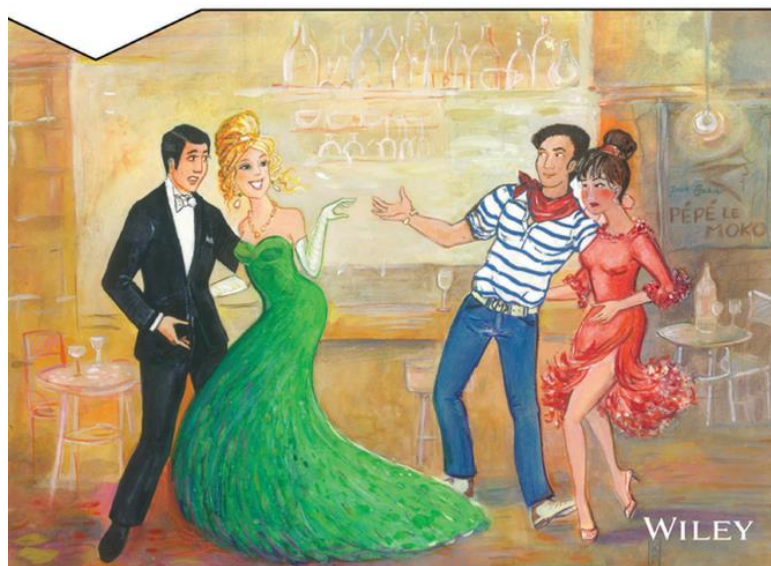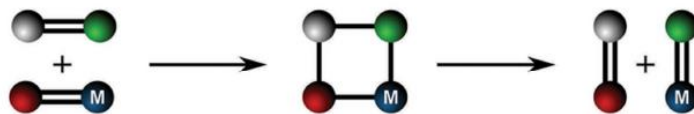# Olefin metathesis

https://www.youtube.com/watch?v=PbGreFTTsGg

The Nobel Prize in Chemistry 2005

Photo: U. Montan

Yves Chauvin

Prize share: 1/3

Chauvin was the first to produce a viable mechanism for olefin metathesis.
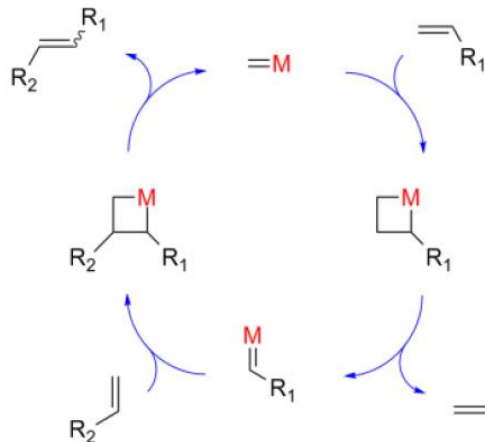

Photo: R. Paz

Robert H. Grubbs

Prize share: 1/3

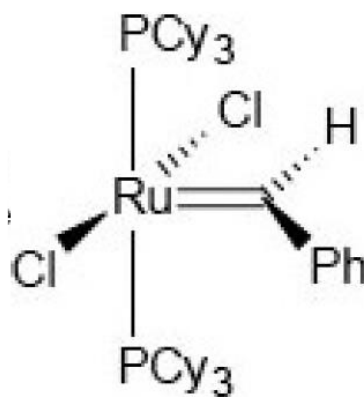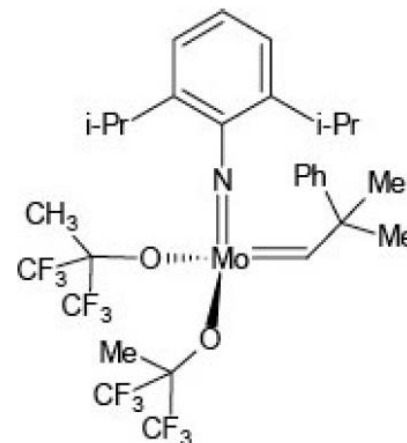Grubbs gave synthetic chemists an air stable and water-soluble metal carbene.

Photo: L.B. Hetherington

Richard R. Schrock

Prize share: 1/3

Schrock accidently created first stable metal carbene catalyst at MIT.

In 1971 **Yves Chauvin** was able to explain in detail how metatheses reactions function and what types of metal compound act as catalysts in the reactions. Now the "recipe" was known. The next step was, if possible, to develop the actual catalysts.

Richard Schrock was the first to produce an efficient metal-compound catalyst for methasesis. This was in 1990. Two years later **Robert Grubbs** developed an even better catalyst, stable in air, that has found many applications.

Metathesis is used daily in the chemical industry, mainly in the development of pharmaceuticals and of advanced plastic materials. Thanks to the Laureates' contributions, synthesis methods have been developed that 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", reducing potentially hazardous waste through smarter production. Metathesis is an example of how important basic science has been applied for the benefit of man, society and the environment.
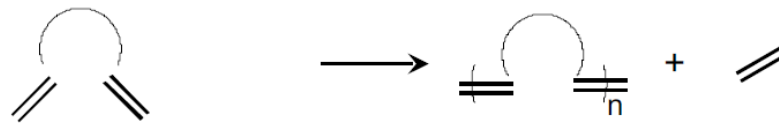
Cross Metathesis (CM)

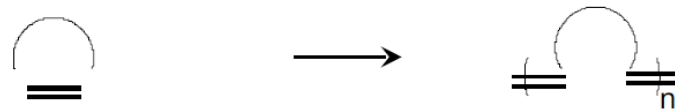R^1 ⟍⟋ R^1 + R^2 ⟍⟋ R^2 ⟶ 2 R^1 ⟍⟋ R^2
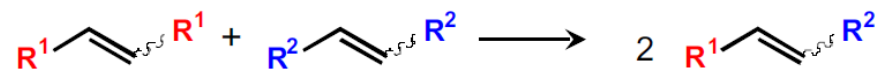
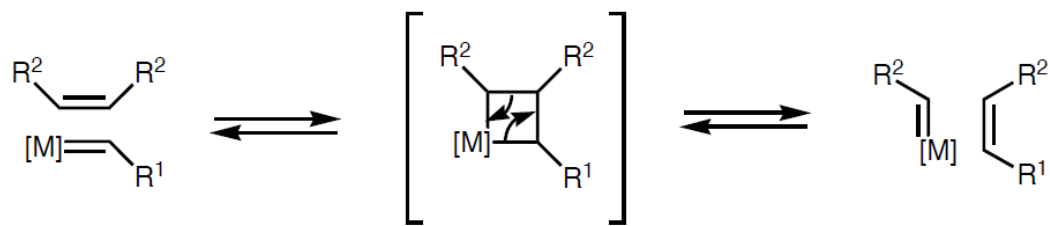**Ring Closing Metathesis (RCM)**

Acyclic Diene Polymerization (ADMET)

Ring Opening Metathesis (ROMP)

