

Prelog Lecture 2001

Eidgenössische Technische Hochschule Zürich
 Laboratorium für Organische Chemie

Abstract: On Monday, November 12, 2001, the rector, Prof. Dr. K. Osterwalder, presented the Prelog Medal 2001 to **Prof. Dr. Robert H. Grubbs**, California Institute of Technology. The title of the lecture that followed was 'The Design and Use of Ruthenium-Based Metathesis Catalysts'.

Keywords: Grubbs, R.H. · Prelog Lecture



Konrad Osterwalder, Robert H. Grubbs,
 François Diederich

Foto: R. Häflicher

Born February 27, 1942 near Possum Trot, Kentucky, USA, **Prof. Robert H. Grubbs** obtained his Bachelor of Science degree in Chemistry at the University of Florida, Gainesville, Florida in 1963. After a Masters degree (1965), Prof. Grubbs earned a Ph.D. under the direction of Prof. R. Breslow at Columbia University, New York, New York in 1968. Following his stay as a National Institute of Health post-doctoral fellow (1968–1969) in the laboratories of Prof. J.P. Collman at Stanford University, Stanford, California, he started his independent academic career at Michigan State University in 1969. In 1978, he moved to the California Institute of Technology in Pasadena, California, where he is the Victor and Elizabeth Atkins Chair Professor of Chemistry.

The research program of Prof. Grubbs has involved the design, and synthesis of transition-metal complexes that mediate preparatively useful reaction chemistry. The work has always been characterized not only by its innovation and novelty, but also by the meticulous mechanistic work that accompanies each of the processes he has discovered and developed. His investigations have had unparalleled impact in the development of well-

defined complexes that function as catalysts in small molecule and polymer synthesis. His most recent work on the metathesis reaction of olefins has revolutionized strategies for the construction of molecules and, in particular, C–C bond formation. His pioneering interest in this phenomenal reaction pre-dates 1972 when he documented in a paper a mechanistic discussion of putative intermediates in the tungsten-catalyzed olefin metathesis reaction. The current family of Ru-based catalysts for this reaction are characterized by the efficiency and, importantly, by their functional-group tolerance as well as the ease with which such reactions, which had earlier demanded glove-box techniques, can be now conducted. The profound impact that his work in this area has had can be appreciated by the fact that the use of the Grubbs metathesis reaction is widespread, and it is rather common to find in any chemistry journal research work utilizing this reaction in applications as diverse as natural products and polymer synthesis as well as chemical biology. It is a transformation that has become as important to molecular sciences as the Diels-Alder cycloaddition and Wittig olefination reactions. His highly productive research program has

produced over 30 patents and more than 350 refereed publications.

Prof. Grubbs has been honored with a plethora of domestic and international awards. These include: Alfred P. Sloan Fellow (1974–76); Camille and Henry Dreyfus Teacher-Scholar Award (1975–78); Alexander von Humboldt Fellowship (1975); American Chemical Society National Award in Organometallic Chemistry (1988); Arthur C. Cope Scholar Award (1990); American Chemical Society Award in Polymer Chemistry (1995); Nagoya Medal of Organic Chemistry (1997); Fluka Reagent of the Year (1998); Mack Award (1999); Benjamin Franklin Medal in Chemistry (2000); American Chemical Society Herman F. Mark Polymer Chemistry Award (2000); and the Herbert C. Brown Award for Creative Research in Synthetic Methods (2001). Prof. Grubbs is a member of the National Academy of Sciences (1979) and a fellow of the American Academy of Arts and Sciences (1994).

