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VETENSKAPSAKADEMIEN
THE ROYAL SWEDISH ACADEMY OF SCIENCES



Information Department, Box 50005, SE-104 05 Stockholm, Sweden

Phone: +46 8 673 95 00, Fax: +46 8 15 56 70, E-mail: info@kva.se, Website: www.kva.se

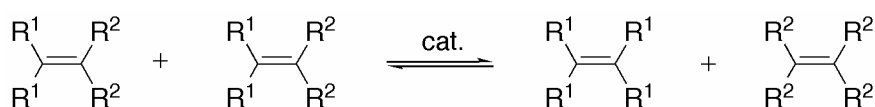
Development of the metathesis method in organic synthesis

Three researchers share this year's Nobel Prize in Chemistry: Dr. **Yves Chauvin** at the Institut Français du Pétrole, Rueil-Malmaison, France; Professor **Robert H. Grubbs**, California Institute of Technology, Pasadena, California, USA and Professor **Richard R. Schrock**, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA.

The Royal Swedish Academy of Sciences citation runs "for development of the metathesis method in organic synthesis". The discoveries of the laureates have had great effects on academic research, the development of new drugs and other biologically active compounds, polymeric materials and industrial syntheses. Below the background to their discoveries is described.

Introduction

Derived from the Greek words *meta* (change) and *thesis* (position), metathesis is the exchange of parts of two substances. In the reaction, $AB + CD \rightarrow AC + BD$, B has changed position with C. In Scheme 1 an olefin metathesis reaction is shown. Through carbene (alkylidene) exchange between the two starting olefins two new olefins have been formed.



Scheme 1

Catalysts for metathesis have been developed into enormously powerful and versatile tools in organic synthesis. The wealth of synthetic transformations that can be accomplished is astonishing.

Below the unravelling by Yves Chauvin of the metathesis mechanism and the following discoveries by Richard Schrock and Robert Grubbs of metathesis catalysts and their uses are described.

Nobel Prizes for synthetic methodologies

To date only a tiny fraction of the enormous diversity of organic molecules has been explored by synthetic chemists yet it has already given us new pharmaceuticals, agrochemicals, materials etc. that we can not live without. Further exploration of this diversity will result in even greater benefits to mankind – the potential is enormous. However, progress demands access to new selective synthetic methods!

Since the establishment of the Nobel Prize over a century ago advances in synthetic methodology in organic chemistry have received recognition of five of the Nobel Chemistry Prizes. All involve the carbon-carbon bond – its construction and chemistry. This is not surprising given the importance of carbon-carbon bonds, and the enabling nature of organic synthesis. Thus the 1912 Prize to V. Grignard and P. Sabatier recognized the importance of the Grignard reagents in forming carbon-carbon bonds for the construction of molecular frameworks and the use of metals in catalytic hydrogenation of unsaturated compounds. In 1950, the Diels-Alder reaction was recognized, in its simplest form this reaction reorganizes carbon-carbon double bonds to form new carbon-carbon bonds – two single and one double – and a six-membered ring. The prize to H.C. Brown and G. Wittig in 1979 was a recognition of their contributions to the chemistry of the carbon-carbon bond (hydroboration of unsaturated carbon-carbon bonds and the chemistry thereof) and its formation (the Wittig reaction), respectively. In 2001, the chemistry of the carbon-carbon bond was again the central theme of the asymmetric catalysis prize to W.S. Knowles and R. Noyori (reduction of the double bond) and to K.B. Sharpless (oxidation of the double bond). This years' laureates have been rewarded for their development of the metathesis method in which carbon-carbon double bonds are broken and formed catalytically.

The discovery of the olefin metathesis reaction

Catalyzed metathesis was discovered in the industry following observations in the 1950s of the polymerization of ethylene by Ziegler (Nobel Prize in Chemistry 1963). In a series of patents novel processes were reported; but their mechanisms were not understood. One of the reports was filed in 1957 by H.S. Eleuterio at Du Pont. It described the formation of unsaturated polymers. Such a polymer was obtained from the highly-strained starting material norbornene when it was added to molybdenum oxide on alumina combined with lithium aluminium hydride.^{1a} In the same year another patent application claimed an additional and seemingly novel transformation – disproportionation of olefins – as evidenced by the conversion of propene into ethene and butene upon treatment with a mixture of triisobutylaluminum and molybdenum oxide on alumina.^{1b,c}