■ Chauvin-type mechanism: model proceeds through a metallacyclobutane intermediate
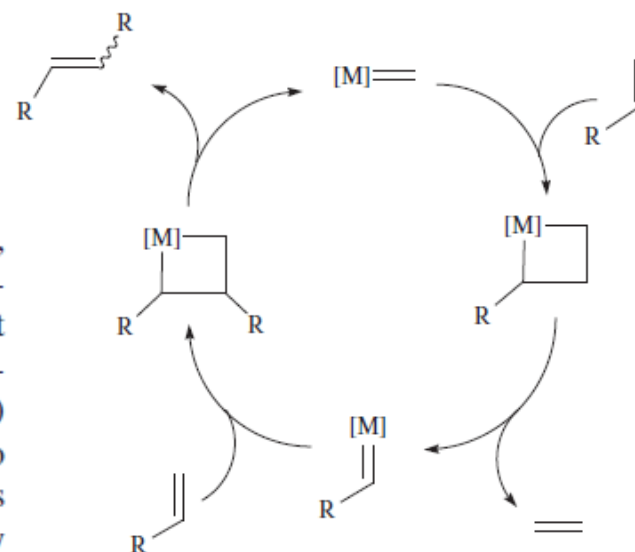
Chauvin Mechanism

The Chauvin mechanism involves a metal–carbene species (or more precisely metal–alkylidene), the coordination of the olefin onto the metal atom of this species, followed by the shift of the coordinated olefin to form the metallocyclobutane intermediate, and finally the topologically identical shift of the new coordinated olefin in the metallocyclobutane in a direction perpendicular to the initial olefin shift. This forms a metal–alkylidene to which the new olefin is coordinated, then liberated. This new olefin contains a carbene from the catalyst and the other carbene from the starting olefin. The new metal–alkylidene contains one of the two carbenes of the starting olefin and it can re-enter a catalytic cycle of the same type as the first one
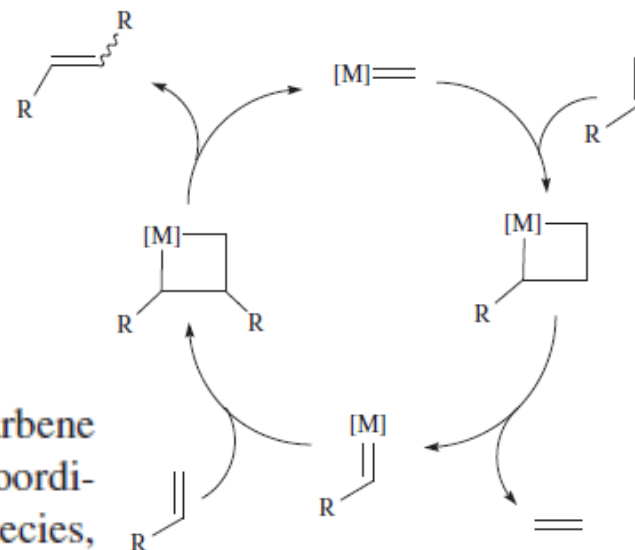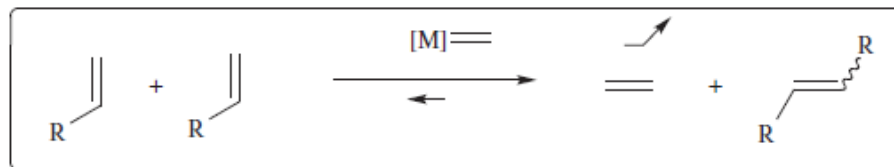
Chauvin Mechanism



Chauvin's mechanism introduced several new ideas. First, he proposed a metal–carbene complex to initiate the catalysis of the metathesis reaction. This idea first suggested that one could just synthesize unsaturated metal–alkylidene complexes (i.e., with 16 valence electrons on the metal or less) and let them react as catalysts or pre-catalysts with olefins to carry out the metathesis reaction. Of course, many authors later engaged in such research directions, first delineated by Chauvin. The induction time was long, however. Relatively few chemists became interested in such a route in the first half of the decade following Chauvin's proposal.

The second key point mentioned above was the explanation of the "black box" of the American industrial chemists: a d^0 metal–alkyl complex formed using such a mixture undergoes the formation of a metal–methylene or metal–alkylidene species that serves as a catalyst for alkene metathesis. For that purpose, Chauvin included in his metathesis mechanism the crucial proposition of an α-H elimination, a pioneering idea that was reactivated and rationalized by its σ-bond mechanism only much later.
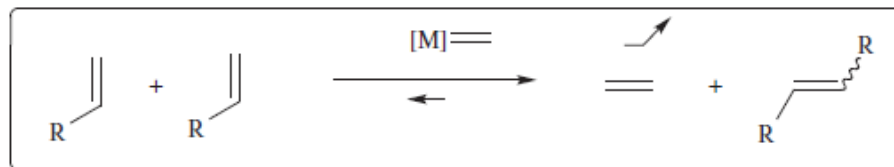
Chauvin Mechanism
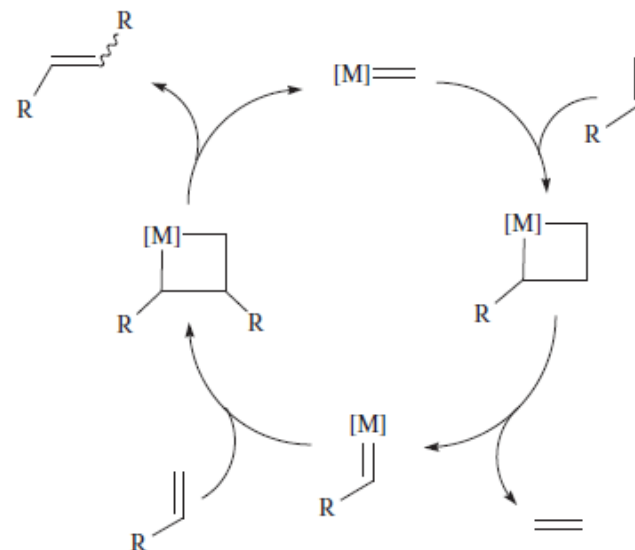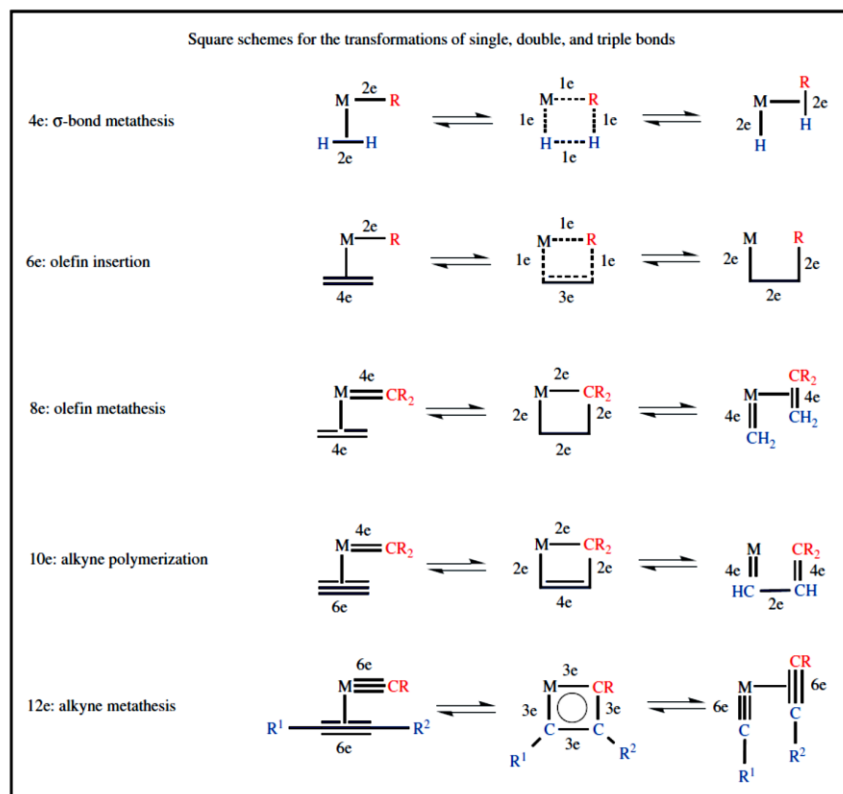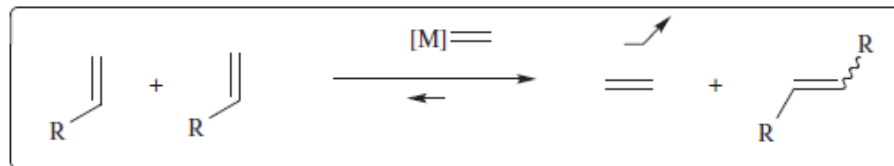
Finally, it is possible to represent a generalization of the metallosquare formed by the shift of the olefin coordinated to the metal in the metal–alkylidene species (25). The metallosquare is not only involved as an intermediate or transition state in alkene metathesis, but also in many other catalytic organometallic mechanisms. Indeed, the metathesis of alkynes and the metathesis polymerization of cycloalkenes and alkynes formulated by Katz (41) are completely analogous. Moreover, it is possible to represent by a metallo-square scheme the mechanisms of σ-bond metathesis and β-elimination. Scheme 1.3 gathers together the different organometallic reactions involving a metallo-square (that can eventually have puckered shapes).

