

The 2010 Chemistry Nobel Prize: Pd(0)-Catalyzed Organic Synthesis

Gopalpur Nagendrappa and Y C Sunil Kumar



(left) G Nagendrappa was a Professor of Organic Chemistry at Bangalore University, and Head of the Department of Medicinal Chemistry, Sri Ramachandra (Medical) University, Chennai. He is currently in Jain University, Bangalore. He continues to teach and do research. His work is in the area of organosilicon chemistry, synthetic and mechanistic organic chemistry, and clay-catalysed organic reactions (Green Chemistry).

(right) Sunil Kumar is a PhD from Mysore University. He has the industrial experience of working in Syngene (Biocon) and has worked as post doctoral fellow at the Indian Institute of Science, Bangalore before joining Jain University, Bangalore.

The 2010 Nobel Prize in Chemistry was awarded to three scientists, R F Heck, E-I Negishi and A Suzuki, for their work on “Palladium – Catalyzed Cross Couplings in Organic Synthesis”. It pertains to research done over a period of four decades. The synthetic procedures embodied in their work enable construction of C–C bond selectively between complex molecules as in simple ones at desired positions without disturbing any functional groups at other parts of the reacting molecules. The work finds wide applications in the synthesis of pharmaceuticals, agricultural chemicals, and molecules for electronics and other applications. It would not have been possible to synthesize some of the complex natural products or synthetic compounds without using these coupling reactions in one or more steps.

Introduction

In mythical stories and folk tales we come across characters that, while uttering some *manthras* (words of charm), throw a pinch or fistful of a magic powder, and suddenly there appears the object or person they wished for or an event happens the way they want. A large number of movies have been made with such themes and characters that would be depicted as ‘scientists’. In fact many of us (scientists) do imagine, despite knowing full well that existence of such a *manthra* or magic powder is against scientific laws, to get hold of a *manthra* which, if uttered in front of the reaction flask, or a magical powder which, if thrown into the reaction mixture, would make the reaction proceed exactly the way we want. The 2010 Nobel Prize in Chemistry was awarded to three scientists who discovered organometallic catalysts which work like the mythical magic powder. The use of the word ‘magic’ in this context is not to undermine the truly great scientific quality of

their work. But these catalysts work so efficiently in forming a C–C single bond between two carbon atoms of even complex molecules that it would not be an exaggeration to term them as magical.

Organometallic compounds (compounds in which there is one or more direct σ or π bonds between a metal atom and carbon atom) have been important tools in the armoury of synthetic organic chemists since the latter part of the nineteenth century. For nearly a century, till the middle of the twentieth century, only a few of them, such as Grignard reagents, had practical value. Since the middle of the twentieth century research in the area of organometallic compounds has grown vastly and its scope has widened greatly. They find application in the production of a large number of industrial chemicals. The prospects seem to be limitless, as their use bestows a variety of benefits. Organometallic compounds are used as reactants, as reagents and as catalysts. The organometallic compounds that are used more commonly in organic synthesis contain magnesium, zinc, boron, silicon (a metalloid), aluminium, lithium, iron, chromium, nickel, rhodium, platinum, palladium, mercury, tin, germanium, sodium, potassium and a few others combined with one or more organic molecules. The study of organometallic compounds has enriched all the branches of chemistry. The organometallic compounds find application in producing materials needed in many fields of human activity and have helped in vastly improving the quality of life and our life style.

The palladium(0) catalyzed cross-coupling reaction is essentially a nucleophilic displacement at a sp^2 carbon, and takes place under mild conditions. The yields are generally good to excellent, the products are formed regio- and stereo-selectively, the synthetic routes require fewer steps for given target molecules, and the reactions are scalable to industrial production level and satisfy several 'Green Chemistry' principles. Although Heck, Negishi and Suzuki coupling reactions differ from one another in the type of reactants used, all of them use palladium(0) complexes as catalysts. The two reaction partners separately hitch to palladium

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Keywords

Nobel Prize 2010, Palladium(0), Heck reaction, Negishi coupling, Suzuki coupling.

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Box 1. The Three Chemists Sharing the Honour

Richard F Heck was born in 1931 at Springfield, Massachusetts, USA. He obtained his PhD degree from the University of California at Los Angeles, USA. He is a citizen of USA and is presently the Willis F Harrington Professor Emeritus at the University of Delaware, Newark, Delaware, USA.



Akira Suzuki was born in 1930 at Mukawa, Japan. He got his PhD degree from Hokkaido University, Sapporo, Japan. He is a Japanese citizen and is presently affiliated to the same university as Distinguished Professor Emeritus.



