

The 2005 Nobel Prize in Chemistry



PhotoCaption: 2005 Chemistry Laureates (L-to-R) Grubbs, Schrock and Chauvin

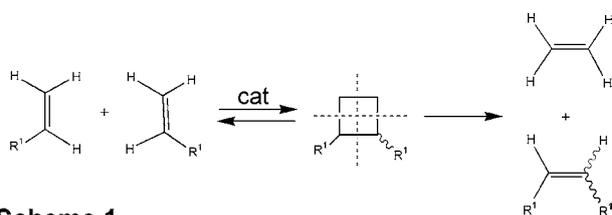
Synopsis

This year's Nobel Prize in Chemistry has much more connection with NZ than many might imagine. This is because one of the laureates, Prof. Bob Grubbs, was at Canterbury University on an Erskine Fellowship when the prize was announced on October 5. More coincidental is the fact that his first publication in the chemical literature is co-authored by Prof. Halton (Victoria University) from time at the University of Florida where Grubbs completed an MSc degree under the supervision of Prof. Merle Battiste, a former Erskine Fellow and visitor at Canterbury. It is even more coincidental that an original off-print of the communication was jointly signed in Wellington some hours ahead of the announcement being made.

The Prize for 2005 is shared by Americans Robert H. Grubbs and Richard R. Schrock, and Frenchman Yves Chauvin who are cited for the development of the metathesis method in organic synthesis. Their contributions have assumed major significance in the chemicals industry, opening up new opportunities for synthesising molecules that will streamline the development and industrial production of pharmaceuticals, plastics, and other materials. Production will become cheaper and more environmentally friendly.

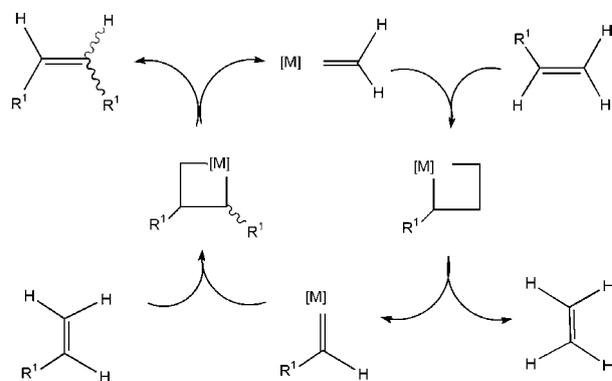
Metathesis – a change-your-partners dance!

The reaction at the focus of this year's Nobel Prize in Chemistry is *metathesis*. Derived from the Greek *meta* (change) and *thesis* (position), metathesis is the exchange of parts of two substances, e.g. in the reaction, $AB + CD \rightarrow AC + BD$, B has changed position with C, while Scheme 1 shows olefin (alkene) metathesis they key reaction of this year's award. Formally, two alkenes can come together in one direction and separate in the opposite one whereby one alkene exchanges its CHR^1 moiety for the CH_2 group in the other – hence the concept of a *change your partners dance*. However, for the reaction to proceed a catalyst is needed. While it has long been possible to produce new molecules this way, it was in 1970 that Chauvin proposed the first mechanism showing that the catalyst functions as a metal carbene. His experimental results tallied with the new mechanism and could not be explained by anything previously proposed.



Scheme 1

Scheme 2 shows how a metal methylene catalyses the exchange of alkylidene units between two different alkenes giving two entirely new alkenes ($[M]$ designates binding of the metal to other groups). This is also shown in Fig. 1 where it may be viewed as a dance in which the *catalyst pair* and the *alkene pair* dance round and change partners with one another. The metal and its partner hold hands with both hands and when they meet the *alkene pair* (a dancing pair consisting of two alkylides) the two pairs unite in a ring. After a while they let go of each other's hands, leave their old partners and dance on with their new ones. The new *catalyst pair* is now ready to catch another dancing *alkene pair* for a new ring dance – continuation of catalyst activity in metathesis. Thus researchers were given a new challenge to grapple with, namely to construct new efficient catalysts. Here Grubbs' and Schrock's fundamental research enters the picture as they have provided catalysts that are so useful today.



Scheme 2. Chauvin's mechanism for olefin metathesis involving metalacyclobutanes.

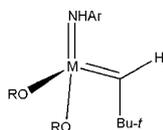


Fig. 1. Chauvin's mechanism viewed as a dance in which the catalyst pair and the alkene pair meet, dance round, and exchange partners.