Scheme 1.3   Square schemes involved in the mechanisms of catalytic organometallic reactions (the metallosquares can eventually have puckered shapes).

Metal-carbon double and triple bonds in which the transition metal is in a "low oxidation state" were discovered by E. O. Fischer.
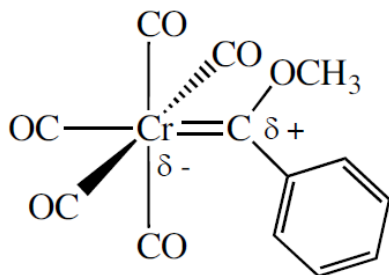
1964

"carbene"
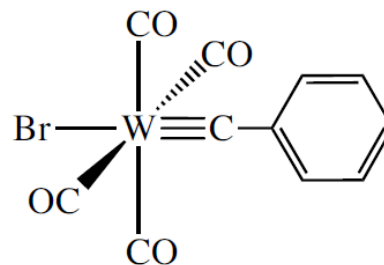
1973

"carbyne"

Beta hydride elimination in an ethyl complex

Known Group 4 Peralkyl Complexes (M = Ti, Zr, Hf) in 1973

All alkyls lack one or more hydrogen atoms
on the atom β with respect to the metal.

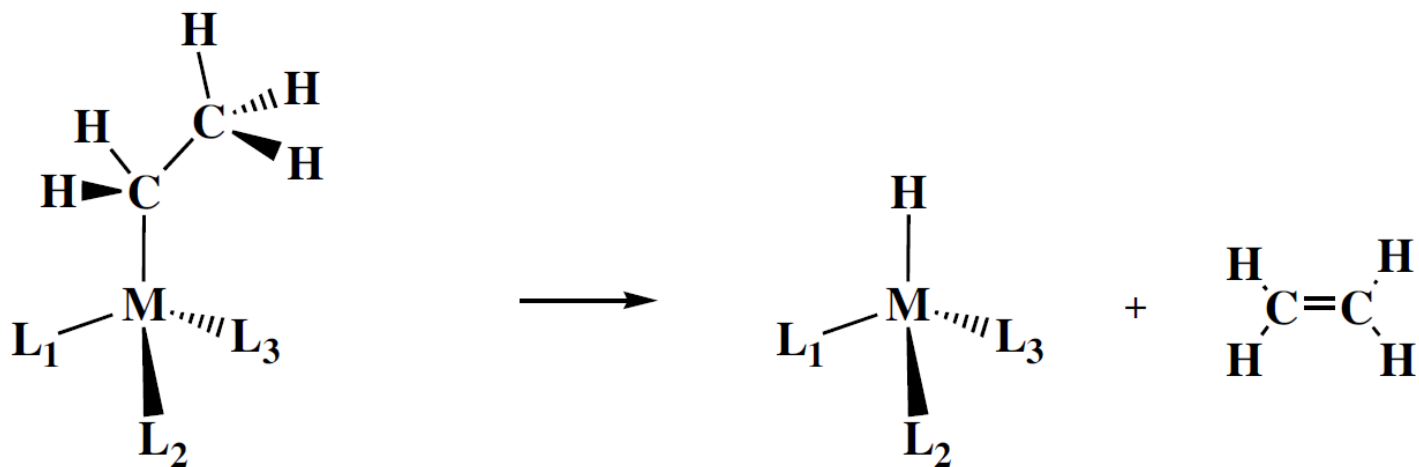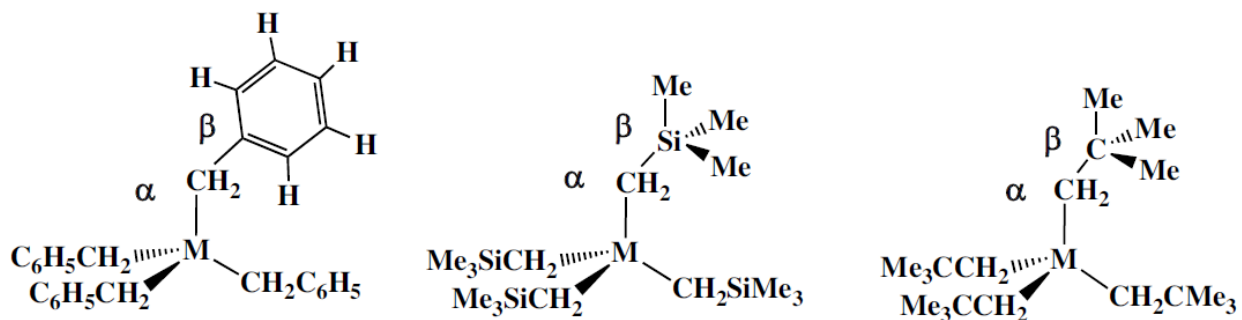Also inspired by Schmidbauer' synthesis of pentaalkyl phosphorous and arsenic derivatives, Schrock, then at Du Pont, synthesized [TaMe₅], [Ta(CH₂Ph)₅] (47) and