

Metathesis: A “Change-Your-Partners” Dance

Chemistry Nobel Prize – 2005

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K Sivapriya is interested in the design and development of new and potent carbohydrate based glycosidase inhibitors, the study of enzyme mechanisms based on carbohydrate-protein interactions and to develop novel carbohydrate based drugs. She also studies sulfur and selenium derived organic molecules in biological systems.

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On 5th October 2005, The Royal Swedish Academy of Sciences decided to award the Nobel Prize in Chemistry for 2005 jointly to Yves Chauvin, Institute of French Petroleum, France, Robert H Grubbs, California Institute of Technology, USA and Richard R Schrock, Massachusetts Institute of Technology, USA for the development of the metathesis method in organic synthesis. This increasingly important organic process allows researchers to synthesize certain kinds of complex molecules that were previously difficult and inefficient to make. Their research has opened the door to faster and more efficient methods for developing new drugs and polymers. Imagination will soon be the only limit to what molecules can be built in the laboratory!

Introduction

Organic chemistry, the chemistry of carbon compounds, is a fascinating subject. The element carbon has a fantastic ability to form strong bonds with other carbon atoms to generate long chains and rings. It can also bind to other elements like hydrogen, oxygen, nitrogen, and sulfur, to form complex organic molecules. The versatility of carbon is critical in the formation of many such molecules that are important for sustaining life on Earth. Several organic compounds can also be made artificially using organic synthesis by making substances react in certain ways: new molecules built with the help of other molecules. The diversity of organic molecules is so enormous that, so far, only a small proportion of all the possible organic molecules have been investigated. It is among these molecules that we find new medicines and new materials with interesting and unusual properties undreamed of a few years ago.

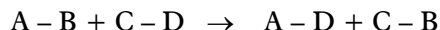
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Metathesis, organic synthesis, catalysis, green chemistry.

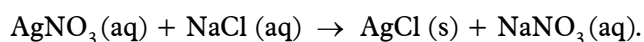


What is Metathesis?

In general, a chemical reaction is referred to as ‘metathesis’ or exchange reaction, if it is of the type



where parts of two reacting structures swap places. This type of process can occur between two inorganic salts when one product is insoluble in water, driving the reaction forward as in



This reaction is also called ‘double decomposition’.

In organic chemistry, metathesis is one of the most important new reactions wherein the bonds between different atoms are broken and new bonds formed. The word metathesis is derived from the Greek word *meta* (change) and *tithemi* (place). It looks as if that word should be pronounced like something from a philosophy course (metathesis), but chemists put the accent on the second syllable and almost skip over the third: meh-TA theh-sis. Here it refers to the interchange of atoms between two molecules. The olefin metathesis reaction can be thought of as a reaction in which all the carbon-carbon double bonds in an olefin (alkene) are broken and then rearranged in a statistical fashion. This does not happen by itself. It happens with the assistance of special molecules called catalysts (*Figure 1*). Metathesis can be compared to a dance in which the couples change partners.

In the process two alkenes can be blended into a new one which is very useful. Many of the applications of this reaction have been with cyclic compounds. If the two alkenes are part of the



Yves Chauvin

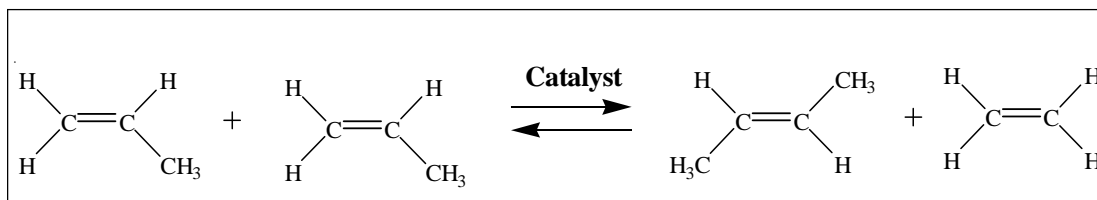


Robert H Grubbs



Richard R Schrock

Figure 1. Two propene molecules undergo olefin metathesis with the help of a catalyst, producing two new alkenes, butene and ethene.