Schrock's creation of the first well-defined useful catalysts

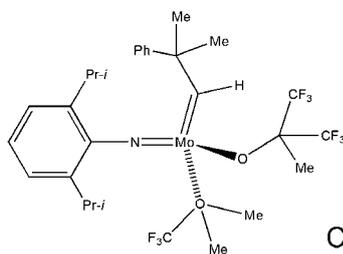
Chemists began to realise that metathesis could assume great importance for organic synthesis if reliable and effective catalysts could be found. Early studies used undefined catalysts, sensitive to air and moisture with relatively short life-time. The need was for stable and well-defined catalysts with reactivity that could be adjusted depending on the purpose. In addition, they had to be selective reacting only with double bonds and leaving other parts of the molecules intact. A number of chemists made major contributions to the development of metathesis catalysts and their applications; but the crucial progress in this area was made by Grubbs and Schrock.

Richard Schrock started research on new alkylidene complexes in the early 1970s trying catalysts containing different metals such as tantalum, tungsten, and molybdenum. He gradually developed an understanding of what metals could be used in the catalysts and how they functioned. For Schrock, molybdenum and tungsten soon appeared to be the most suitable metals and catalysts were produced with those metals, but there was still uncertainty as to what groups would bind to the metal to give stable yet active alkylidene complexes. A breakthrough came in 1990 when Schrock and co-workers reported the construction of a group of very active, well-defined catalysts shown generically by **1** and specifically by a commercial example (Scheme 3). With this discovery chemists began to realise that olefin metathesis could be used for general purposes in organic synthesis and it gained increasing attention among researchers active in synthetic chemistry. It turned out that it can replace a number of traditional synthesis methods while, at the same time, permits en-



1

General formula of Schrock's catalyst; M = Mo or W, R and Ar are bulky groups



2

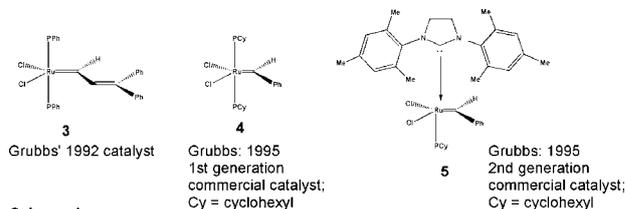
Commercially available Schrock catalyst

Scheme 3

tirely new approaches to the synthesis of organic molecules. Molybdenum catalysts, such as **2**, are sensitive to *e.g.* oxygen and moisture but, with the right treatment, are very powerful tools in organic synthesis.

Grubbs discovery of practical catalysts

Yet another breakthrough in the development of metathesis catalysts came in 1992 when Grubbs and his co-workers published their discovery of a ruthenium catalyst, stable in air and with higher selectivity but lower reactivity than Schrock's catalysts. The new catalyst **3** also had the ability to initiate metathesis in the presence of alcohols, water, and carboxylic acids. Grubbs subsequently improved his catalysts with the compound **4** (Scheme 4). This now commercial compound is the first well-defined catalysts for general metathesis applications in ordinary laboratories, is generally named Grubbs' catalyst, and has become the standard with which all new catalysts are compared.

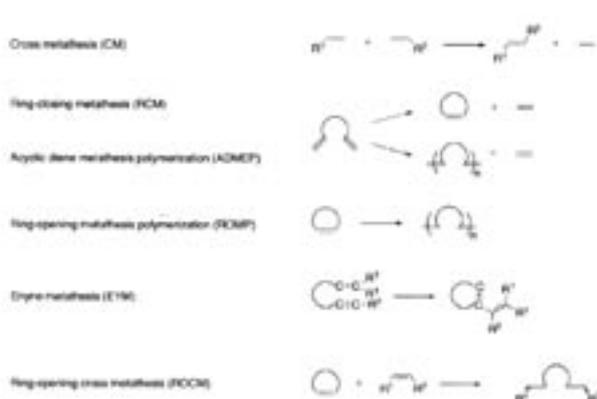


Scheme 4

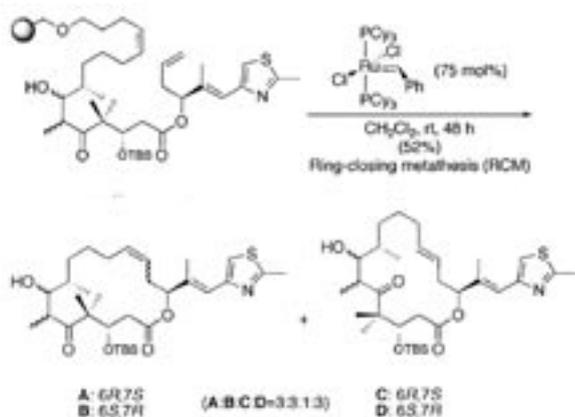
Grubbs bases his catalyst design on detailed mechanistic studies. He has continued development of Ru-based metathesis catalysts into yet more powerful tools for synthesis, including that of polymers with special properties. In a number of difficult ring-closing reactions, the life-time of the catalyst was insufficient to give high yields of products with reasonable catalyst loadings - catalysts with improved properties were needed. Detailed mechanistic studies led Grubbs' group to conclude that the reaction first involved the dissociation of one of the phosphine ligands to generate the reactive ruthenium intermediate. By replacing just one of the phosphines with a cyclic bis-amino carbene ligand Grubbs found the dissociation to be accelerated and the dissociation rate of the remaining phosphine increased, thus increasing metathesis activity. The new, more reactive, catalyst **5**, termed a second generation Grubbs' catalyst, is currently the most used catalyst for efficient cross-metathesis reactions and it is available commercially. The general applicability of Grubbs' catalyst has given rise to future prospects of the possibilities of organic synthesis.