tried to synthesize [Ta(CH₂CMe₃)₅], which, analogously, would not contain β-hydrogens and thus, according to this principle, should have been stable. An α-elimination reaction occurred, however, upon attempting to coordinate the fifth neopentyl group, which produced one mole of neopentane and led to the isolation of the first stable metal–alkylidene complex, [Ta(CH₂CMe₃)₃(=CHCMe₃)] that was reported in 1974 (Scheme 1.4) (50).
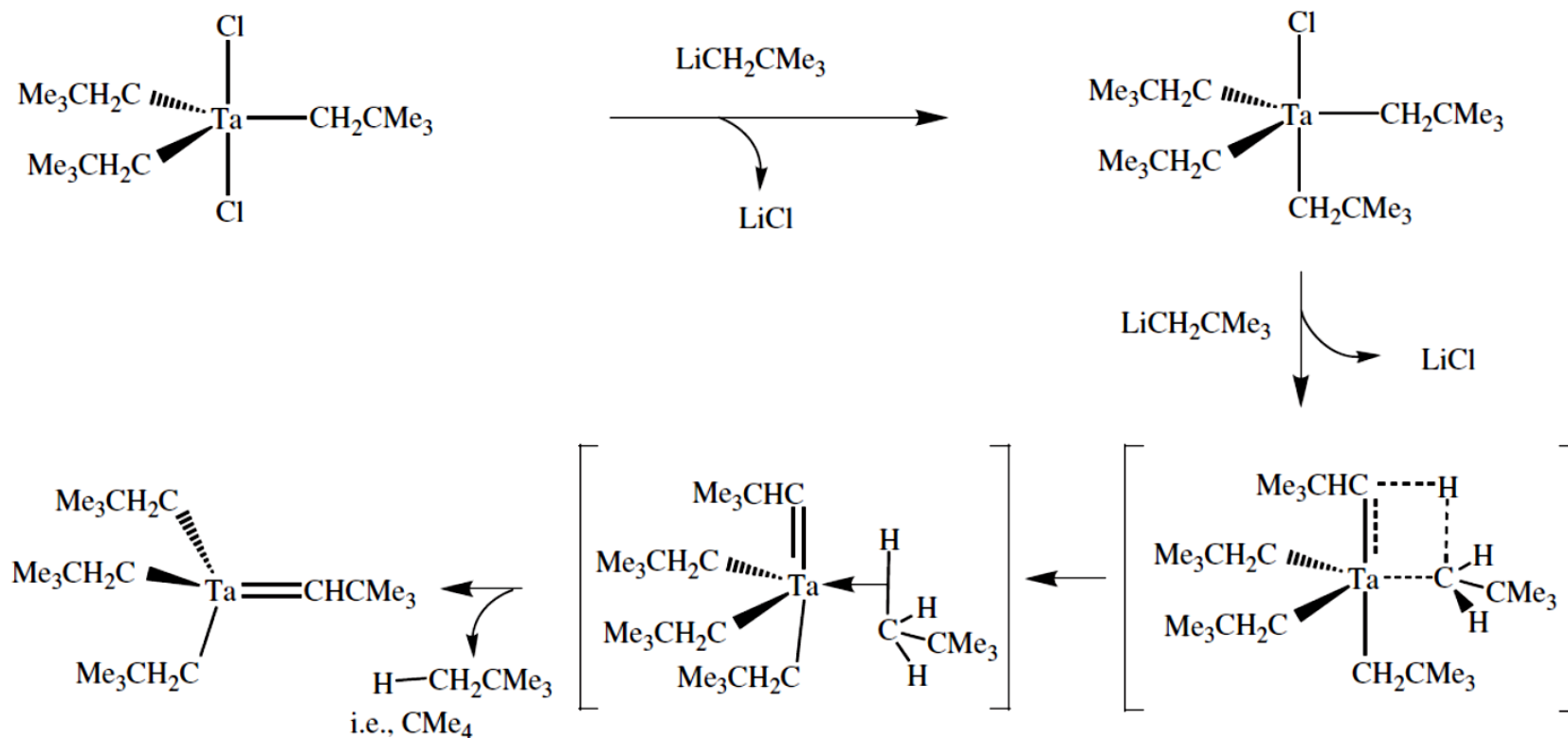
Scheme 1.4 σ-bond metathesis mechanism in the formation of Schrock's first neopentylidene complex.
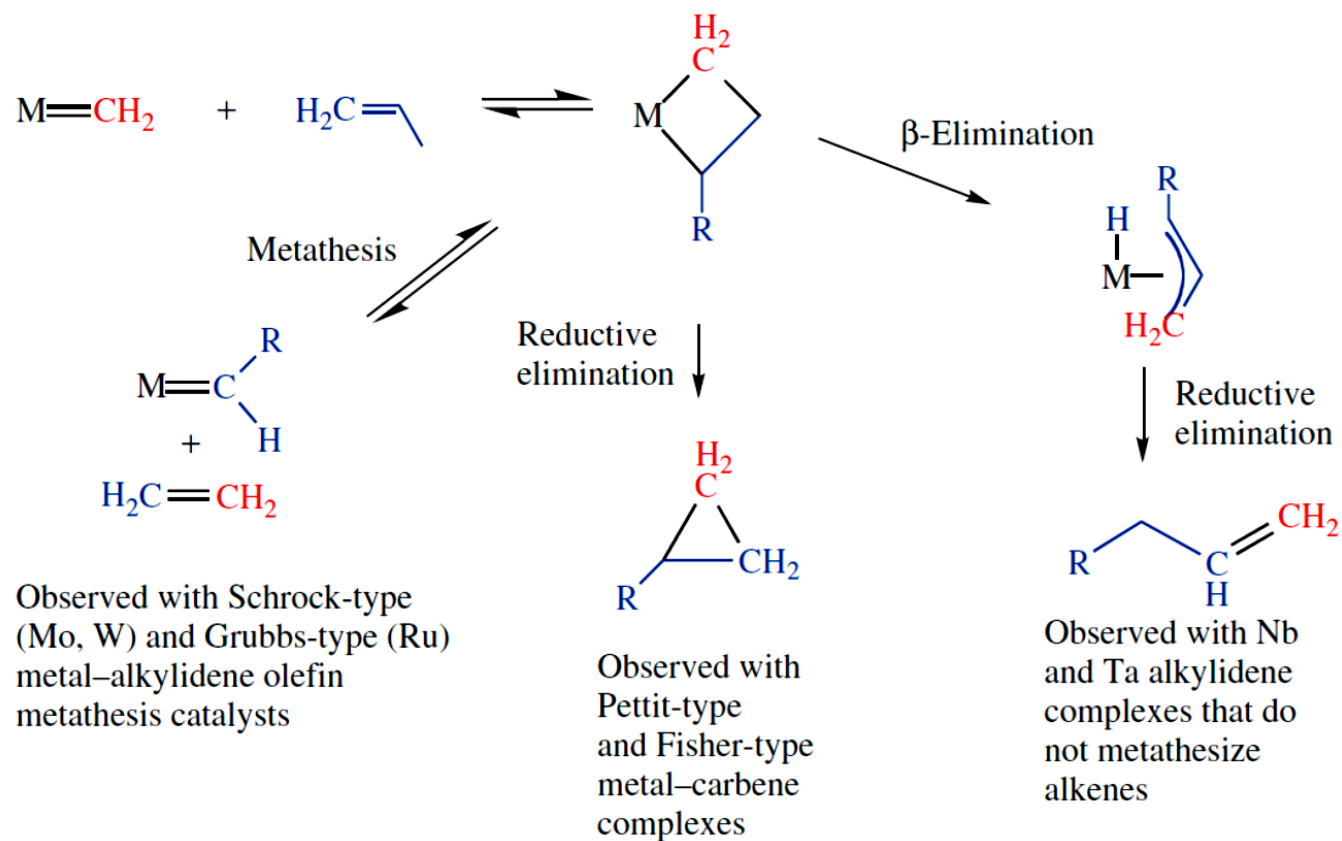
Scheme 1.5 The three modes of evolution of metallacyclobutanes formed by reaction between a metal–carbene complex and an olefin.
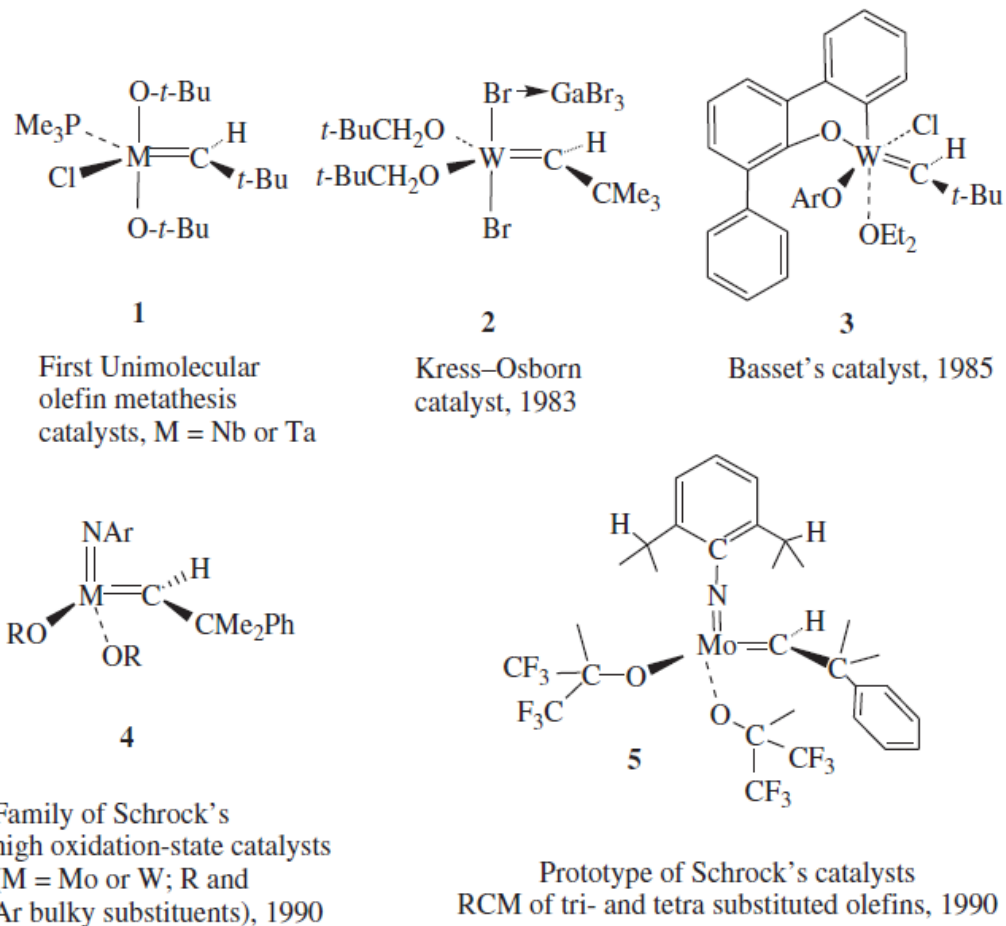
Primi catalizzatori per metatesi