Ei-ichi Negishi was born in 1935 at Chang Chun, China. He obtained his PhD degree in 1963 from University of Pennsylvania, Philadelphia, Pennsylvania, USA. He holds a Japanese citizenship and is affiliated at present to Purdue University, West Lafayette, Indiana, USA as Herbert C Brown Distinguished Professor of Chemistry.

atom, then link together by forming C–C bond and finally leave as a single molecule.

The three leading scientists, among several others, who formulated these wonderful, invaluable and widely applicable synthetic methodologies, are Richard F Heck, Ei-ichi Negishi and Akira Suzuki (*Box 1*). Their discoveries have become textbook material and are part of MSc Chemistry course curricula for many years now.

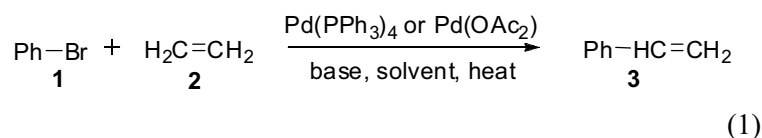
This article very briefly presents, with a few illustrative examples, how each one of these great chemists used palladium catalysts in constructing carbon–carbon single bond between two simple or complex molecules to get one single molecule of defined structure.



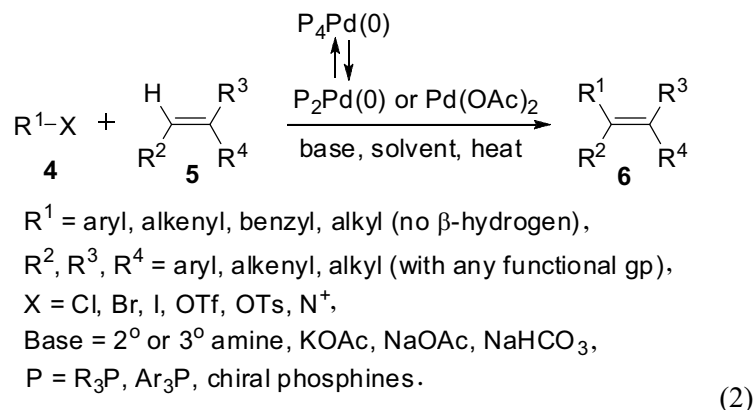
The Heck Reaction

Heck's work initially focussed on the synthesis of styrene, an important industrial raw material used in the manufacture of polystyrene and several other chemicals. (Note: Styrene is not manufactured by Heck method, but by dehydrogenation of ethylbenzene or dehydration of 2-phenylethanol).

The Heck synthesis of styrene (**3**) is in essence the displacement of a hydrogen in ethylene by a phenyl group. The actual reaction uses bromobenzene, ethylene, a trialkyl- or triaryl-phosphine-Pd(0) complex and a mild base, (see (1)).

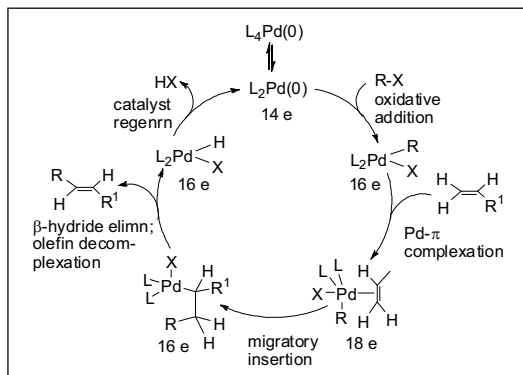


Soon the reaction was extended to other reaction partners. The overall reaction can be represented by a general equation (see (2)).



Heck studied the mechanism and explained the stereochemical course of the reaction. The mechanism is shown in *Scheme 1*.

The reaction sequence involves mainly five steps as depicted in *Scheme 1*. This has been possible because palladium(0) is able initially to reduce R-X by transferring two electrons and inserting itself between R and X as Pd(II). In the next step, olefin links