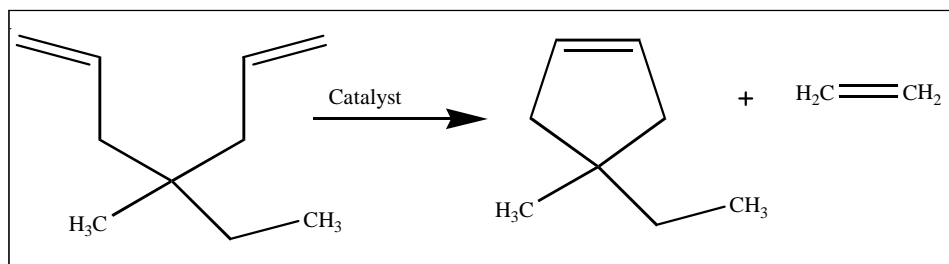


Figure 2.

same molecule, the blending reaction forms a new ring. This reaction, referred to as *Ring-Closing Metathesis* (RCM), became the most popular reaction with organic chemists in the mid-1990s with everyone trying to experiment with it to see what it can do (*Figure 2*). It is also interesting that one can run the process in reverse – if you have a ring with an alkene in it, the reaction can break it open into two separate alkenes.

All this sounds very simple and easy but it is difficult to put into practice. More often than not, simple looking problems are the most difficult to solve. Nobel Prizes in science have generally been awarded to those who came up with ingenious solutions to apparently simple but useful problems.

Evolution of Metathesis Reaction

The phenomenon of metathesis was discovered in the nineteen-fifties. Just like many other discoveries in organic chemistry, it all began in the industry, with a serendipitous observation. In 1956 Eleuterio at Dupont, USA obtained a propene-ethene copolymer from a propene feed passed over molybdenum – on alumina catalyst (*Figure 1*). Analysis showed that the output gas was a mixture of propene, ethene and butene. Chemists at other petrochemical industries observed similar results. It was only in 1967 that Calderon at the Goodyear Tire & Rubber company came up with an explanation for the process and speculated that the unexpected products are due to cleavage and reformation of olefin double bonds. The Goodyear researchers named the reaction *olefin metathesis*. In spite of the far reaching implications of this new process, nobody knew what the actual catalyst looked like, or how it worked: all that was known was that it *did* work.

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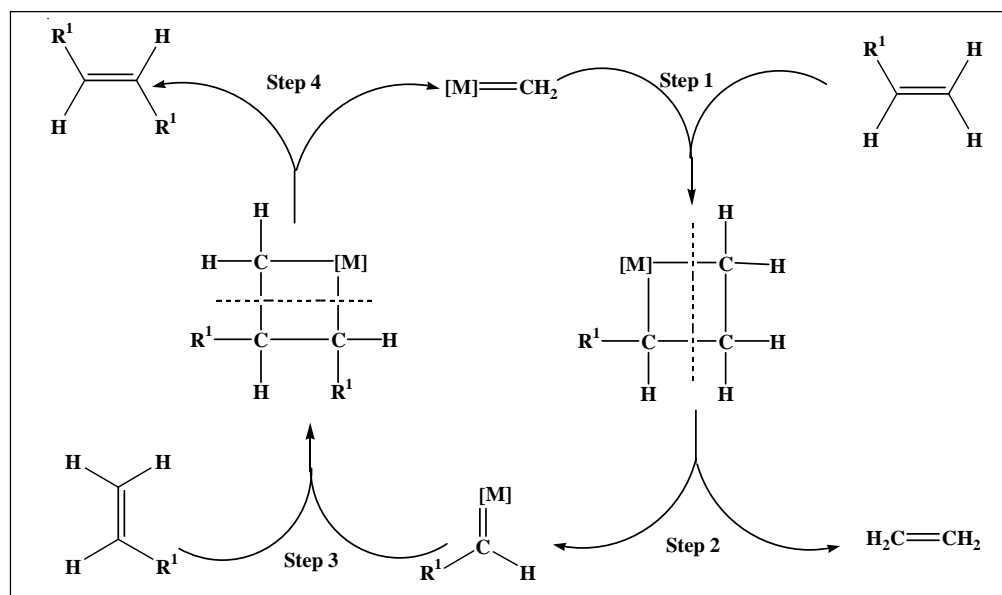


