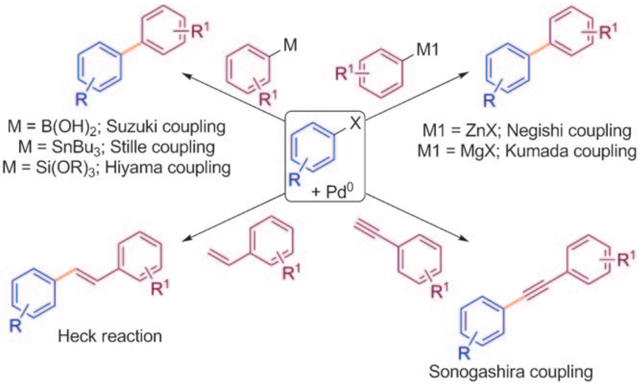
cross-coupling · Heck reaction · Negishi coupling · palladium · Suzuki coupling

Palladium is known to a broad audience as a beautiful, but expensive jewellery metal. In addition, it is nowadays found in nearly every car as part of the automotive catalysts, where palladium is used to eliminate harmful emissions produced by internal combustion engines. On the other hand, and not known to the general public, is the essential role of palladium catalysts in contemporary organic chemistry, a topic which has now been recognized with the Nobel Prize for Chemistry 2010.

Have a look at any recent issue of a chemical journal devoted to organic synthesis and you will discover the broad utility of palladium-based catalysts. Among these different palladium-catalyzed reactions, the so-called cross-coupling reactions have become very powerful methods for the creation of new C–C bonds. In general, bond formation takes place here between less-reactive organic electrophiles, typically aryl halides, and different carbon nucleophiles with the help of palladium.

Remember the situation 50 years ago, when palladium began to make its way into organic chemistry. At that time C–C bond formation in organic synthesis was typically achieved by stoichiometric reactions of reactive nucleophiles with electrophiles or by pericyclic reactions. Ironically, however, oxidation catalysis was the start of today's carbon–carbon bond-forming methods: The oxidation of olefins to carbonyl compounds, specifically the synthesis of acetaldehyde from ethylene (Wacker process) by applying palladium(II) catalysts,[1] was an important inspiration for further applications. Probably also for Richard Heck, who worked in the 1960s as an industrial chemist with Hercules Corporation. There, in the late 1960s, he developed several coupling reactions of arylmercury compounds in the presence of either stoichiometric or catalytic amounts of palladium(II). Some of this work was published in 1968 in a remarkable series of seven consecutive articles, with Heck as the sole author![2] Based on the reaction of phenylmercuric acetate and lithium tetrachloropalladate under an atmosphere of ethylene, which afforded styrene in 80% yield and 10% *trans*-stilbene,[2a] he described in 1972 a protocol for the coupling of iodobenzene with styrene, which today is known as the "Heck reaction".[3] A very similar reaction had already been published by Tsutomo Mizoroki in 1971.[4] However, Mizoroki didn't follow up on the reaction and died too young from cancer.

The coupling protocol for aryl halides with olefins can be considered as a milestone for the development and application of organometallic catalysis in organic synthesis and set the stage for numerous further applications. Hence, palladium-catalyzed coupling reactions were disclosed continuously during the 1970s (Scheme 1). One of the related reactions is the Sonogashira coupling of aryl halides with alkynes, typically in the presence of catalytic amounts of palladium and copper salts.[5]



Scheme 1. Selected examples of palladium-catalyzed C–C coupling reactions.

Instead of using alkenes of alkynes as the coupling partner in palladium-catalyzed coupling reactions, Negishi[6] and Murahashi[7] applied arylzinc and arylmagnesium reagents, respectively. Nowadays, these Negishi coupling and Kumada coupling reactions are well-known and have broad application. Although similar cross-coupling reactions are known to proceed with nickel catalysts, palladium is superior with respect to reactivity, selectivity, and functional-group tolerance. Somewhat later, Suzuki and Miyaura[8] developed the coupling of arylboronic acids and esters with aryl halides

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under palladium catalysis for the synthesis of symmetrical and unsymmetrical biaryls. The main advantage of their coupling reaction is the use of air-stable and readily accessible arylboronic acids as the coupling partner. All these methods were developed further and are now applied regularly on an industrial scale. Similarly, Stille[9] and Hiyama[10] discovered the palladium-catalyzed coupling of aryltin and arylsilane reagents, respectively, as coupling partners for aryl halides for the synthesis of biaryls. In addition to the generation of new C–C bonds, highly efficient C–O and C–N bond formations are also known nowadays. Most notable is the important development of the Buchwald–Hartwig amination.[11]