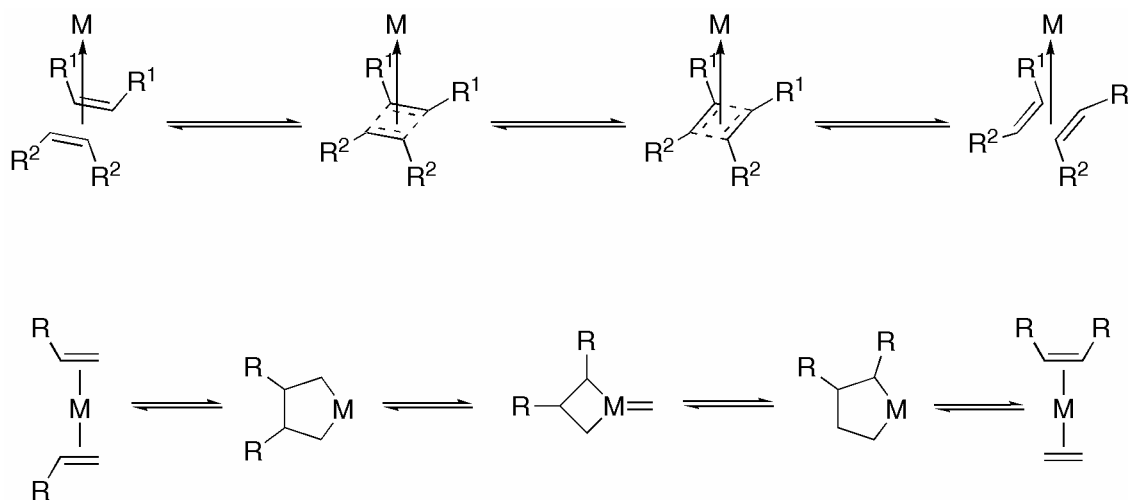
In 1966 G. Natta (Nobel Prize in Chemistry 1963) and co-workers showed that combinations of tungsten hexachloride with either triethylaluminum or diethylaluminum chloride polymerize cycloheptene, cyclooctene and cyclododecene.² The following year N. Calderon and co-workers reported their extension of these findings to other cycloolefins using a mixture of tungsten hexachloride and ethylaluminum chloride as initiator.^{3a,b} Calderon suggested that the polymerization of cyclic alkenes to polyalkenemers and the disproportionation of acyclic alkenes are the same type of reaction and named the reaction olefin metathesis.^{3d} Their results draw the attention of other researchers into organic and organometallic reactions to the potential of this novel reaction. However, the mechanism underlying metathesis remained a mystery.

Unravelling how metathesis works - the Chauvin mechanism

Several mechanistic hypotheses were in existence during this early period of olefin metathesis exploration. At first it was questioned whether olefin metathesis exchanged alkyl or alkylidene groups. Experiments by Calderon and by J.C. Mol using isotopically labelled alkenes demonstrated that the groups interchanged in olefin metathesis were alkylidenes.^{3a-c} But the mechanism by which interchange occurred and the role played by the metal species remained mere guesswork.

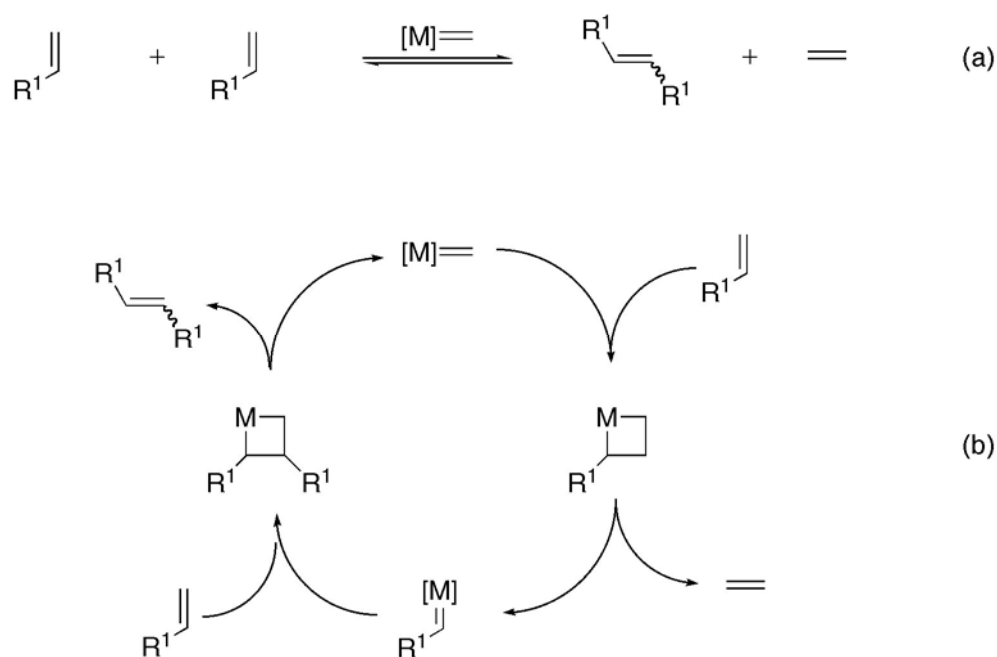
Among several ideas about the mechanism circulating at the time to explain alkylidene exchange were the metal-coordinated cyclobutane model of Calderon^{3d}, and later the

metallacyclopentane model of Grubbs.^{8a} The first of these models tended to be depicted in different ways by different authors (Scheme 2).