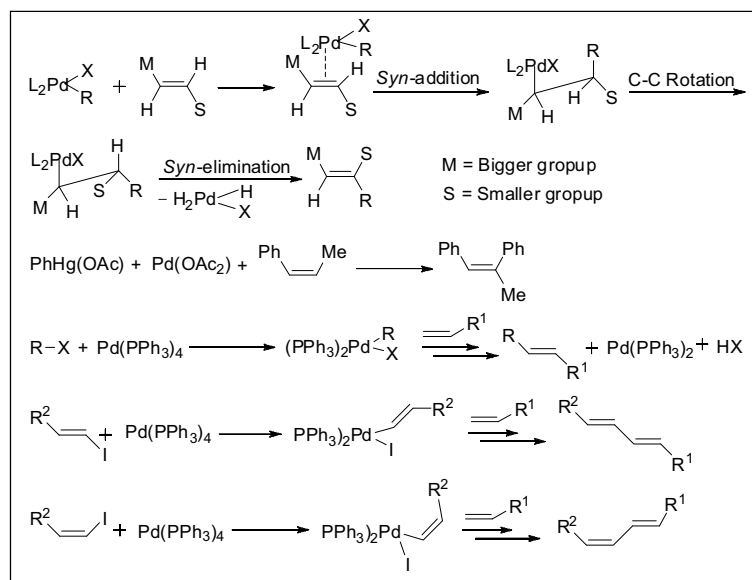


Scheme 1. Mechanism of Heck reaction.

dium manifests in various oxidation states as indicated in *Scheme 1*.

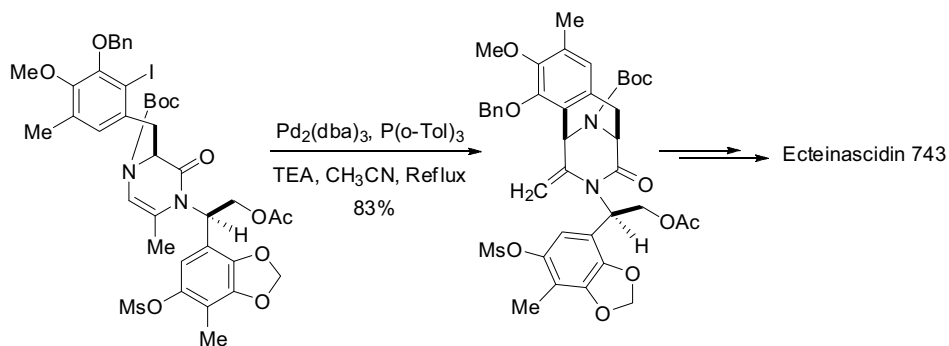
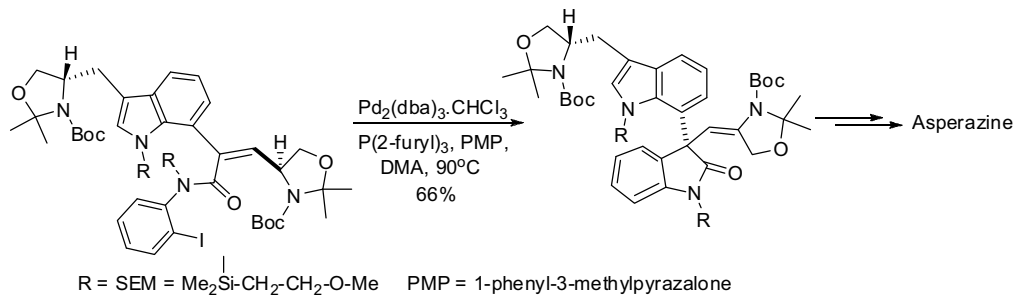
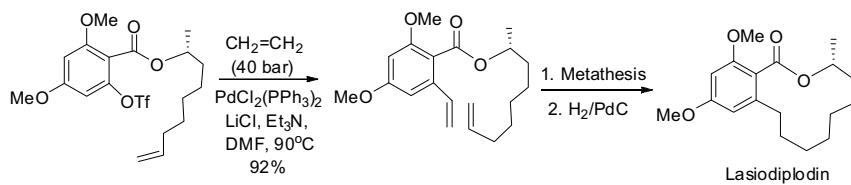
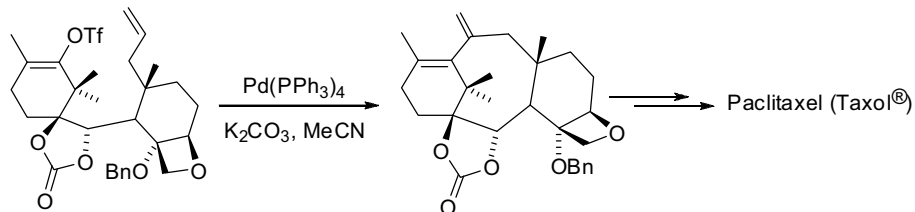
Regiochemistry and Stereochemistry