Former Prelog Lecturers

1986	Kurt Mislow
1987	Meier Lahav and Leslie Leiserowitz
1988	K. Barry Sharpless
1989	Jeremy R. Knowles
1990	Henri B. Kagan
1991	Clayton H. Heathcock
1992	J. Michael McBride
1993	Hisashi Yamamoto
1994	Jean-Pierre Sauvage
1995	Yoshito Kishi
1996	David M.J. Lilley
1997	Günter Helmchen
1998	Lia Addadi
1999	David Evans
2000	Helmut Schwarz

Cross Metathesis of Functionalized Olefins

Robert H. Grubbs*

Abstract: The development of highly active ruthenium alkylidene catalysts for olefin metathesis has enabled new applications in organic synthesis, especially with the cross-metathesis reaction.

Keywords: Catalysis · Olefin metathesis · Organic synthesis · Ruthenium

Introduction

Olefin metathesis has grown from a reaction useful only in hydrocarbon chemistry to one that finds wide application in natural product and functional polymer synthesis [1]. The growth of this field is due to the development of catalyst families that tolerate a variety of functional groups. The early homogeneous catalysts were mixtures of early metal halides and alkylaluminum or other reducing/alkylating agents [2]. These mixtures produced very active, ill-defined catalysts that were extremely sensitive to organic functional groups and to air and water. These catalysts were used mostly to prepare unfunctionalized polymers. Starting in the 1980s, the discovery of well-defined, single-component catalysts started the new age of metathesis chemistry. Although these catalysts were sensitive to oxygen and water, they showed improved functional group tolerance [3]. Late metal systems developed in the early 1990s showed further improvements in functional group tolerance [4]. Table 1 illustrates these changes in the relative reactivities of organic functionalities as the metal center is varied. For the broadest application of olefin metathesis, the reactivity of an olefin relative to other functionalities must be maximized, as in the case of ruthenium.

Titanium	Tungsten	Molybdenum	Ruthenium
Acids	Acids	Acids	Olefins
Alcohols, Water	Alcohols, Water	Alcohols, Water	Acids
Aldehydes	Aldehydes	Aldehydes	Alcohols, Water
Ketones	Ketones	Olefins	Aldehydes
Esters, Amides	Olefins	Ketones	Ketones
Olefins	Esters, Amides	Esters, Amides	Esters, Amides

↑
Increasing reactivity

Table 1. Relative reactivities of organic functional groups as a function of the central metal in metathesis-active alkylidene complexes.