Scheme 2

However, it was not until Yves Chauvin at the Institut Français du Pétrole, in his efforts to understand the metathesis mechanism, combined reports by E.O. Fischer (Nobel Prize in Chemistry 1973) on the synthesis of a tungsten-carbene complex, Natta on the polymerization of cyclopentene through ring-opening catalyzed with a mixture of WCl_6 and $AlEt_3$ and Banks and Bailey on the formation of ethylene and 2-butene from propene catalyzed with $W(CO)_6$ on alumina, that a viable mechanism was presented. In 1971 Yves Chauvin and his student Jean-Louis Hérisson published their metathesis mechanism as illustrated in modified form in Scheme 3.^{4a}



Scheme 3

In Scheme 3a a metal carbene (metal methylene) is acting as catalyst to metathesize two terminal alkenes into an internal alkene (mixture of *E* and *Z* isomers) and ethylene. The metathesis is a reversible reaction but in this case removal of ethene drives the reaction to completion in this case.

In Scheme 3b the Chauvin catalytic cycle is shown.⁴ The metal methylene (metal alkylidene) reacts with the olefin, forming a metallocyclobutane intermediate. This intermediate then cleaves, yielding ethylene and a new metal alkylidene. The ethylene formed contains one methylene from the catalyst and one from the starting olefin. The new metal alkylidene contains the metal with its ligands (indicated by the brackets around the metal) and an alkylidene from the substrate alkene. This metal alkylidene reacts with a new substrate alkene molecule to yield another metallocyclobutane intermediate. On decomposition in the forward direction this intermediate yields the product internal alkene and metal methylene. This metal alkylidene is now ready to enter another catalytic cycle. Thus each step in the catalytic cycle involves exchange of alkylidenes – metathesis.

Chauvin and co-workers also presented experimental support for the mechanism which could not be explained by the other proposed mechanisms.⁴ The mechanism has also experimental support by Grubbs, T.J. Katz, Schrock and others and is now generally accepted as *the* mechanism for metathesis.

Chauvin's mechanism, with a metal alkylidene initiating metathesis, suggested that one could just synthesize metal-alkylidene complexes and let them react as catalysts with olefins to carry out the metathesis reaction. [The Fisher-type transition metal carbene complexes known at the time were not metathesis catalysts.]

Many researchers have contributed to the ensuing development of catalysts, and important early contributions were made by M.F. Lappert on rhodium (I) complexes as catalysts^{5a}, C.P. Casey on metathesis with tungsten complexes^{5b} and others. Here, however, the focus is on the breakthroughs made by Schrock and by Grubbs in the development of the metal-alkylidene complexes that have had such a dramatic influence on modern organic synthesis.

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

Many researchers foresaw the great synthetic potential of metathesis. But applications to organic chemistry were generally complicated by the sensitivity of the traditional catalysts to air and moisture, by side-reactions and by relatively short lifetimes. Progress required identifiable, relatively stable compounds that would behave as long-lived catalysts, whose reactivity could even be "tuned" for the desired task.

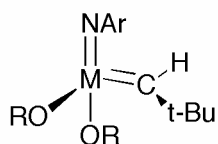
Schrock at Du Pont in early 1970s tried to synthesize $[\text{Ta}(\text{CH}_2\text{CMe}_3)_5]$, which was expected to be a stable compound. However, what he isolated instead was the first stable metal-alkylidene complex, $[\text{Ta}(\text{CH}_2\text{CMe}_3)_3(=\text{CHCMe}_3)]$, which has the high oxidation state of V.^{6a}

Schrock then synthesized other tantalum-alkylidene complexes, including the first methylene complex. These complexes were characterized using X-ray crystallography and NMR. He also found that metallocyclobutanes were formed. But metathesis had to wait since none of these alkylidene complexes catalyzed the metathesis of olefins.^{6b}

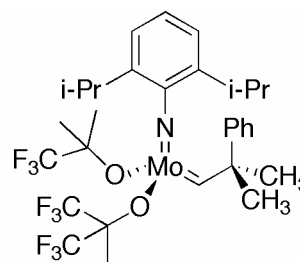
In 1980, Schrock and his group at MIT reported a tantalum-alkylidene complex $[\text{Ta}(=\text{CHC}(\text{CH}_3)_3)\text{Cl}(\text{PMe}_3)(\text{O}-\text{C}(\text{CH}_3)_3)_2]$, which catalyzed the metathesis of *cis*-2-pentene. The reason that this complex worked, whereas the other members of the family of the niobium- and tantalum-alkylidene complexes failed to do so, was the presence of alkoxide ligands.^{6c,d}

As indicated above, molybdenum and tungsten were the most active metals in alkene metathesis. Schrock and his group increased their efforts to find stable molecular alkylidene and alkylidyne complexes of these metals. The search eventually produced a whole family of molybdenum- and tungsten-alkylidene complexes of the general formula