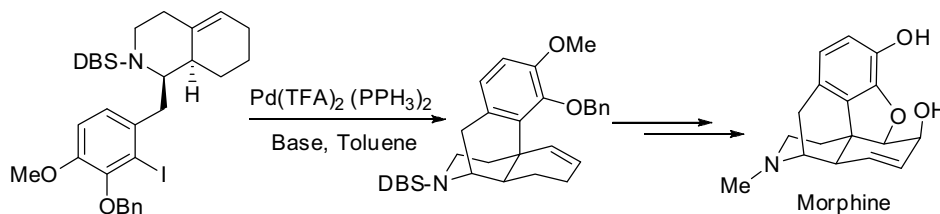
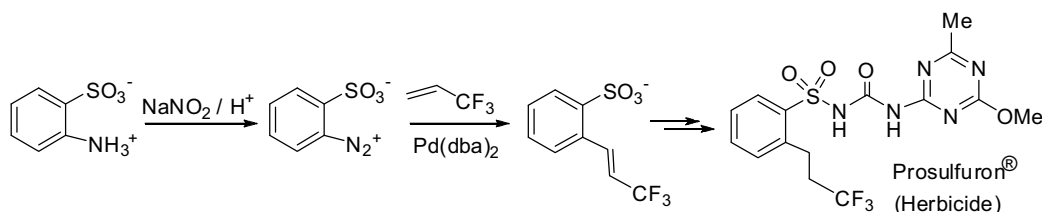
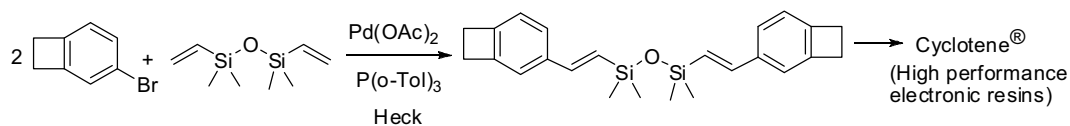
In the migratory insertion stage (Step 3) R and Pd addition is *syn* with R usually adding to the less hindered carbon (=CHS). In the next step, the Pd-H elimination also takes place by *syn* mode. Consequently, the overall configurational change at the double bond is to give an olefin with M and S groups on the same side of the double bond. When the coupling partner R-X is an alkenyl halide the geometry of its double bond is retained. These aspects are depicted in *Scheme 2*.



Scheme 2. Stereochemical course of Heck reaction.

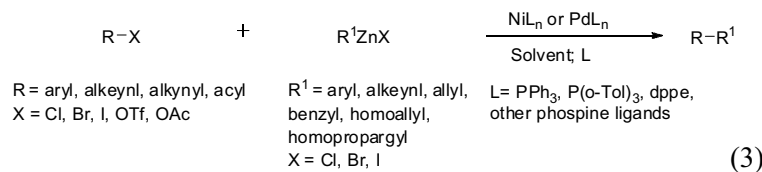
Application of Heck Coupling in Synthesis

1. *Ecteinascidin 743* or *Trabectedin* (An anticancer drug).2. *Asperazine* (A selective cytotoxic alkaloid).3. *Lasiodiplodin* (A potential antileucomic macrolide, plant growth regulating properties).4. *Taxol*® (*Paclitaxel*) (A potent anticancer natural product).

5. *Morphine* (Opium alkaloid, opiate analgesic medicine).6. *Prosulfuron*[®] (A herbicide).7. *DVS-bis-BCB* (Monomer for high performance electronic resin *cyclotene*[®]).**Negishi Cross-Coupling Reaction**

Negishi in 1976 started using initially organozirconium and organoaluminium reagents for cross coupling with (aryl, alkyl and vinyl) organohalides in the presence of a palladium catalyst. In 1977, he used much milder and more selective organozinc compounds for palladium-catalyzed cross coupling with organohalides. The results were far better than in the case of other organometallic compounds (RMgX , RZrX_n , and RAlX_2) in terms of yields, selectivity and mildness of reaction. The use of RZnX reagents eliminated the drawbacks encountered while using other organometallic reagents. This made it possible to use reaction partners that contain a variety of functional groups, and hence apply it to the synthesis of a wide range of organic compounds. A general representation of Negishi cross-coupling reaction is shown in (3). Negishi reaction has also been carried out using L_2NiX_2 as

catalysts in place of the usual Pd(0) catalysts.



Negishi found in 1978 that alkylboranes work as well as organozinc compounds, but he did not pursue it further. Suzuki was more successful in widening the scope of organoboron compounds in using them for cross-coupling reactions.

The Mechanism of Negishi Coupling

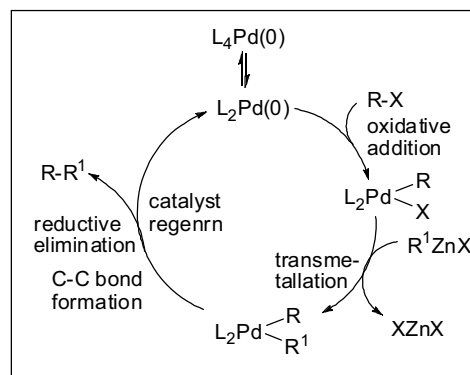
The mechanism of Negishi coupling is shown in *Scheme 3*.