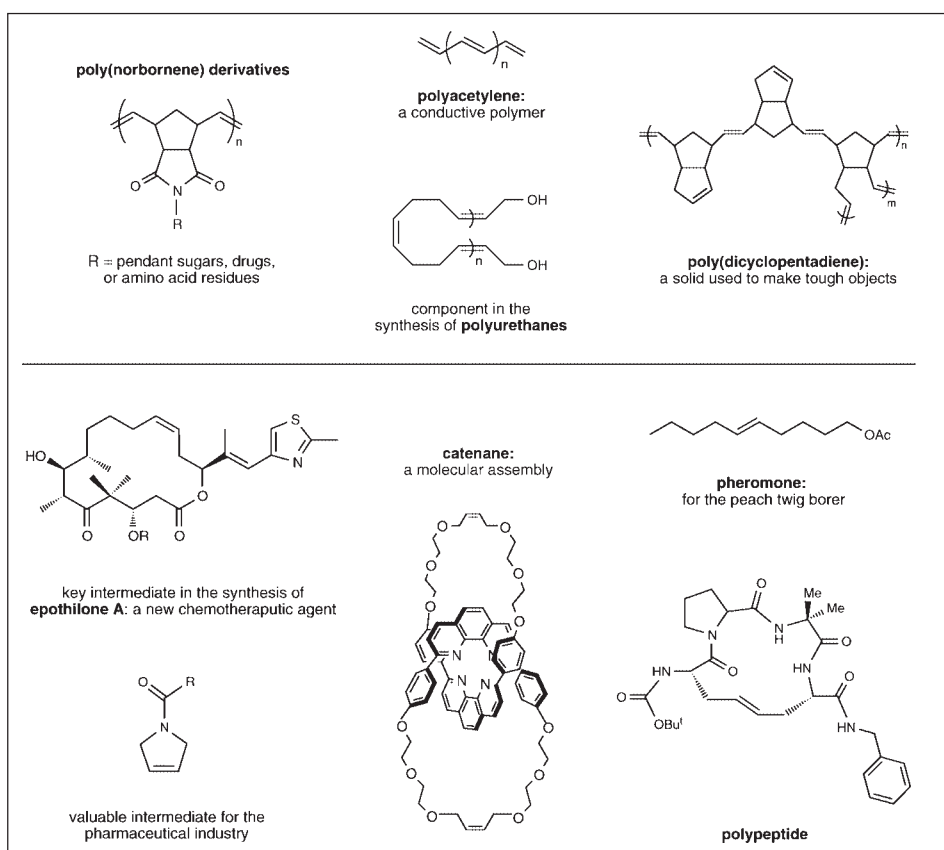


Fig. 1. Polymers (top), fine chemicals, and pharmaceuticals (bottom), synthesized by olefin metathesis. The carbon-carbon double bond formed in the reaction is highlighted.

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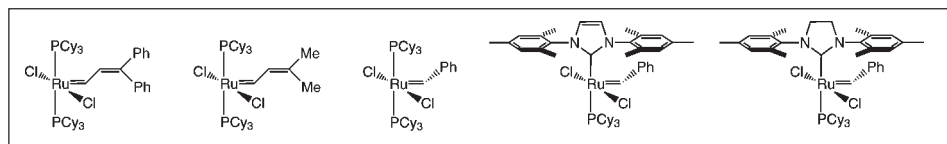


Fig. 2. Well-defined ruthenium alkylidene catalysts for olefin metathesis. The first three examples are bis(phosphine) derivatives, whereas the last two examples contain one phosphine ligand and one N-heterocyclic carbene ligand.

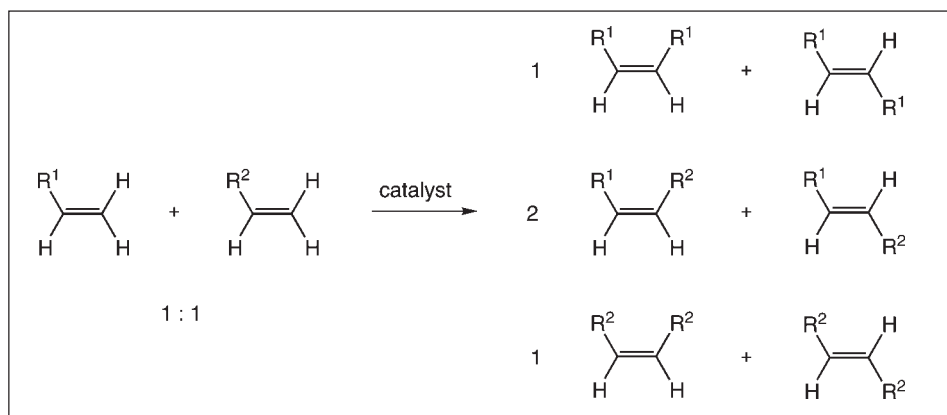


Fig. 3. The simplest case of the cross metathesis reaction, which results in a statistical mixture of olefins.