Figure 1.4 Early and optimized "unimolecular" Nb, Ta, Mo, and W metal–alkylidene catalysts of olefin metathesis.

Schrock's Metathesis Catalyst

■ Commercially available, as is synthetic precursor Mo(CHt-Bu)(NAr)(OTf)$_2$(dme)

■ Must be handled under Ar or N$_2$ using dry solvents and substrates

■ Relatively intolerant of protons on heteroatoms (RCOOH, RSH, ROH, etc.) and some functionalities (eg. RCHO)

■ Tolerant of S, P and nitrile functional groups

■ High reactivity
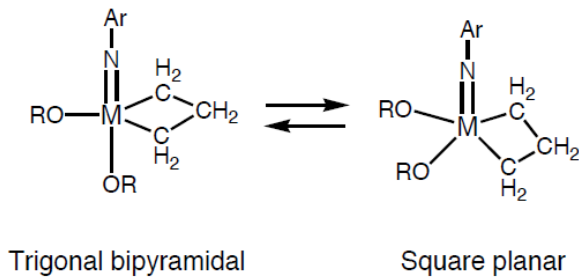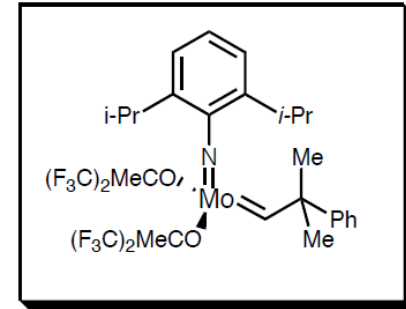
Structural Features

■ Electon deficient Mo(VI), 14 electron species

■ Pseudo-tetrahedral coordination sphere

■ NAr ligand, OR ligands, and initial alkylidene need to be bulky to allow for isolation.

■ Electron withdrawing alkoxides increase electrophilicity of metal center, hence increasing reactivity.

Trigonal bipyramidal   Square planar

Metal-Centered-Functional Group
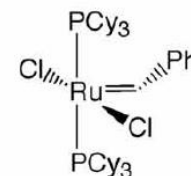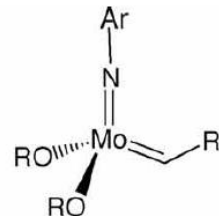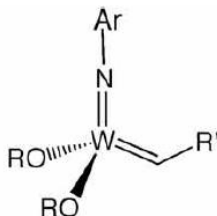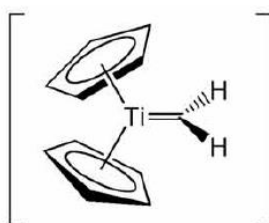
Titanium	Tungsten	Molybdenum	Ruthenium
Acids	Acids	Acids	**Olefins**
Alcohols, Water	Alcohols, Water	Alcohols, Water	Acids
Aldehydes	Aldehydes	Aldehydes	Alcohols, Water
Ketones	Ketones	**Olefins**	Aldehydes
Esters, Amides	**Olefins**	Ketones	Ketones
Olefins	Esters, Amides	Esters, Amides	Esters, Amides

Increasing order of reactivity ↑

functional group tolerance →

← Activity →

Background: Metal Carbenes

$L_nM{=}C{\overset{X}{\underset{Y}{\big<}}}$
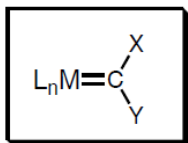
- Definition: Transition metal complex possessing a formal metal to carbon double bond
- X, Y = alkyl, aryl, H, or heteroatom (O, N, S, Halogen)
- Two types of metal carbenes: Fischer-type and Schrock-type

$Cp_2(Me)Ta{=}CH_2$ Schrock-type
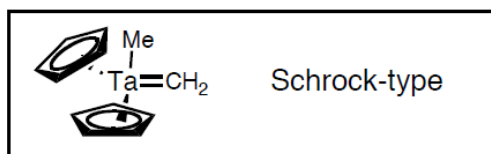
- high oxidation state early TM