$[M(=CHMe_2Ph)(=N-Ar)(OR_2)]$, R being bulky groups. These compounds are at present the most active of the alkene metathesis catalysts known (Scheme 4).^{6e-h}



General formula of the family of Schrock's metathesis catalysts (M= Mo or W; R and Ar are bulky substituents)



Schrock catalyst commercially available

Scheme 4

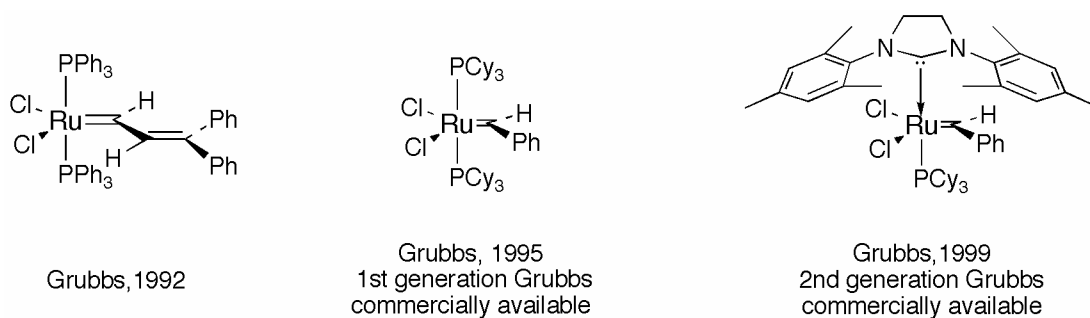
Other chemists including J. Osborn in Strasbourg and J.-M. Basset in Lyon have also made important contributions reporting tungsten complexes that are active as olefin metathesis catalysts.

The advantage of Schrock's catalysts, of which the most efficient were reported in 1990, was that besides being extremely active, they are molecular (without additives). One has been made commercially available (Scheme 4). Schrock has also developed chiral catalyst for asymmetrically catalyzed metathesis together with A.H. Hoveyda. Below some syntheses employing Schrock's catalysts are shown.

Grubbs discovery of practical catalysts

Grubbs had early been interested in the metathesis reaction, as indicated by his mechanistic proposal of a metallocyclopentane intermediate.^{8a} After some exploration that started in the mid 1980's of ill-defined catalysts that were prepared from late metal salts Grubbs and his co-workers found that ruthenium trichloride polymerized olefins even in water.^{8b} Actually ruthenium chloride had already been used by Natta as a catalyst for polymerisation of cyclobutene by ring opening.⁷ Grubbs assumed that this catalyst system also operated by a metal carbene mechanism. Their results initiated the development of well-defined catalysts that can be used with standard organic techniques and tolerate a broad range of functional groups.

As a result of their development work Grubbs and co-workers 1992 reported their first molecularly well-defined ruthenium-carbene complex that was not only active towards polymerization of norbornene but was also stable in presence of protic solvents.^{8c} The complex was of the vinylidene type $[RuCl_2(PR_3)(=CH-CH=CPh_2)]$ with R=Ph (Scheme 5). To increase the reactivity of the catalyst the phenyl groups were exchanged for cyclohexyl groups (R=Cy).^{8d,e} This change produced the desired reactivity and the catalyst polymerized unstrained olefins and induced reactions with acyclic olefins. It promoted many of the same reactions as the Schrock molybdenum-based alkylidene complexes but had greater functional group tolerance and could be handled using standard organic techniques.^{8f} A.F.Noels' group also reported 1992 on Ru-catalyzed ROMP of cycloolefins.