There are essentially three steps in Negishi coupling reaction. In the first step, as in Heck reaction, an oxidative addition of R-X to Pd(0) gives an organopalladium intermediate which exchanges its X with the R¹ group in R¹ZnX (second step) and brings the two organic groups (R and R¹) into close proximity on the same palladium atom. In the third and final step, the R and R¹ groups link by forming a C-C bond and leave (eliminated) from the palladium atom which keeps two electrons in the process (reduction) and becomes Pd(0) to start a new reaction cycle all over again.

Stereochemistry and Regiochemistry in Negishi Coupling

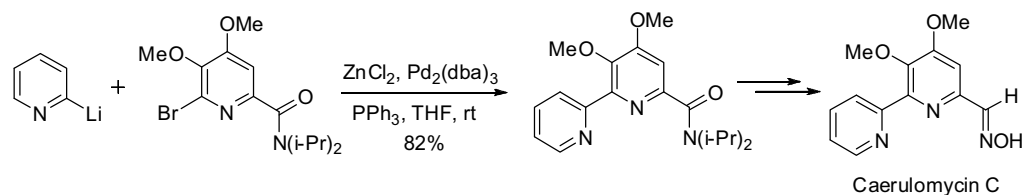
The organic group R¹ in the organozinc compound replaces the halogen/triflate/tosylate (X in R-X) with retention of configuration of the double bond in R of the product R-R¹. In effect, it is like nucleophilic displacement at a *sp*² carbon, with the nucleophile taking the position of the leaving group. If the attacking nucleophile is a vinylic carbon, the corresponding double bond of the nucleophile will also retain its geometry in the product, (e.g., Motuporin).

Scheme 3. Mechanism of Negishi coupling.

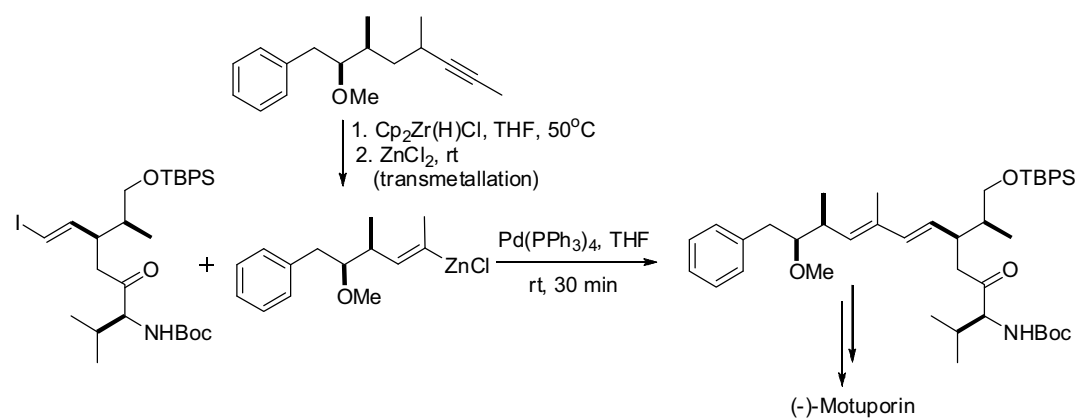


Synthetic Application of Negishi Coupling

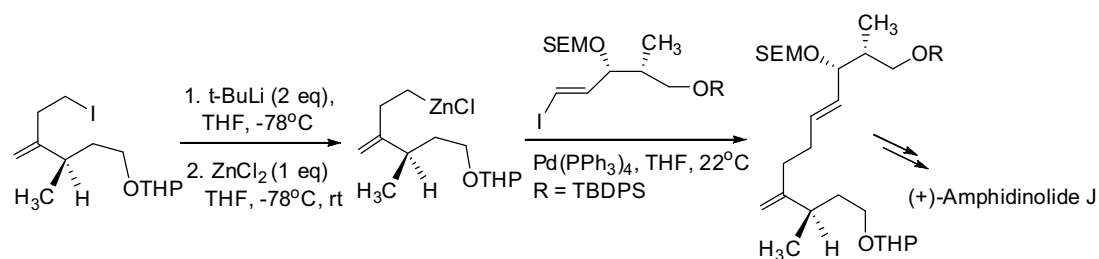
1. *Caerulomycin C* (An antifungal antibiotic produced by *Streptomyces caeruleus*).