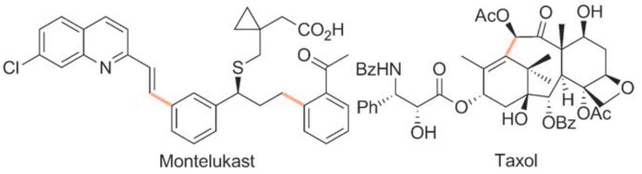
Since their discovery, palladium-catalyzed cross-coupling reactions have come a long way. There are several reasons for their continuing popularity and success: Striking features of the methods are their tolerance of a wide range of functional groups on both coupling partners. Hence, it is possible to construct complex organic building blocks efficiently in fewer steps than by traditional stoichiometric reactions. Furthermore, the development of ligands and co-catalysts allows for a fine-tuning of the reactivity. Hence, it is not surprising that these reactions are widely employed for various applications. To our knowledge, in the last two decades, there has been no other organometallic method that has so often made the transfer from gram-scale synthesis in academic laboratories to ton-scale production in the pharmaceutical, agrochemical, and fine-chemical industries.[12] Their importance and excellence in organic chemistry has resulted in this year's Nobel Prize being awarded for the three major coupling reactions: The Heck reaction, the Negishi coupling, and the Suzuki coupling reaction, which will be discussed in more detail below.

Heck Reaction

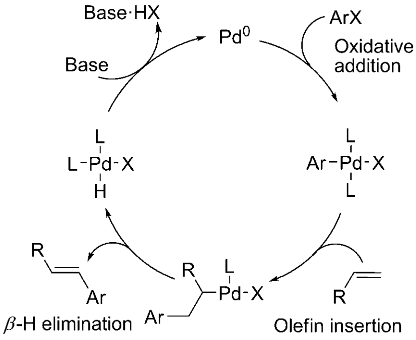
In the Heck reaction (probably better called as the Mizoroki–Heck reaction) (hetero)aryl, alkenyl, and benzyl halides are coupled with all kinds of alkenes in the presence of palladium catalysts to give the corresponding substituted alkenes (Scheme 1).[13] In general, the reaction proceeds with high stereo- and regioselectivity. The reaction was discovered independently by Heck and Mizoroki in the early 1970s. After further development in the 1980s and 1990s, the synthesis community benefited enormously from the Heck reaction, especially for the synthesis of pharmaceuticals and agrochemicals.

Scheme 2 shows two representative examples of current drugs where the Heck reaction is applied as an important step either in the industrial production process or the academic synthesis. Remarkably, it took around 15 years from the basic discovery of the method to the first practical application, which was realized by Hans-Ulrich Blaser and his research group at Ciba-Geigy.[14] The process for the agrochemical Prosulforon makes use of a variant of the Heck reaction (the so-called Matsuda–Heck olefination) of an aryldiazonium salt.

The generally accepted reaction mechanism is shown in Scheme 3. The reaction begins with the oxidative addition of the aryl-X compound (X = I, Br, Cl, OTf, OTs, N$_2$BF$_4$, COCl, SO$_2$Cl, etc.) to an active ligated Pd^0 center to form the respective Pd^{II} species. Subsequent coordination and then insertion of the alkene at the Pd^{II} center generates an alkylpalladium complex. After rotation of the carbon–carbon bond, β-H elimination takes place and the substituted alkene is released as the terminal product. Finally, the active Pd^0 catalyst is regenerated with base (Scheme 3).



Scheme 2. Two representative examples of the application of Heck reactions in the synthesis of pharmaceuticals (bonds which are formed are highlighted in red).



Scheme 3. General reaction mechanism for the Heck reaction.

Besides the typical intermolecular reactions of aryl halides with ethylene, styrenes, acrylates, enol ethers, etc., intramolecular variants exist, which form unsaturated carbo- or heterocycles. Furthermore, the Heck reaction has proven to be very useful as part of novel domino reactions.

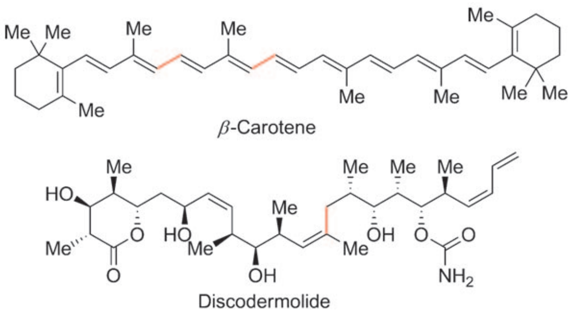
Negishi Coupling

Ei-ichi Negishi and his group studied fundamental aspects of the coupling of various organometallic derivatives including aluminum, magnesium, zinc, and zirconium compounds with aryl halides in the presence of palladium or nickel catalysts.[15] However, the name Negishi coupling is nowadays associated with the nickel- and palladium-catalyzed cross-coupling reaction of organozinc compounds and organohalides.

From a synthetic perspective the Negishi coupling is advantageous over the related Kumada coupling, which utilizes organomagnesium reagents, because of the relative stability of organozinc reagents. The functional-group tolerance is hence superior compared to the more reactive organomangesium reagents. In addition to classical C(sp^2)–C(sp^2) bond formation, the coupling of alkylzinc compounds allows for the formation of C(sp^3)–C(sp^2) and C(sp^3)–C(sp^3)

bonds. Hence, the Negishi coupling protocol has been utilized extensively in the synthesis of natural products.