Scheme 5

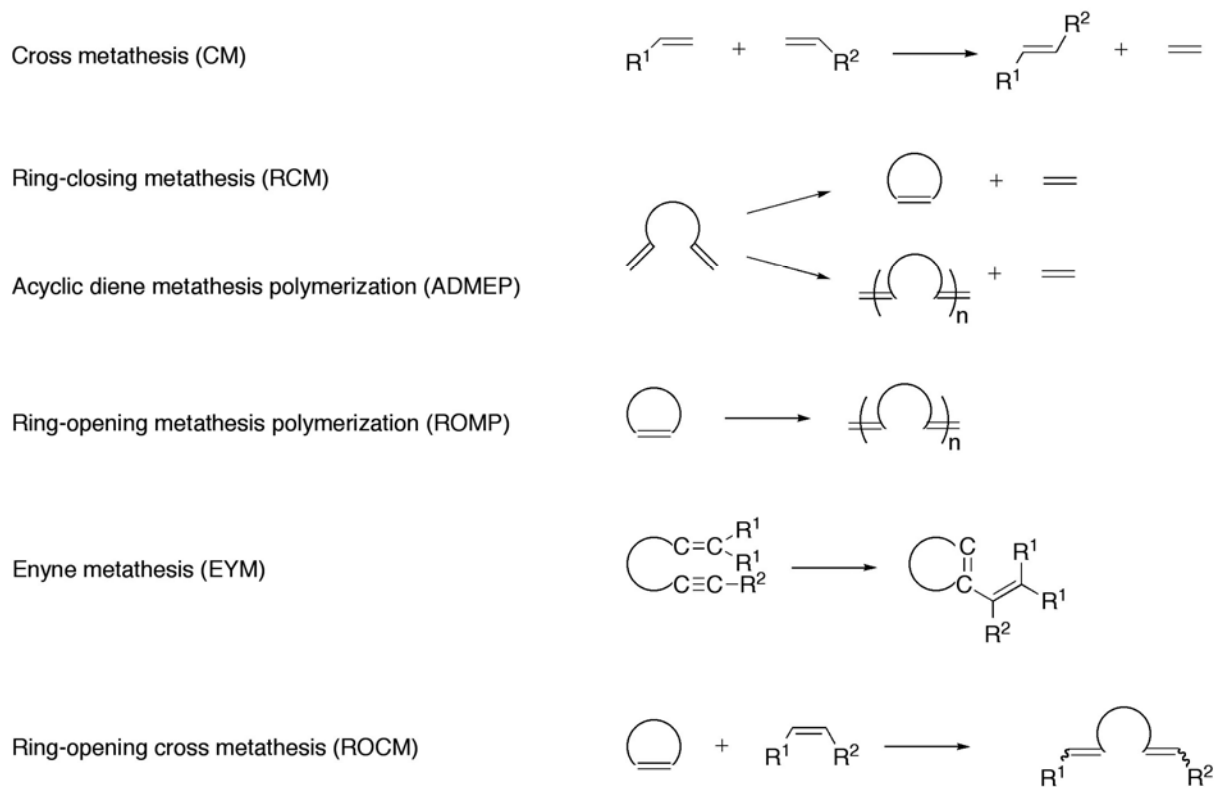
As the need for larger quantities of catalyst grew, more efficient methods for its synthesis were required. A practical route to ruthenium benzylidene complexes was developed. In 1995 Grubbs reported new molecularly-well-defined catalysts $[\text{Ru}(=\text{CHPh})\text{Cl}_2(\text{PR}_3)_2]$, $\text{R} = \text{Ph}$ or Cy (cyclohexyl).^{8g,h} These structures are closely related to the vinylidene ones. The compound with $\text{R} = \text{Cy}$ $[\text{Ru}(=\text{CHPh})\text{Cl}_2(\text{PCy}_3)_2]$ has been commercialized and is known as the first-generation Grubbs catalyst (Scheme 5). This compound is still the metathesis catalyst most used by organic chemists, because of its stability in air and compatibility with a large variety of groups.

In a number of difficult ring-closing reactions, the lifetime of the catalyst was insufficient to give high yields of products with reasonable catalyst loadings. Apparently 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 phosphines to generate the reactive ruthenium intermediate. To accelerate the dissociation Grubbs replaced one of the phosphines with a cyclic bis-amino carbene ligand. A. Herrmann had earlier synthesized ruthenium complexes with two such carbene ligands, but the catalytic activity of such compounds was modest. In Grubbs' catalysts containing only one such ligand the dissociation rate of the remaining phosphine is increased, increasing metathesis activity. Similar results were published 1999 almost simultaneously by S.P. Nolan and by A. Fürstner and Herrmann in 1999. The new, more reactive, catalysts are called second generation Grubbs' catalysts. $[\text{RuCl}_2\{\text{C}(\text{N}(\text{mesityl})\text{CH}_2)_2\}(\text{PCy}_3)(=\text{CHPh})]$ (Scheme 5) is currently the most used catalyst for efficient cross-metathesis reactions.⁸ⁱ This new ruthenium catalyst, with its greater thermal stability is now also available commercially.

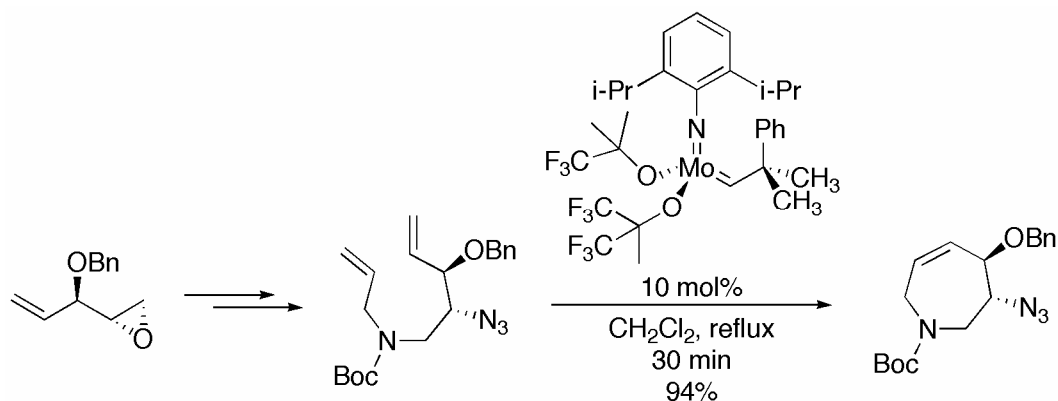
Grubbs' success has inspired also other researchers Hoveyda, P. Hofmann, K. Grela and S. Blechert and others to improve ruthenium-based catalysts for new tasks. Below are shown some syntheses using Grubbs catalysts.