- Substituents (X & Y) are H or alkyl

- Ligands are generally good σ or π donors

- Nucleophilic carbenes: electrophile attacks at $C_{carbene}$

- $C_{carbene}$ is X_2-type ligand: metal oxidation state changed by +2

Metal   carbene (sp)
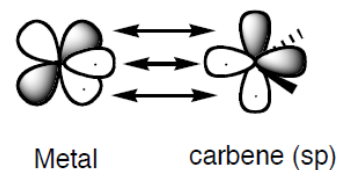
Catalyst Comparisons

Grubbs Catalyst(s)

- Less reactivity; greater selectivity for less bulky and or strained alkenes

- Bench stable

- Higher substrate functional group tolerance

Schrock alkylidene

- Greater reactivity with bulky and e^- deficient alkenes

- Inert condition-stable

- Low substrate functional group tolerance

Grubbs: Ru

Among the late transition metals, ruthenium is known as a *magic metal* by organometallic chemists. Despite a promising start with Pettit's (21,53) elusive methylene complex and its cyclopropanation chemistry upon reaction with olefins, an iron-based metathesis catalyst has not yet been discovered. The first ruthenium carbene complex, $[RuCp\{=C(Me)OMe\}(CO)(PCy_3)][PF_6]$, an 18-electron complex of Fischer-type, was synthesized by Malcolm Green's group in Oxford (78) but did not show any metathesis activity. The success of Grubbs' approach to stable benzylidene complexes containing the electrophilic benzylidene ligand may appear, by comparison, somewhat surprising, but it is due to the neutrality of the complexes, thus affording a considerably reduced electrophilicity of the carbene ligand compared to cationic complexes, and the great versatility of ruthenium that forms stable 16-electron complexes.

Grubbs: Ru – 1° generation

This catalytic reaction was all the more remarkable as it was conducted in water (81). Shortly afterward, he could show, in the course of the same reaction, the formation of a Ru-alkylidene intermediate, then the polymerization of cyclooctene, an olefin with little constraints, when the alkylidene ligand source was ethyl diazoacetate added to the aqueous solution of $[Ru(H_2O)_6](OTs)_2$ (82). Consecutively and according to the same logic, a great step forward was accomplished by Grubbs in 1992. He reported the first molecularly well-defined ruthenium−carbene complex that promoted the ROMP of low strain olefins as well as the catalytic RCM of functionalized dienes without the need of a co-catalyst (83). Grubbs showed that these vinylidene complexes, $[RuCl_2(PR_3)(=CH−CH=CPh_2)]$ (R = Ph, **7**, or Cy), were efficient molecular catalysts for these polymerization

The complex $[Ru(=CHPh)Cl_2(PCy_3)_2]$, **8**, is now known as the *first-generation Grubbs catalyst* and is even today the metathesis catalyst most used by organic chemists, because of its stability in air and compatibility with a large variety of functional groups (except for amines, nitriles, and basic media) (87). Subsequently, the best organometallic research groups also offered astute alternative syntheses to Grubbs' catalysts in the late 1990s (88−91).

6 Grubbs (1988)

7 Grubbs (1992)

8 Grubbs (1995)
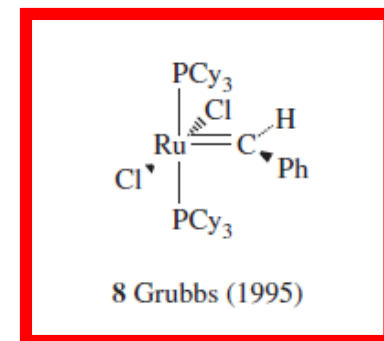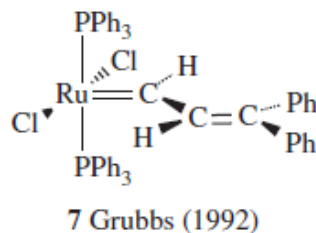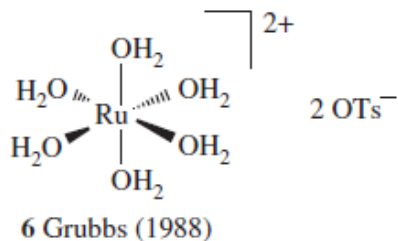
Grubbs: Ru – 2° generation

Fine mechanistic studies with this catalyst led Grubbs' group to conclude that the mechanism first involved the dissociation of one phosphine to generate the reactive 14-electron ruthenium intermediate for coordination of the olefin. In order to supposedly favor this dissociative step, Grubbs introduced, in place of one phosphine, an *N*-heterocyclic (NHC) bis-amino carbene ligand that is relatively stable, even in the free form obtained by deprotonation of the corresponding imidazolium cation (92). These NHC ligands are excellent σ-donors without π-acceptor properties and have been 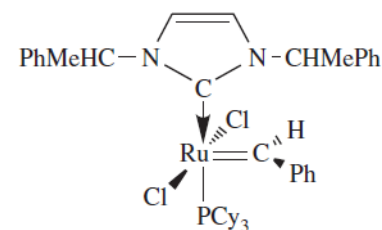known for several decades, but they have only recently become very popular in organometallic chemistry and catalysis (92–95). It was Herrmann's group (93) that first synthesized ruthenium complexes with two such NHC carbene ligands in the context of the catalysis of olefin metathesis, but their catalytic activity was shown to be modest. In Grubbs' second-generation catalysts **9** and **10** containing only one such ligand, the electron density at the ruthenium center is increased, which favors alkene coordination from the 14-electron intermediate. Thus, the second generation of Grubbs catalysts [RuCl$_2$\{C(N(mesityl)CH$_2$)$_2$\}(PCy$_3$)(=CHPh)] containing a single NHC carbene ligand and its catalytic activity in metathesis were successively proposed within a few months by the groups of Grubbs (96,97), Nolan (98), and, with a variation of the NHC ligand, Fürstner and Herrmann (99)
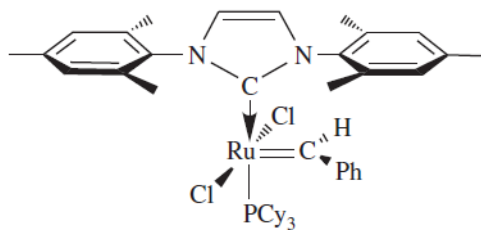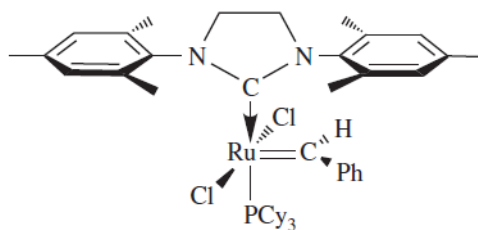
9 Nolan, Grubbs (1999)   **10** Grubbs (1999)   **11** Fürstner, Herrmann (1999)

Grubbs: Ru – 3° generation

Grubbs' catalyst **15**, simply obtained upon addition of a pyridine to **10**, are presently the most used catalysts for efficient cross-metathesis reactions. These commercially available catalysts are even more active than Grubbs' first-generation catalyst **8**, although they are also more thermally stable than **8** (Fig. 1.5) (100–107).
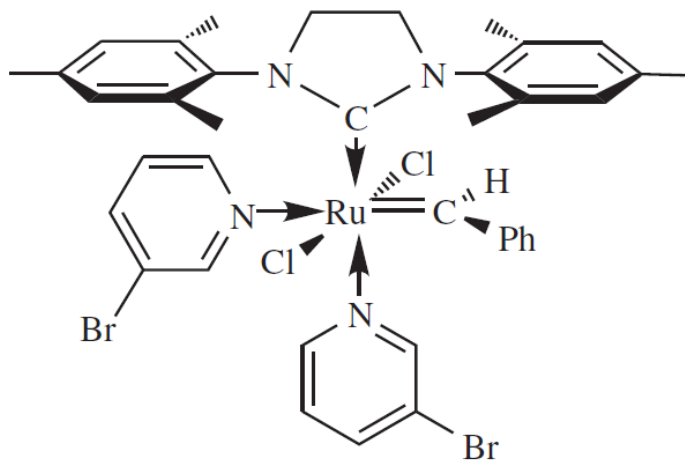

15 Grubbs (2001)

Grubbs: Ru

Probably more than 500 ruthenium metathesis catalysts have been reported to date, including all ligand variations, and all these complexes react with olefin eventually, after phosphine or ether (or other heteroatom) ligand decoordination, that is, at the 14-electron stage, to give metathesis via 14-electron ruthenacyclobutane intermediates (130).