The multitude of applications

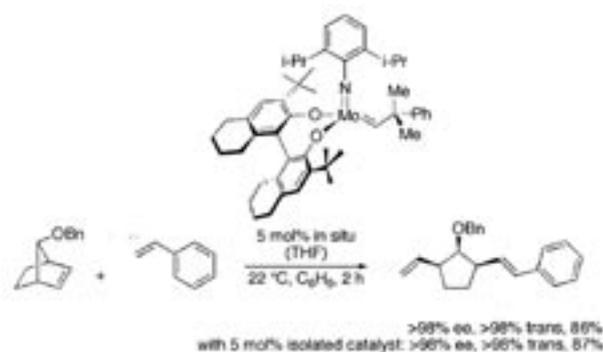
The Grubbs and Schrock catalysts offer synthetic chemists widespread opportunities. Their extensive use in organic chemistry is due to their tolerance of a large variety of functional groups, combined with their efficiency and, for Grubbs' catalysts, their ease of handling in air. Scheme 5 shows the different types of olefin metathesis reactions that can take place with the examples of Schemes 6-8 serving to illustrate the power of the novel catalysts.



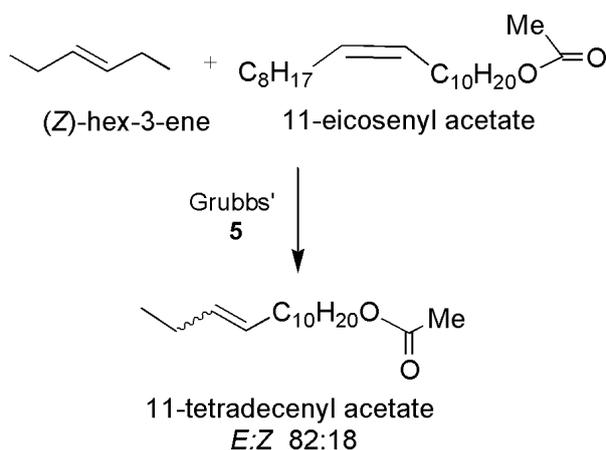
Scheme 5. Use of olefin metathesis in synthesis.



Scheme 6. A solid phase synthesis used by Nicolaou in the syntheses of epothilone A and its various derivatives using a ring-closing metathesis (RCM) cyclization/cleavage strategy; see Fürstner, A., and Thiel, O.R., *J. Org. Chem.*, **2000**, *65*, 1738.



Scheme 7. An efficient stereoselective cross metathesis (CM) using *in situ* prepared and isolated chiral catalyst, respectively, see: Teng, X., Cefalo, D., Schrock, R.R., and Hoveyda, A.H., *J. Am. Chem. Soc.*, **2002**, *124*, 10079.



Scheme 8. The omnivorous leafroller (OLR) is a pest of apples, pears, peaches, and nectarines. The OLR pheromone is an 82:18 ratio of *E* to *Z*-tetradecenyl acetate isomers. The synthesis of OLR pheromone is a particularly attractive target for metathesis because this CM reaction, using the second generation Grubbs' catalyst, produces the desired isomeric ratio; see: Pederson, R.L., Fellows, I.M. Ung, T.A. Ishihara, H., and Hajela, S.P., *Adv. Synthesis Cat.*, **2002**, *344*, 728.

Further catalyst development

Catalyst design (or redesign in some cases) remains vibrant, and seldom a month passes without the disclosure of a new catalyst for metathesis applications. Many of these novel systems are inspired by, or derived from, efforts to facilitate the construction of highly functionalized, complex molecules. Given the established ability of metathesis to effect transformations otherwise difficult to achieve, this trend is likely to continue.

Consequences and applications

It is important to emphasize the great significance of the laureates' discoveries and improvements for both academic research and industry for the development of commercially viable compounds. Considering the short time during which Grubbs' and Schrock's catalysts have been available, the breadth of applications is truly remarkable. We have witnessed the synthesis of polymers with special properties, additives to polymers and fuels, and biologically active compounds such as insect pheromones, herbicides and drugs. Importantly, catalytic metathesis uses shorter synthetic routes to products that are formed in higher yields than previously, thereby offering major possibilities for a greener chemistry.

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