The multitude of applications

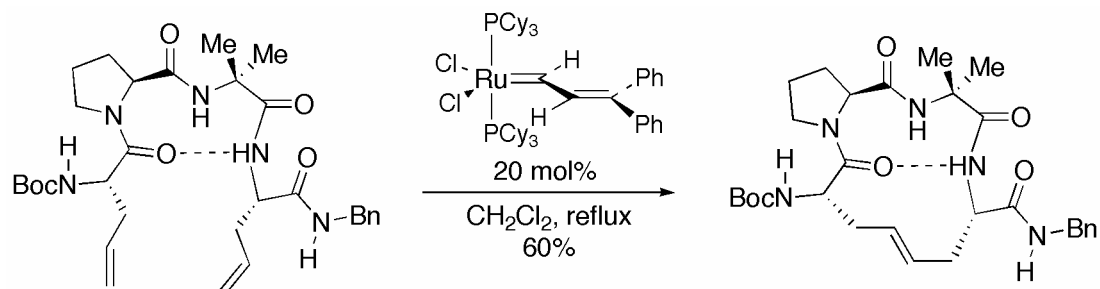
The Grubbs and Schrock catalysts offer synthetic chemists novel opportunities. Their widespread use in organic chemistry is due to their tolerance of a large variety of functional groups, combined with their efficiency and, for Grubbs' catalysts, their ease of handling in air.⁹ In Scheme 6 is shown different types of metathesis reactions and the following examples illustrate the power of the novel catalysts.