Negishi et al. synthesized β-carotene (Scheme 4) in three steps, including two Negishi coupling reactions. Another representative example of the utility of this method is the enantioselective synthesis of discodermolide, a potent inhibitor of tumor cell growth and a polyketide natural product isolated from the Caribbean marine sponge *Discodermia dissolute*. This fairly complicated molecule was synthesized on a gram scale by employing the Negishi coupling reaction as a key step.

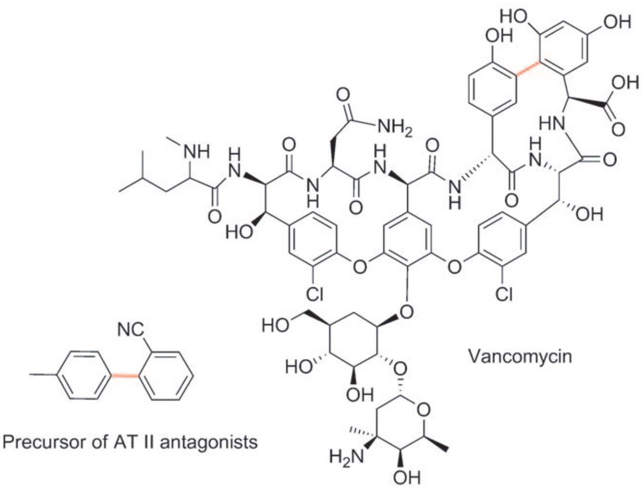


Scheme 4. Selected applications of the Negishi cross-coupling reaction in the synthesis of two important natural products (bonds which are formed are highlighted in red).

Suzuki Coupling

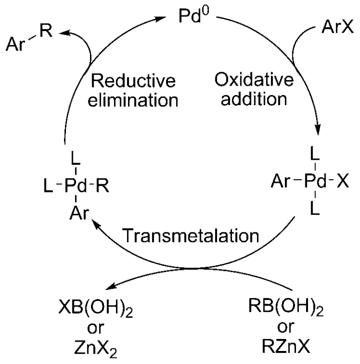
Similar to the Negishi and Kumada cross-coupling reactions, where the coupling partner is an organometallic reagent with a nucleophilic polarized carbon atom, the Suzuki coupling reactions makes use of organoboron reagents as nucleophiles.[16] Organoboronic acids and boronates are able to transfer their organic moieties to the palladium center in base-assisted transmetalation reactions. Nowadays, the Suzuki reaction is probably the most important method for the synthesis of all kinds of biaryl derivatives, because the required arylboronic acids or borates can be easily synthesized from trialkylborates with Grignard or organolithium reagents. Furthermore, they are stable towards air and moisture, tolerate many functional groups, and show only low toxicity. Since biaryls are ubiquitous substructures in natural products, pharmaceuticals, agrochemicals, and new electronic materials it is not surprising that the Suzuki reaction is used not only in academic research but also for the industrial production of fine chemicals.

In this respect, an important example constitutes the production of intermediates for AT II antagonists on a multiton scale by Clariant AG (Scheme 5). Furthermore, biaryl components for LCD applications are produced by Merck in Germany. On the academic side, the synthesis of the more complicated drug vancomycin is an illustrative example of the synthetic power of this method. This glycopeptide antibiotic is used as a so-called drug of last resort in cases when other antibiotics fail. It was synthesized by Nikolaou et al. by using the Suzuki reaction as an important step to form the biaryl unit shown in Scheme 5.[17]



Scheme 5. Two representative examples of the application of the Suzuki coupling reaction (bonds which are formed are highlighted in red).

The mechanism of the Negishi and Suzuki coupling reactions follow similar steps, including: 1) oxidative addition of the aryl halide to the Pd^0 center; 2) transmetalation with the organometallic reagent, and 3) reductive elimination to yield the product and regenerate the active Pd^0 catalyst (Scheme 6). Clearly, the two coupling reactions differ most in the transmetalation step, where the organometallic reagent is transferred (zinc or boron).



Scheme 6. General reaction mechanism for the Negishi and Suzuki cross-coupling reactions.

The pioneering work in the 1960s and 1970s of the three Nobel Prize winners has led to cross-coupling reactions nowadays becoming extremely valuable and reliable transformations in complex natural product syntheses, and even more importantly for numerous pharmaceutical and agrochemical applications, as well as for the production of new materials.[18] Clearly, numerous cross-coupling reactions are sufficiently efficient to be run in industry on a ton scale.

This has only been made possible by the numerous important contributions from research groups all over the world. The ideas generated in cross-coupling chemistry were often a result of the interaction between various research groups. It is a typical example of how science nowadays moves forward. Congratulations to everyone who has been involved!

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