More and more chemists started to realize that metathesis could offer great potential in organic synthesis. But nobody anticipated how great it was to become. While many proposals were put forward to explain the process, the breakthrough came in 1971 with a publication by Yves Chauvin of France. He was able to explain in detail how metathesis reactions function and what types of metal compounds act as catalysts in the reactions [1]. He proposed that the actual catalyst was a metal carbene (a compound in which the metal is bound to the carbon with a double bond).¹

¹ Metal carbene: $M=CHR$ (M = metal; R = alkyl, aryl or other substituents)

In the first stage of the reaction, the metal carbene combines with one alkene to form a ring of four atoms. The ring consists of the metal atom and three carbon atoms bound to one another with single bonds. In the next step two of the single bonds are broken and a new alkene (ethene) and a new metal carbene are obtained. In the third step of the reaction the new metal carbene unit combines with one of the original alkenes to form a new four membered ring containing the metal. In the last stage of the catalytic cycle this four membered ring is broken apart to give the product of metathesis and re-formation of the original metal carbene. (Figure 3)

Figure 3.



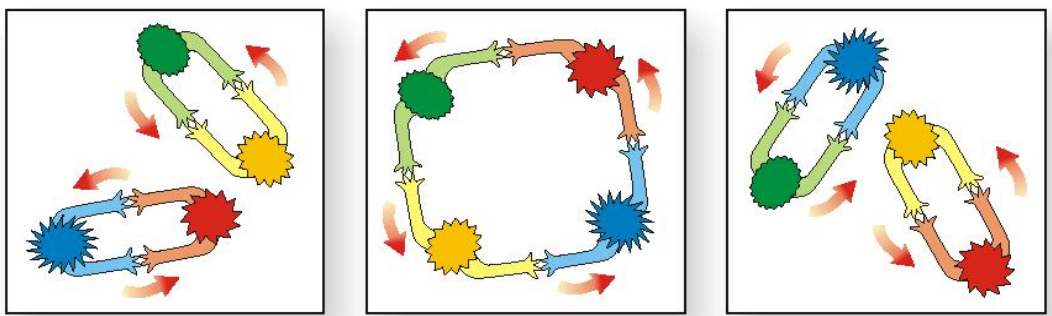


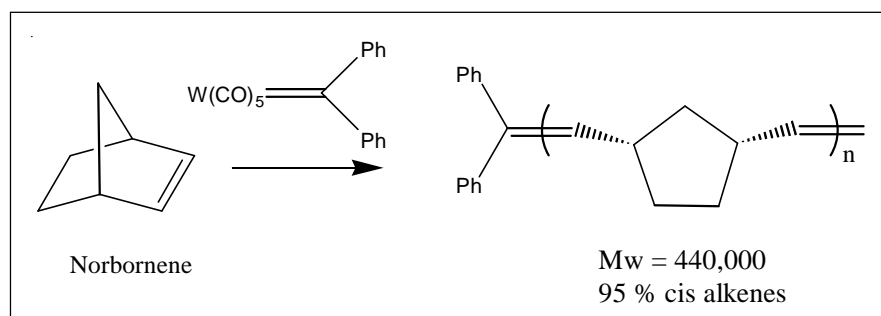
Figure 4. Adapted from <http://nobelprize.org/chemistry/2005>