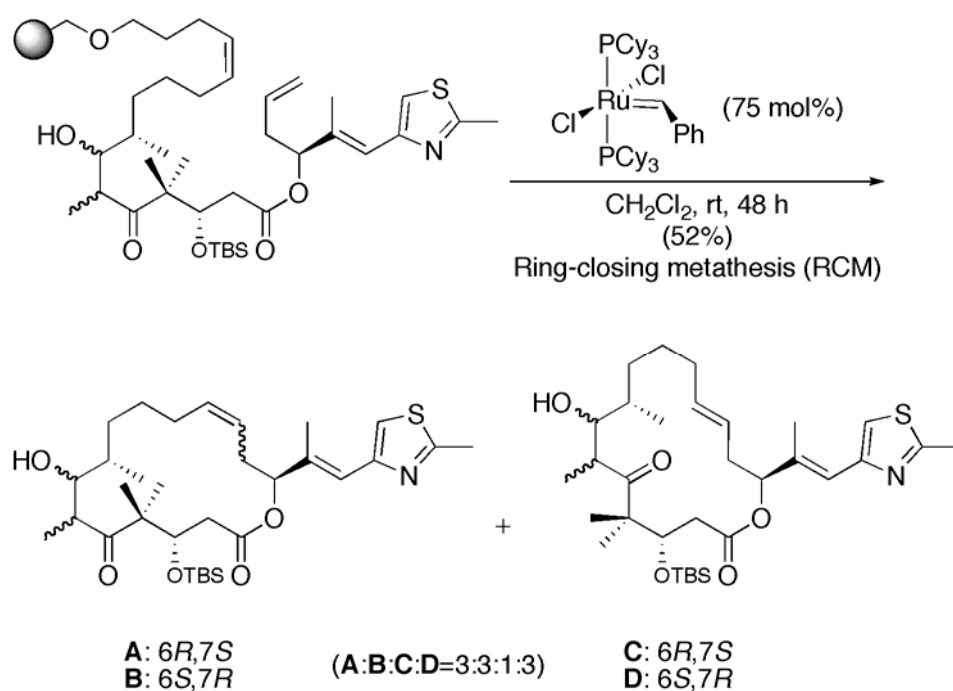
Scheme 6



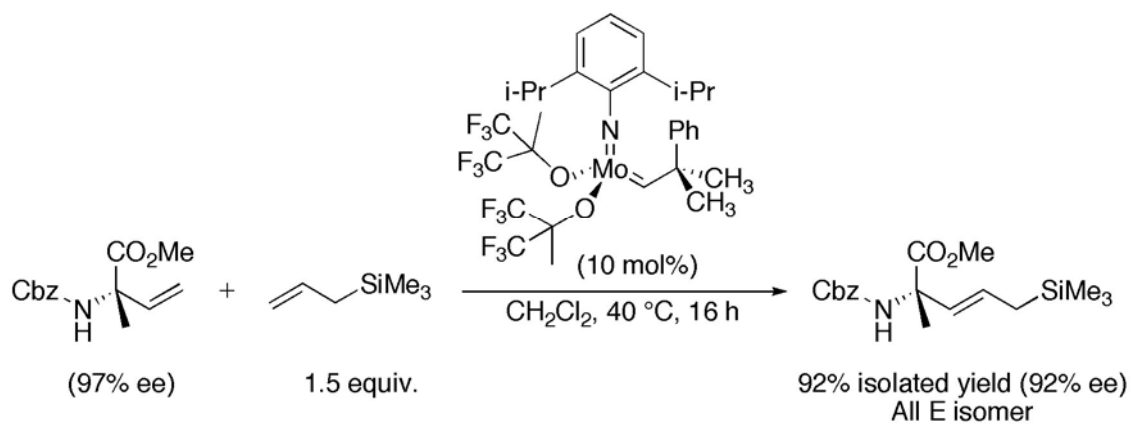
Scheme 7. The efficient RCM-based synthesis shown is due to Fürstner in his approach to balanol.¹⁰



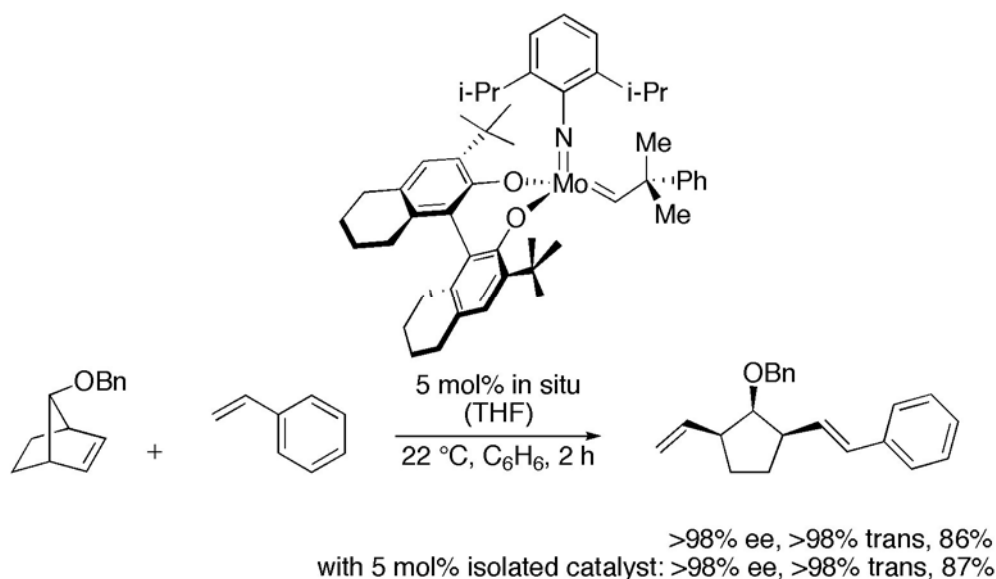
Scheme 8. The example of the formation of a dicarba-analogue of a disulfide β -turn by RCM was disclosed by Grubbs.¹¹



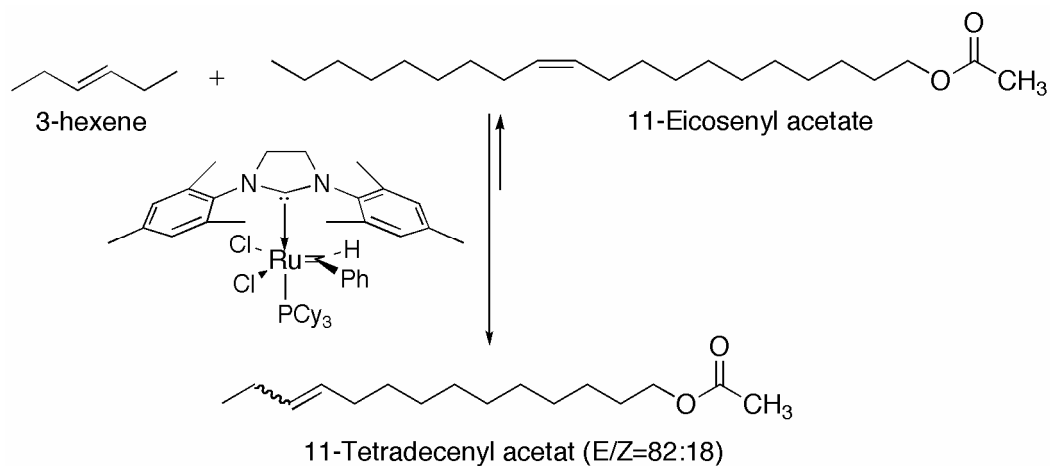
Scheme 9. Solid phase synthesis used by Nicolaou in the syntheses epothilone A and its various derivatives. A RCM cyclization/cleavage strategy is used.¹²



