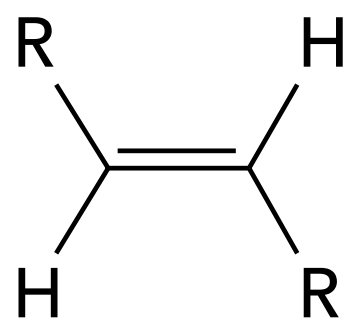
*Z or Cis**E or Trans*

# Making the grade: selective synthesis of alkene isomers

The production of specific isomers of commercially significant alkenes is fundamental to exploit their properties. **Professor Schrock** at the Massachusetts Institute of Technology (MIT) and **Professor Hoveyda** at Boston College are developing new methods of synthesising alkenes with previously unobtainable selectivity, which is destined to have a lasting impact on drug discovery and development.

**A**lkenes are a type of hydrocarbon, which contain at least one carbon-carbon double bond, and therefore have at least two fewer hydrogen atoms than their alkane equivalents. While alkenes are still relatively stable, they are more reactive than their single-bonded counterparts. Also known as olefins, they are found in many chemicals in the chemical and pharmaceutical industries and biology.

## DOUBLING UP

Manipulation of carbon-carbon bonds is best managed through the use of transition metal catalysts. Olefin metathesis (OM) is the name given to the process in which two olefins react together to form two new olefins through the scission and reorganisation of the carbon-carbon double bond. Prof Schrock jointly won the 2005 Nobel Prize in Chemistry for his work on elucidating these mechanisms; in fact, molybdenum- and tungsten-based catalysts are known as Schrock Catalysts. Not content to rest on his laurels however, Prof Schrock

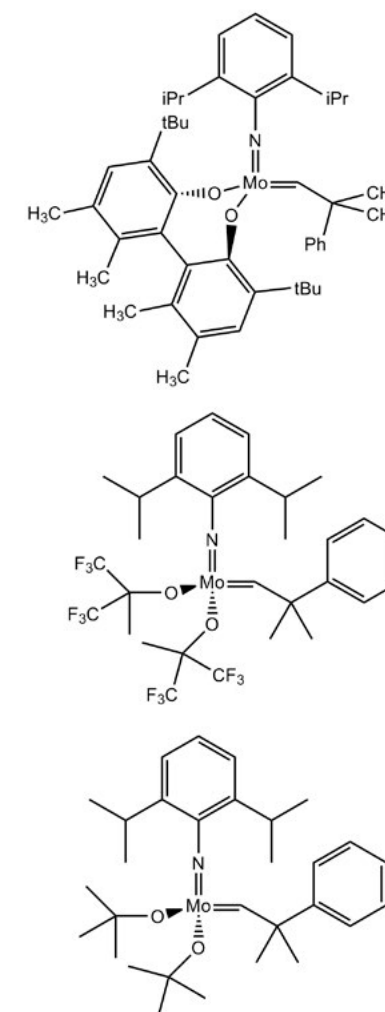
is turning his attention to the next major challenge in olefin metathesis.

## HANDEDNESS IS NOT SO HANDY

Due to the fact that alkenes are found in two different conformations (cis or trans, also called Z or E), the formation of one isomer is an important goal in any organic chemical synthesis. Z and E isomers are different geometrical arrangements of the same molecular bond structure. Usually only a single isomer (E or Z) is found in biological systems, and enzymes, in particular, will typically only interact with one type of isomer.

Until a few years ago it was not possible to generate solely Z or E isomers in chemical synthesis, as they are energetically approximately the same and therefore produced as mixtures that are difficult and expensive to separate. Prof Schrock is investigating how this can be resolved by utilising novel catalysts that are themselves highly specific for forming a given Z or E isomer.

**Olefins are important chemicals in the industrial and pharmaceutical industries due to their ability to polymerise, if cyclic, or to add new chemical groups at the site of their double bond**



**Commercially available Schrock catalysts**



## Detail

### RESEARCH OBJECTIVES

Dr Schrock has an extensive scientific background in inorganic chemistry, and one of his main research interests is studying catalytic reactions and the mechanisms of reactions involving alkylidene complexes. His latest research looks at improving access to olefins through a process called olefin metathesis. By having access to these alkenes, and enhancing their formation, Dr Schrock believes this exciting area of inorganic and organic chemistry could offer great benefits to medicine and the drug industry.

### FUNDING

National Institutes of Health (NIH) and the National Science Foundation (NSF)

### COLLABORATORS

This work has been accomplished through a collaboration with Professor Amir Hoveyda, who lends his expertise in organic chemistry to the project.

### BIO

Richard Schrock won a Nobel Prize in Chemistry for his work on olefin metathesis. After studying for his PhD at Harvard University in 1971, he joined MIT in 1975 and became a full professor there five years later. Since then, he has become a member of the American Academy of Arts and Sciences, the National Academy of Sciences, a foreign member of the Royal Society of London and the co-founder of a Swiss-based company devoted to commercialisation of metathesis chemistry.