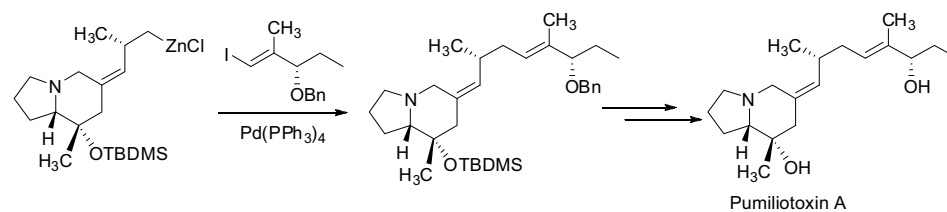
2. *Motuporin* (Cyclopeptide hepatotoxin).

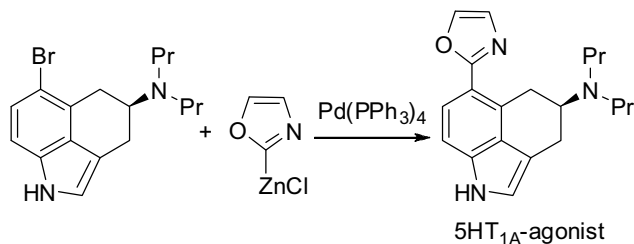


3. (+)-*Amphidinolide J* (Potential anticancer agent).

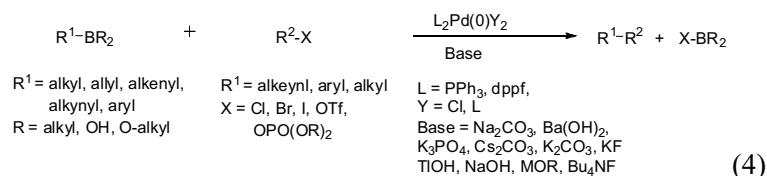


4. *Pumiliotoxin A* (Toxin, a defence alkaloid, in poison dart frog).



5. 5HT_{1A}-agonist (Anxiolytic and antidepressant).**Suzuki Cross-Coupling Reaction**

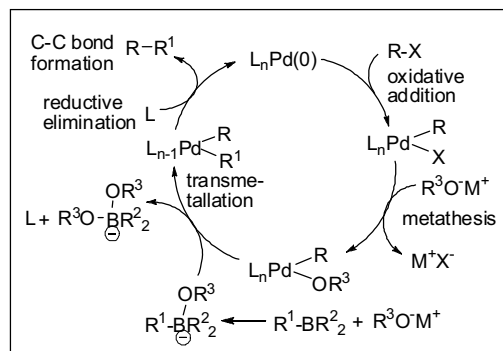
Suzuki and co-workers discovered in 1974 that palladium complexes catalyze, in the presence of a base, the cross-coupling between organoboron compounds and vinyl as well as aryl halides, triflates or phosphates (4).



One of the key steps in the reaction is the transfer of an organic group from the organoboron reagent to palladium, the so-called transmetalation process. This is facilitated by the base through converting the organoboron to boronate that transfers the organic group with ease to palladium. It was later found that arylboronic acids are more efficient coupling partners than organoboranes. A wide range of organoboranes and arylboronic acids can be easily prepared. In addition, they are stable, weakly nucleophilic and participate in the cross-coupling under mild conditions. These attributes have made the Suzuki cross-coupling reaction highly practical.

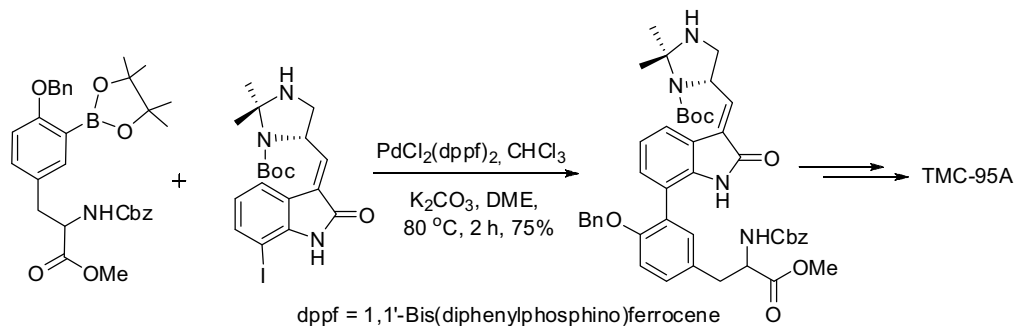
Mechanistically, the Suzuki coupling is very similar to Negishi coupling; it is given in Scheme 4.