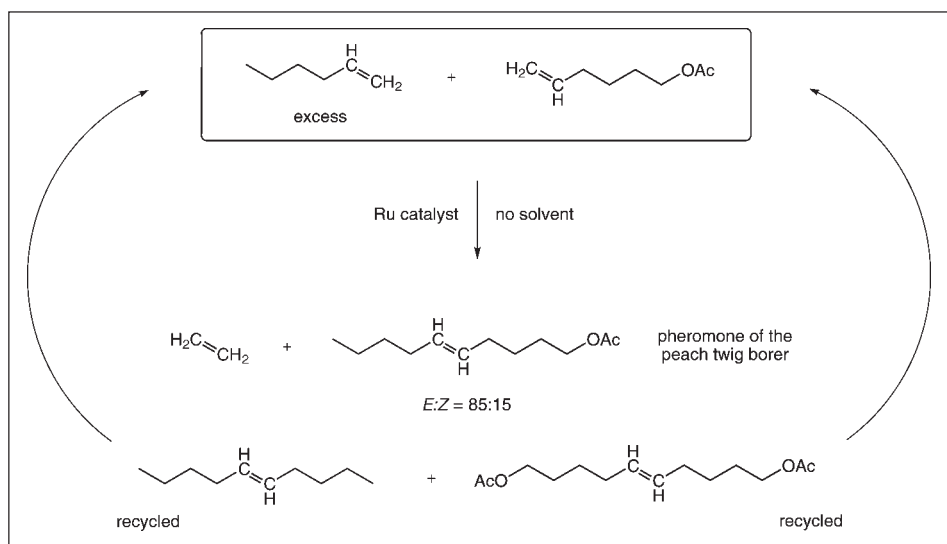


Fig. 4. Iterative process to synthesize the peach twig borer pheromone by cross metathesis.

Ruthenium-based catalysts have been used to produce a variety of new molecules and materials. The examples in Fig. 1 demonstrate that metathesis chemistry can be used to produce polymeric materials [5], as well as multifunctional natural products and molecular assemblies [1][6].

With the basic structure of the active complex defined, $L_2X_2Ru=CHR$, a wide range of studies have been carried out on derivatives of this basic structure that are directed toward improved synthetic routes as well as increased activity (Fig. 2) [4]. The complexes in which one of the phosphine groups is replaced by an N-heterocyclic carbene ligand have opened a new range of possible applications of metathesis (Fig. 2) [7]. For example, they can be used to carry out metathesis on trisubstituted and directly functionalized double bonds. In many applications, these ruthenium-based catalysts show activity that is comparable to

the very active early transition metal catalysts, while at the same time retaining both the functional group tolerance and environmental stability typical of ruthenium-based systems.

Applications in Cross Metathesis

Most of the reported applications of olefin metathesis in organic synthesis have been limited to ring-closing metathesis. A related reaction that may have even broader scope is cross metathesis. This reaction has been less thoroughly explored due to the perceived lack of selectivity. In the simplest case when a pair of olefins is subjected to cross metathesis, the double bonds in the products have similar stabilities to those in the starting material. Consequently, the observed product is a statistical mixture of the three possible products in the equilibrium *E:Z* ratio (Fig. 3).

However, the situation is not so drastic if one of the olefins is readily available. For example, in the synthesis of the peach twig borer pheromone in Fig. 4, one of the cross-partners is much cheaper than the other and can be used in excess [8]. This drives the equilibrium toward the desired cross product of the more expensive olefin. In addition, the by-products can be recovered and recycled because they are reactive in subsequent metathesis reactions. In contrast to ring-closing metathesis reactions, which often requires high dilution, cross metathesis reactions can be carried out neat in pure reagents.

Some olefins, due to electronic or steric factors, do not undergo rapid dimerization but will undergo cross metathesis with other olefins. If equal molar amounts of two alpha-olefins, one of which does not dimerize, are mixed and the reaction is driven to completion by removal of ethylene, the cross product is