Although the ruthenium metathesis catalysts are 16-electron complexes that require ligand decoordination before olefin coordination (Scheme 1.7), Piers' group
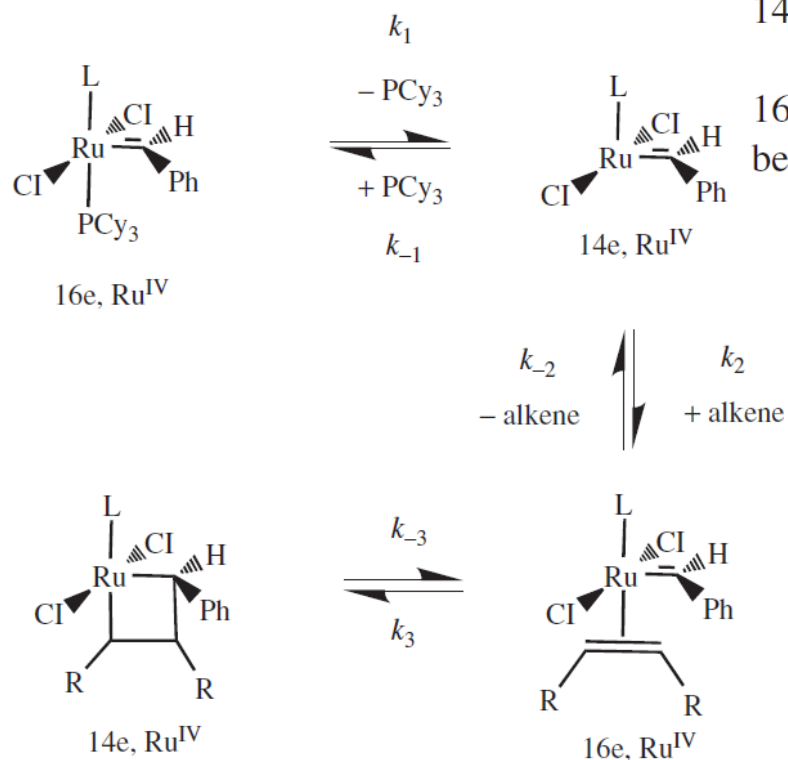
Scheme 1.7 General mechanism of the olefin metathesis reaction with the Ru catalysts. With $L = PCy_3$ (complex **8**), $k_1 = 10^2$; $k_2/k_{-1} = 10^{-4}$; with $L =$ saturated NHC (complex **10**), $k_1 = 1$; $k_2/k_{-1} = 1$. It is the faster complexation of olefins by the 14e intermediate that makes the catalyst **10** more active than **8** (not the phosphine decoordination step) (107).

Metathesis in water

Classic examples include the use of ruthenium benzylidene catalysts such as **21–23** in aqueous solvents leading to homogeneous mixtures when water was added to a water-miscible organic solvent added in sufficient quantities to dissolve the substrates and catalyst (Fig. 1.7) (151,152).
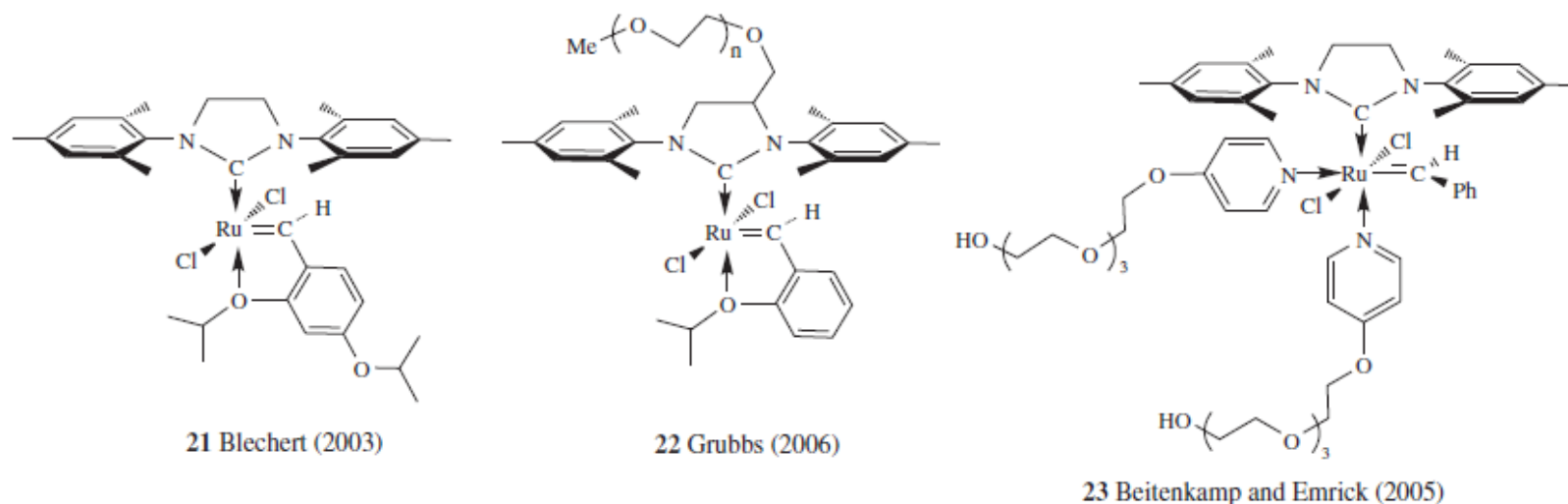

21 Blechert (2003)

22 Grubbs (2006)

**23** Beitenkamp and Emrick (2005)

Figure 1.7 Examples of hydrophilic neutral ruthenium complexes that catalyze metathesis olefin reactions in aqueous solvents: **21** catalyzes RCM (but not CM) in CH_3OH/H_2O or DMF/H_2O mixtures. **22** and **23** catalyze RCM (**22**) and ROMP reactions of some water-soluble substrates (150).