Scheme 4. Mechanism of Suzuki cross-coupling.

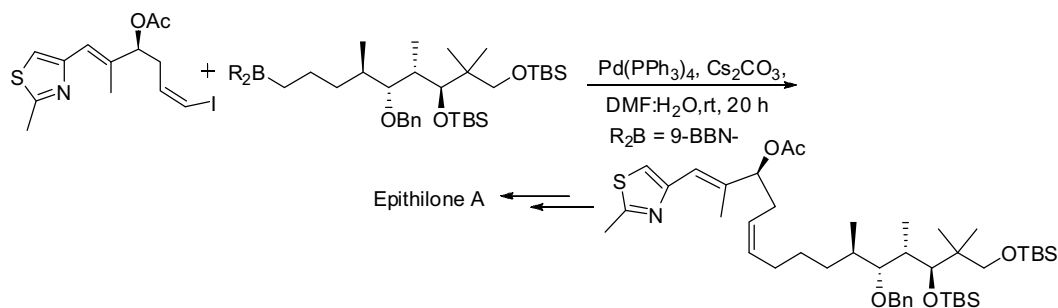


Synthetic Application of Suzuki Coupling

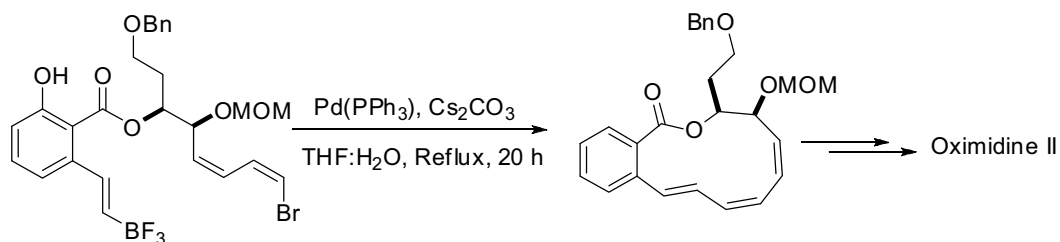
1. TMC-95A (Proteasome inhibitor).



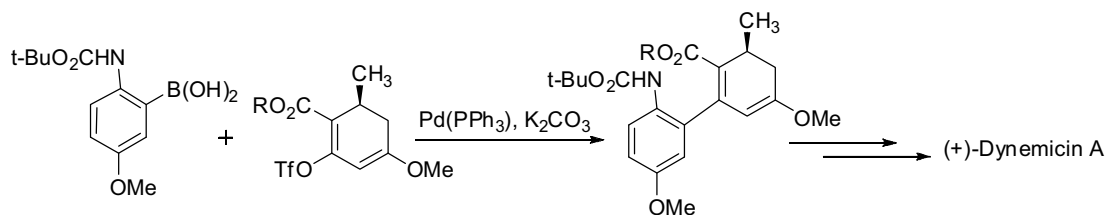
2. Epothilone A (Anticancer agent, works similar to paclitaxel).