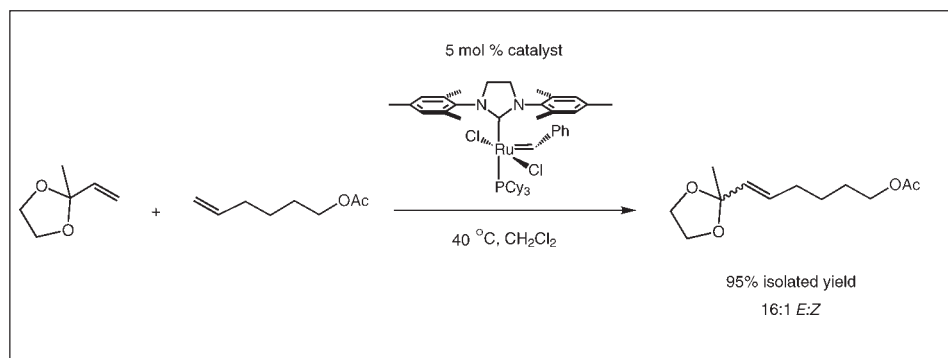


Fig. 5. An example of steric control in cross metathesis.

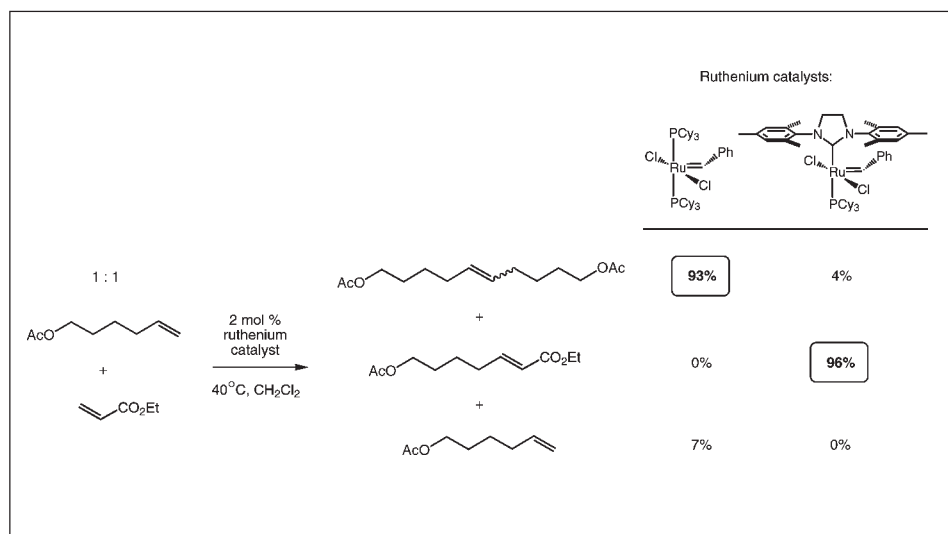


Fig. 6. An example of cross metathesis involving an electron-deficient olefin.

Enone	Equiv.	Product	Isolated Yield
	2.0		95%
	2.0		85%
	2.0		99%
	2.0		95%
	0.5		90%
	0.5		92%

Table 2. The cross metathesis of unsaturated carbonyl compounds with alpha-olefins. The cross partner is apparent from the product structure. An N-heterocyclic carbene coordinated ruthenium catalyst is used in all cases.

the sole product [9]. For instance, olefins with large groups in the allylic position are slow to undergo dimerization. This steric blocking leads to high yields of cross product, as illustrated in Fig. 5.

In a similar way, electron-deficient olefins undergo slow dimerization. Consequently, very high yields of cross products arise from reactions of alkyl olefins with α,β -unsaturated carbonyl compounds. An added bonus is that the products of these reactions are greater than 20:1 *E:Z*. Thus, in these cases, cross metathesis does not produce all six possible products as shown in Fig. 3, but rather a single cross product in high yield (>90%) (Fig. 6) [10].

These cross metathesis reactions readily provide the same products as the Horner-Emmons and Heck reactions. A selection of olefins that have been synthesized is presented in Table 2 [11]. Compared to the Horner-Emmons reaction, cross metathesis starts from a more widely available functionality, an olefin, and it is also catalytic. Compared to the Heck reaction, the conditions for cross metathesis are much milder. For these reasons, cross metathesis should prove to be an extremely useful reaction, even surpassing ring-closing metathesis, especially as the rules that control product selectivity become better understood.

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