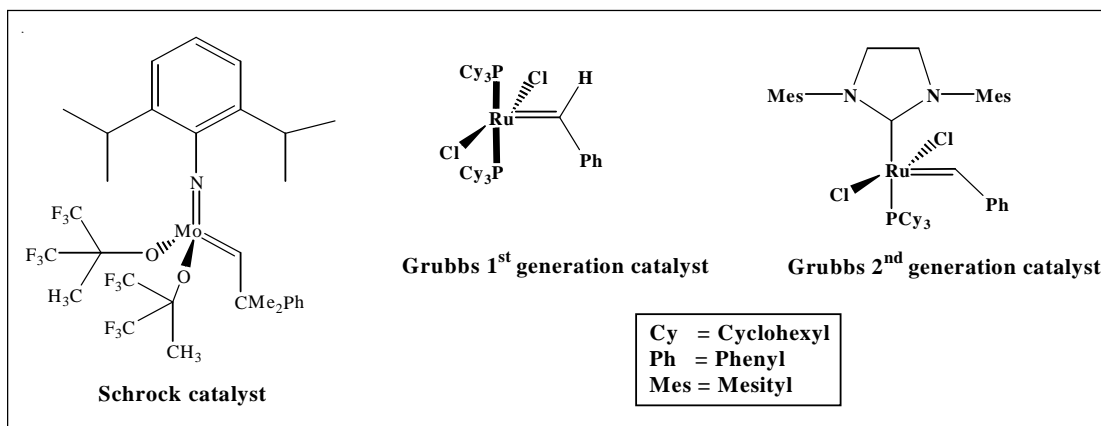
The mechanism resembles a dance. The catalyst, in which the metal holds its carbon partner with both hands, “dances” among carbon/carbon pairs, which are molecules with carbon-carbon double bonds. When the “catalyst pair” meets a carbon/carbon pair, the two dancing pairs unite in a round dance. After a while they let go of each other’s hands, leave their old dance partners and dance along with their new ones. The “catalyst pair” is now ready to catch another dancing carbon/carbon pair for a new round dance. In other words it continues to act as a catalyst for metathesis. (Figure 4)

Chauvin’s results opened the way for the design and construction of catalysts. Now, the big question concerned the detailed design required to obtain efficient catalysts for metathesis.

The first active, well-defined system was a tungsten derived carbene, $(OC)_5W=CPh_2$. This complex would polymerize cyclic olefins like norbornene with modest activity and high selectivity for *cis*-alkene polymers[2]. (Figure 5)

Figure 5.





The critical progress in catalyst design was made by Richard Schrock and Robert Grubbs. Schrock, who initiated his basic research in the early nineteen seventies, used a number of different metals (particularly tungsten and molybdenum) in his investigations. Gradually he discovered which metals worked the best and how the other parts of the catalyst should be constructed. A breakthrough came in 1990 when Schrock presented a group of very active catalysts containing the metal molybdenum[3] (*Figure 6*). Schrock's molybdenum carbene is very sensitive to oxygen and moisture as well as to protic compounds (alcohols, ketones, aldehydes, etc.), but is stable for long periods in an inert atmosphere [4].

In the early 1990's Grubbs developed a series of catalysts based on ruthenium metal that differ from the previous generations in several distinct ways (*Figure 6*). First, the metal is not in its highest oxidation state and is supported by phosphine ligands. Second, these catalysts are so tolerant of functionality that some of them can operate in water on the bench top! Such functional group tolerance comes at the expense of lower metathesis rates than the Schrock catalysts. In 1999 Grubbs came up with a second generation ruthenium catalyst which was even more effective than his first generation catalyst (*Figure 6*).

They have become the first well-defined catalysts for *general* use in metathesis in ordinary laboratories, Many people credit the

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Suggested Reading

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²Green Chemistry is the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture and application of chemical products.

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ruthenium catalysts of Grubbs with putting olefin metathesis in the forefront of organic synthesis [5,6].

Metathesis has great commercial potential in the pharmaceutical and biotechnology industries and in food processing. It has led to the efficient metathesis catalysts that have become such revolutionary general tools in organic synthesis. The new catalysts are also widely applicable in polymer synthesis, although, to date, most successful polymer materials have been manufactured with traditional methods. Considering the relatively short time that Schrock's and Grubbs' catalysts have been available, it is remarkable to note the breadth of applications they have found. These include the synthesis of insect pheromones, herbicides, additives for polymers and fuels, and polymers with special properties. The catalysts are more efficient (fewer reaction steps, fewer resources required, less wastage), simpler to use (stable in air, at normal temperatures and pressures) and environmentally friendlier (non-injurious solvents, less hazardous waste products). This represents a great step forward for 'green chemistry'², reducing potentially hazardous waste through smarter production.

The Nobel committee has done a wonderful job of assigning credit. Chauvin was the first to work out how metathesis reaction runs even though it was not clear as to how to design the catalyst. Schrock was the first scientist to come up with a rational design of a catalyst that would work. And Grubbs designed and developed catalyst systems that were easy to handle and worked on a wide range of compounds.

Metathesis is a clear example of the contribution that basic science has made to the welfare of society and the environment.