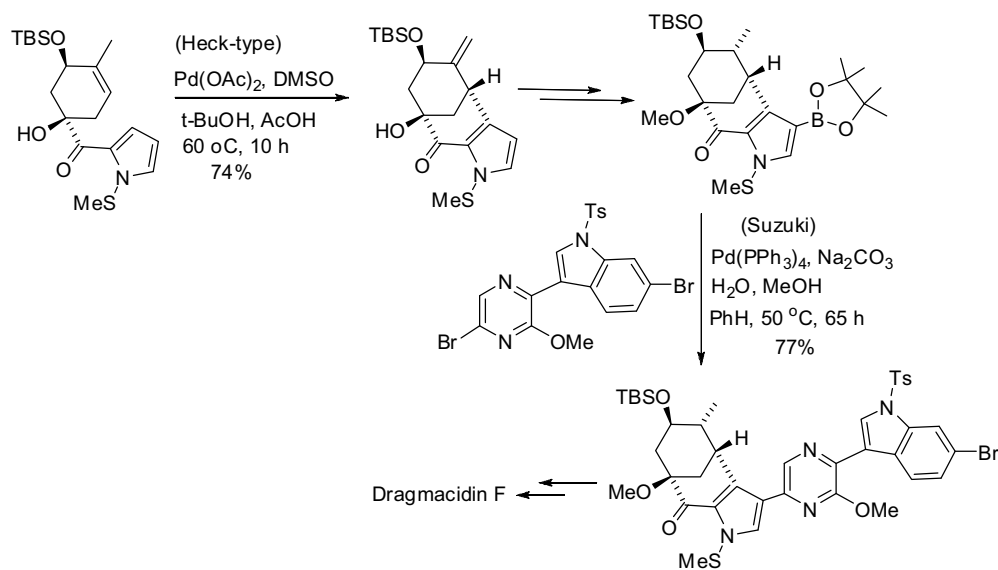
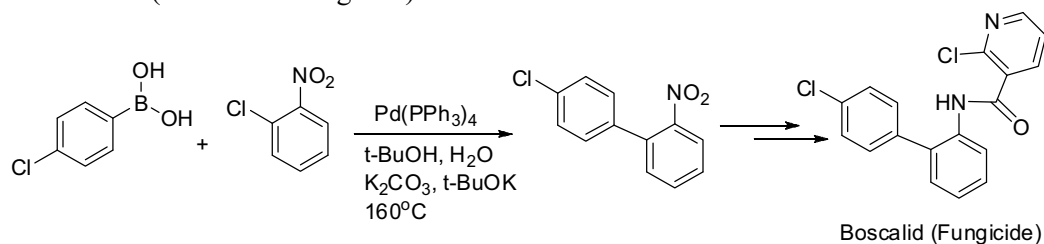
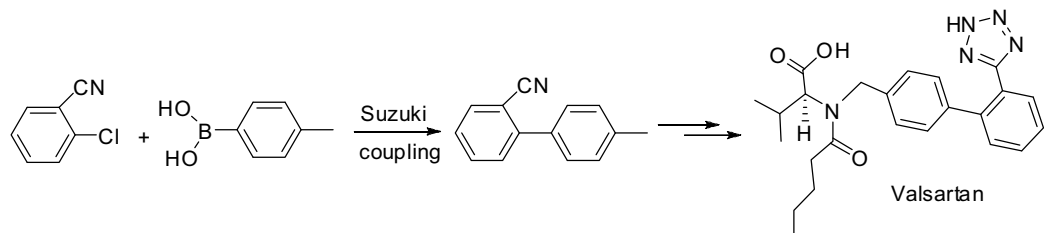
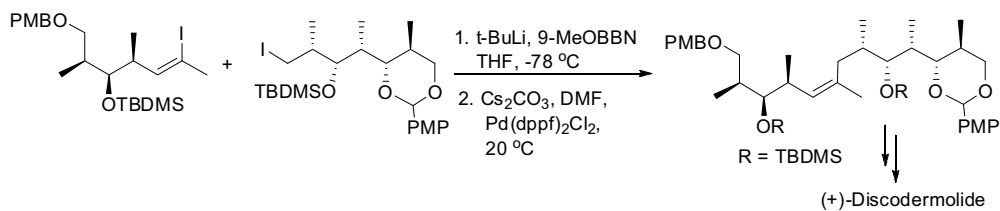


3. Oximidine II (Antitumor macrolide from *Pseudomonas sp.* Q52002).



4. (+)-Dyngemycin A (Potent antitumor antibiotic).



5. *Dragmacidin F* (Antiviral marine bromoindole alkaloid).6. *Boscalid* (Carbamide fungicide).7. *Valsartan* (Angiotensin receptor antagonist, dilates blood vessels: medicine for high BP).8. *Discodermolide* (Polyketide marine natural product; potent inhibitor of tumour cells).

Mechanistically Negishi cross-coupling and Suzuki cross-coupling are almost identical, while Heck reaction differs somewhat after the first step of oxidative addition of RX (or reductive insertion of Pd into R–X bond) takes place which is a common feature of all three cross-coupling reactions; Pd(0) is oxidized to Pd(II), while R–X is reduced by gaining two electrons). In the next stage, the organic group (R¹) of organozinc in the case of Negishi coupling or of organoborate in the case of Suzuki coupling is transferred to palladium (transmetallation). This is followed by the coupling of R and R¹ to form R–R¹. In the case of Heck reaction, Pd–R adds across the double bond forming the C–C bond, then Pd–H elimination occurs creating C=C bond. All three reactions are essentially nucleophilic substitution at *sp*² carbon. While the leaving group in Negishi and Suzuki reactions are halogens, triflate, tosylate or acetate, in Heck reaction it is hydrogen, a most unusual candidate as a leaving group. Such uncommon transformations are made possible because of the special bonding properties of palladium using its *d* orbitals. Palladium plays the role of a facilitator that provides a useful handle to organic chemist to synthesize complex organic molecules which have changed our lives in the last two to three decades.

Suggested Reading

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Address for Correspondence

G Nagendrappa and
Y C Sunil Kumar
Jain University
Jayanagar III Block
Bangalore
Email:
gnagendrappa@gmail.com