Metathesis on water

Metathesis "on water" is a very interesting concept that was developed by Grela's group with standard ruthenium benzylidene catalysts that are, as substrates, water insoluble. Such reactions were conducted using ultrasonification that produces emulsions in which CM (with electron-poor olefins), RCM, and EYM took place smoothly in quantitative yields (153). Metathesis in aqueous emulsions containing a surfactant has been broadly applied to polymer syntheses

ter with Grubbs catalyst **10**. Astruc's group reported efficient RCM, CM, and EYM of water-insoluble substrates with low amounts of commercial Grubbs catalysts **8** and **10** under ambient condition in water only and air, using a water-soluble dendrimer serving as a nanoreactor host with hydrophobic interior. The water-insoluble catalyst was recovered by filtration after the reaction, and the water-soluble dendrimer was used in very small amounts and re-used at least 10 times without loss (162). Nicolaou's group (163) reported the CM catalysis of vancomycin derivatives in a heterogeneous mixture of water and CH_2Cl_2 (>95 : 5) using $[C_{12}H_{25}NMe_3]^+Br^-$ as the phase-transfer catalyst. In another approach, the commercial

R = H or Me

24 Grela (2002)

26
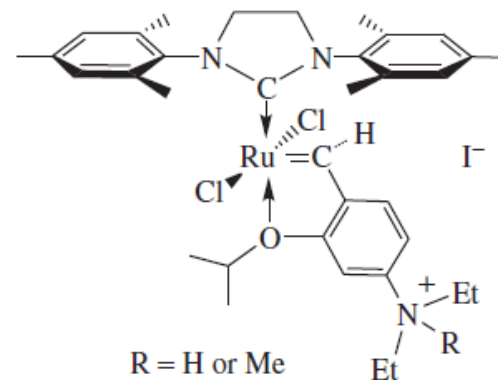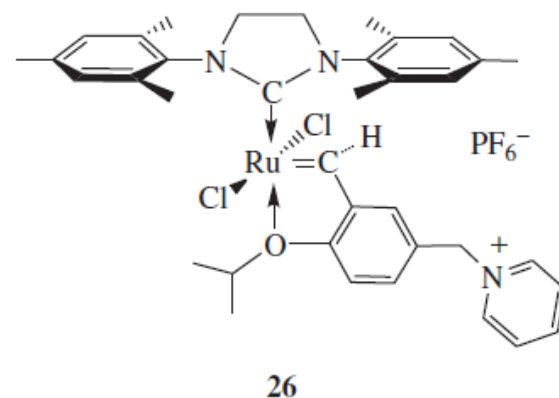
Grela, Mauduit and Clavier (2006)

Scheme III

[Ru]-**2**
(7 mol%)

CH₂Cl₂, 50°C
74%

(R)-(–)-Muscone
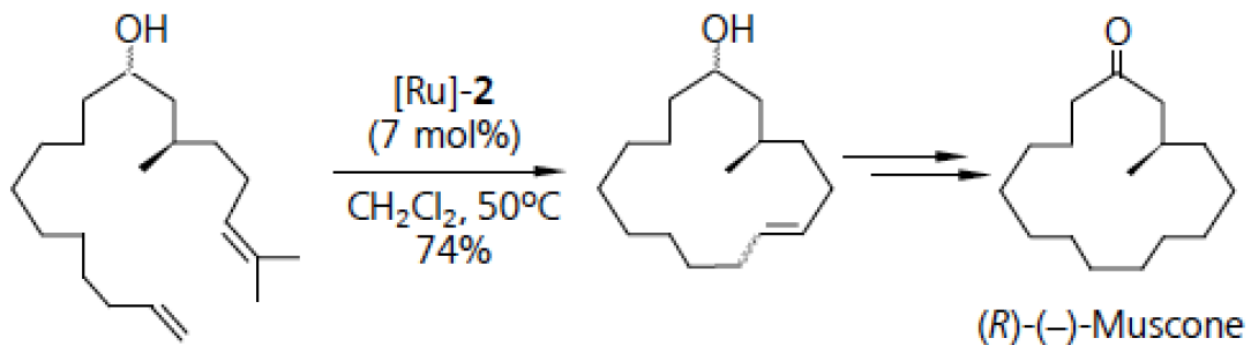
A very soft, sweet, musky odor with a warm animal tonality, reminiscent of the natural Tonkin musk. It can be used to give elegant and warm animal notes and adds lift and diffusion to any perfume. Important for the reconstitution of natural musk.
Widely used in fragrances.

Mo or W catalyzed alkyne metathesis reactions are useful in organic chemistry.
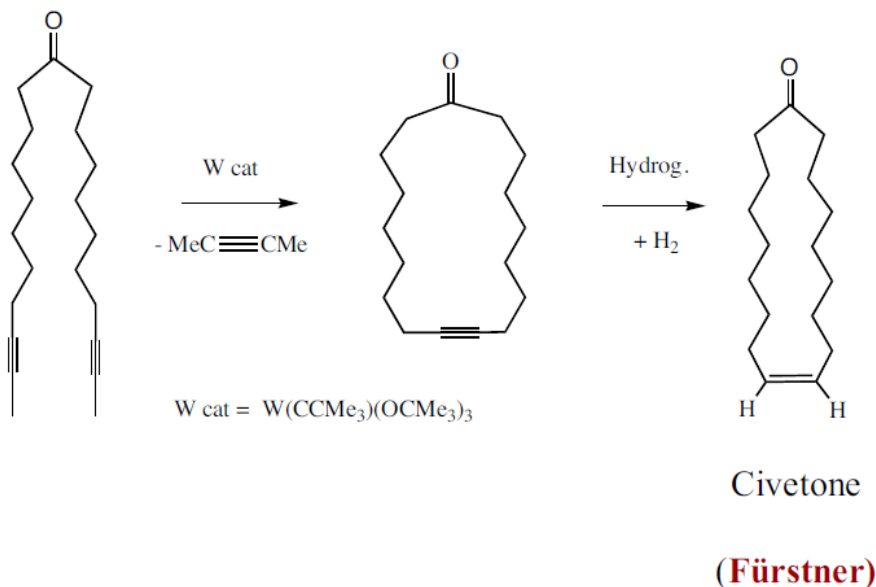
African Civet (wikipedia)

W cat

- MeC≡CMe

Hydrog.

+ H₂

W cat = W(CCMe₃)(OCMe₃)₃

H   H

Civetone

(Fürstner)
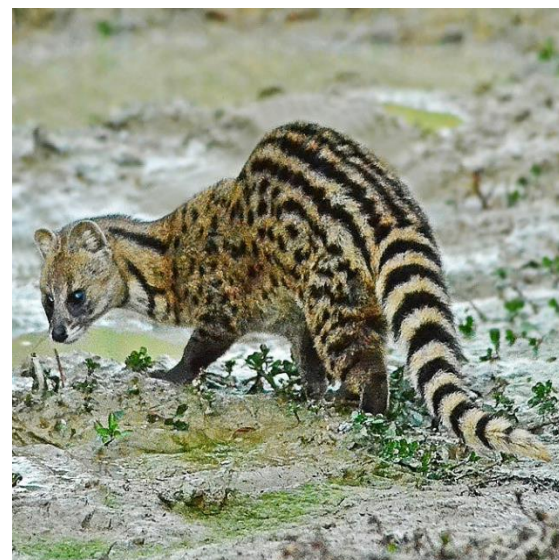
Olefins do not appear to react with M-C triple bonds.

Civetone is a macrocyclic ketone and the main odorous constituent of civet. It is a pheromone sourced from the African civet. It has a strong musky odor that becomes pleasant at extreme dilutions. Civetone is closely related to muscone, the principal odoriferous compound found in musk. Today, civetone can be synthesized from precursor chemicals found in palm oil.