### CONTACT

Richard R. Schrock, PhD  
Department of Chemistry, Massachusetts Institute of Technology (MIT), 6-331  
77 Massachusetts Ave.  
Cambridge, MA 02139, USA  
E: [rrs@mit.edu](mailto:rrs@mit.edu)  
T: +1 617-253-1596

Amir Hoveyda, PhD  
Boston College, Department of Chemistry, Merkert Chemistry Center  
Chestnut Hill, Massachusetts 02467, USA  
E: [amir.hoveyda@bc.edu](mailto:amir.hoveyda@bc.edu)  
T: +1 617-552-3618

## Q&A

### Why are olefins such significant molecules in organic chemistry?

The carbon-carbon double bond is found in some of the most basic molecules in the chemical industry, starting with ethylene, and in biologically relevant molecules.

### What has been the highlight of your years of research in this area?

The highlight has been the design and isolation of catalysts for producing one olefin product specifically in the OM reaction.

### Why is it such an exciting time to be involved in olefin research?

Olefins will continue to be the starting point

in the chemical industry for many important chemicals and will continue to be found in a wide variety of biologically important molecules.

### How would you describe this complex chemistry in layman's terms?

Imagine that you and your dance partner form a ring with another couple and exchange partners that way.

### What impact do you expect from your current research?

There is agreement that the OM reaction will continue to evolve and continue to change the way in which certain organic molecules are made.

**There is agreement that the OM reaction will continue to evolve and continue to change the way in which certain organic molecules are made** ”

Only SP metallacycles have been observed

Even a (reactive) methyldene oxo (a bisHMTO complex) can be isolated!

### A PRODUCTIVE PARTNERSHIP

Dr Schrock and Dr Amir Hoveyda have been collaborating for more than twenty years. Although the fundamental mechanism of olefin metathesis was identified some years ago, controlling the formation of Z and E isomers has seen rapid development in the last decade. It is an exciting time for organic chemistry generally and olefin metathesis and it is now possible to prepare alkenes in a commercially viable manner with a selectivity that was previously thought unobtainable.

As both the substrate and product of the reaction are alkenes, they can regenerate the starting material or any unwanted by-products. The purpose of designing selective catalysts for these reactions is to ensure only one of the thermodynamically possible reactions can occur, giving selective product formation. What the catalyst does is increase the rate of one possible reaction so it occurs faster than all the others, essentially winning the race to product formation.

The breakthrough came with the development of molybdenum catalysts which were particularly effective for generating molecules containing a single Z configuration. The team achieved >99:1

selectivity for the desired Z isomer using their catalysts, but found that even fairly similar substrates needed subtly different complexes to achieve the same result.

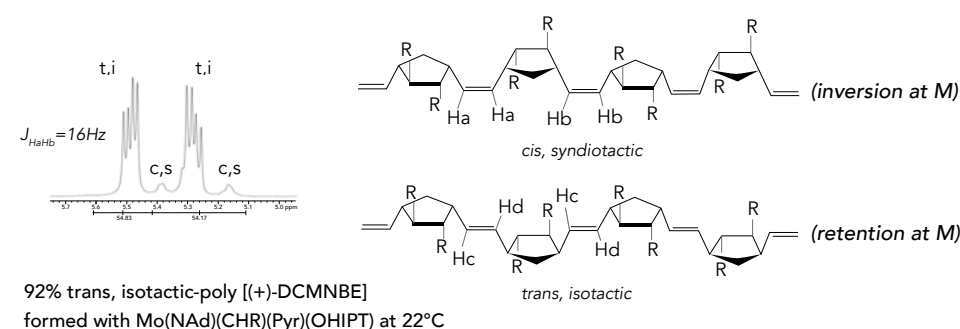
### CRACKING THE 'Z PROBLEM'

Selective production of the high-energy Z alkene isomer is plagued by problems. Some of these problems are resolved by the choice of ligand, which favours a particular orientation of the substrate during formation of the product. The problem is directing a catalyst to form only a single product in high yield. The team was able to adapt their techniques to a range of OM reactions (olefin fusion, ring creation, ring scission and combinations of these). Some responded

much more promisingly to the treatments, and a range of distinct, effective reactions was established.

These advances have pushed this already powerful chemical tool to new heights. Progress in the understanding of the metal centre of the catalyst, and particularly how it is responsible for the stereoselectivity of the reaction, has been vital to move the field forward. The advent of these so-called 'stereochemical-at-metal' catalysts has ushered in an era of unprecedented selectivity of OM.

Many possible OM reactions still do not have suitably selective catalysts to drive them. There are also some reactions that require such high energy, and produce such a range of difficult-to-distil products, that they are not viable for production. Profs Schrock and Hoveyda, with years of experience in the field and a real passion for solving these problems, are well-placed to continue the momentum that this exciting era in inorganic and organic chemistry has initiated.



**Profs Schrock and Hoveyda are well placed to continue the momentum that this exciting era in inorganic and organic chemistry has initiated** ”