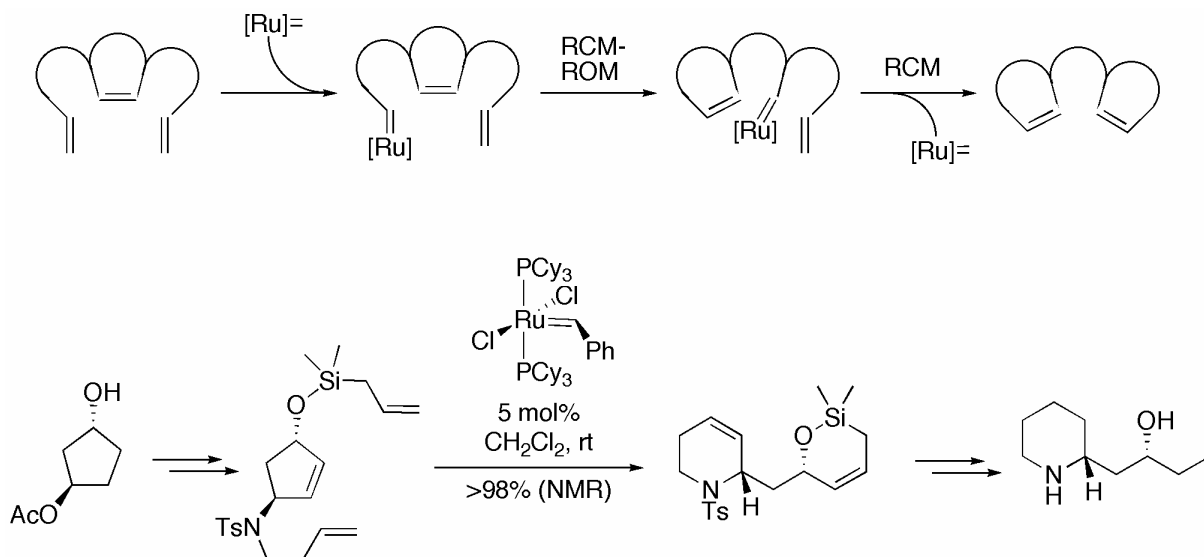
Scheme 10. An efficient CM with allylic stereocontrol observed with a substituted allylic amine.¹³



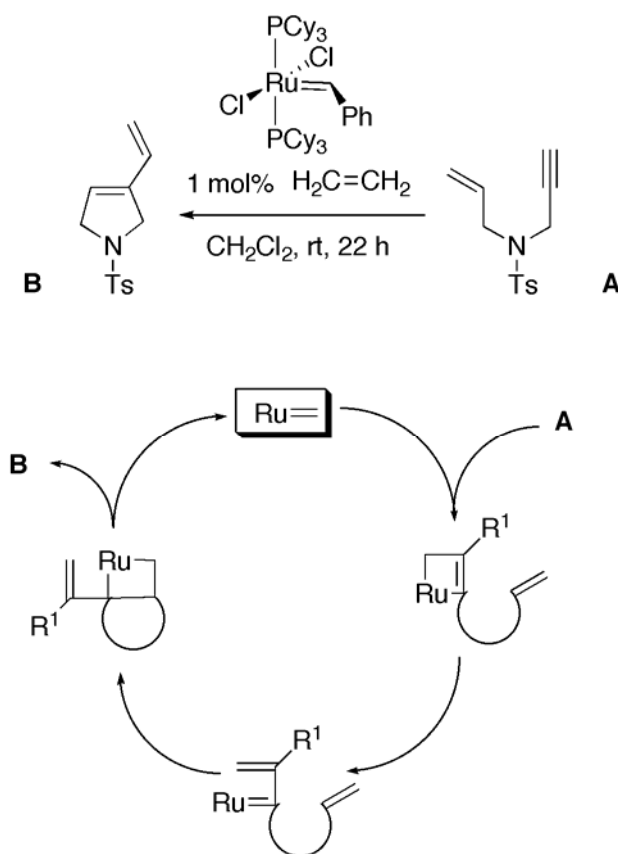
Scheme 11. An efficient stereoselective CM using *in situ* prepared and isolated chiral catalyst, respectively developed by Hoveyda and Schrock.¹⁴



Scheme 12. 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.¹⁵



Scheme 13. At the top a proposed mechanism for RCM-ROM-RCM reaction is shown. Such a tandem or domino reaction has been used in the synthesis of the piperidine alkaloid (-)-halosalin.¹⁶



Scheme 14. A proposed mechanism for enyne metathesis (EYM) using a ruthenium-carbene complex is shown together with a cyclization example.¹⁷

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 difficult to achieve otherwise, 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.⁹ 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.⁹ With catalytic metathesis shorter synthetic routes to the products give higher yields. This gives us novel possibilities to exploit the enormous diversity of organic molecules and contributes to a "greener" chemistry.

Per Ahlberg

Professor of Organic Chemistry, Göteborg University,
Member of the Nobel Committee for Chemistry

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