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OLEFIN METATHESIS REACTIONS: FROM A HISTORICAL ACCOUNT TO RECENT TRENDS

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1.1 INTRODUCTION

Metathesis (1–5) occupies a central place in the synthesis of complex organic molecules and polymers, and the major problems concerning the catalysts have been solved, including the presence of various functional groups in the organic substrates. Unlike palladium catalysis of cross carbon–carbon bond formation that is the other break-through in the formation of organic skeleton architectures, the metathesis reactions do not consume stoichiometric amounts of base, producing stoichiometric amounts of salts as wastes. In this sense, the metathesis reactions belong to the field of green chemistry, saving a number of steps in total syntheses and avoiding the handling and production of inorganic wastes. The discovery of homogeneous catalysis by Osborn and Wilkinson (6), allowing the hydrogenation of olefins, and its efficient asymmetric version by Kagan (7) considerably enhanced the possibilities of bringing about high selectivity and approaching a perfect knowledge of the molecular mechanisms leading to improvements and optimization. Thus, after the pioneering research of American industrial chemists in the 1960s, a significant advance in metathesis chemistry has been the mechanistic insight of Yves Chauvin in the early 1970s in disentangling the "black box" and the intense academic research by organometallic chemists at the end of the twentieth century (8), in particular by the groups of Robert Grubbs at Caltech and Richard Schrock at MIT in their quest for transition-metal-alkylidene (or benzylidene) and alkylidyne metathesis catalysts. Therefore, in this historical chapter, we wish to underline the role of the development of ideas and research efforts that have led to a success story in the advancement of metathesis chemistry and its applications. This chapter also includes examples of the most recent and major developments and applications of the various metathesis reactions, with emphasis on catalyst design and sustainable chemistry.

## 1.2 THE METATHESIS REACTIONS: EXCHANGES OF CARBENES AND CARBYNES

The word metathesis comes from the Greek $\mu\epsilon\tau\alpha\theta\epsilon\sigma\iota\zeta$ that means transposition. Metathesis of ions between two ion pairs is a long-known example of metathesis in which two ion pairs exchange their partners (Eq. 1.1) (8).

$$A^+ B^- + C^+ D^- \rightleftharpoons A^+ D^- + C^+ B^- \qquad (1.1)$$

Likewise, the exchange of the two carbenes of an olefin with those of another olefin molecule (Eq. 1.2) was first called *olefin metathesis* by Calderon (9) in 1967, but this reaction requires a catalyst.

$$\qquad (1.2)$$
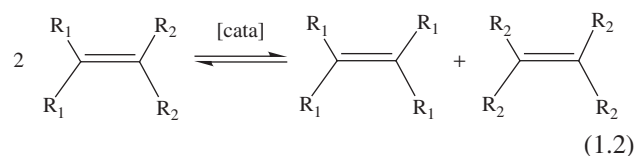
The principle is extended to the exchange of the two carbynes of alkyne molecules

$$2 \; R^1C \equiv CR^2 \; \rightleftharpoons^{\text{cata}} \; R^1C \equiv CR^1 + R_2C \equiv CR^2$$

$$\qquad (1.3)$$
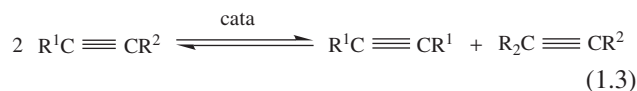
The metathesis reactions are under thermodynamic control, which means that the reactions of Eqs 1.2 and 1.3 present the inconvenient of being equilibrated. The problem is usually solved by using terminal olefins that produce gaseous ethylene as one of the metathesis products, which displaces the reaction toward the metathesis products. For alkyne metathesis, terminal alkyne metathesis is possible (see Section 1.15) but of little use due to competitive alkyne polymerization, so methyl-terminated alkynes are used for metathesis, which produces 2-butyne that is also removed according to the same principle.

1.3 THE EARLY DAYS OF OLEFIN METATHESIS IN AMERICAN INDUSTRY

The uncatalyzed reaction of propene upon heating at 852 °C had been reported in 1931 by Schneider and Fröhlich (10) to give very low amounts of ethene and 2-butenes among other products, but the publication remained ignored for a long time. Ziegler and Natta's discoveries of ethylene and propylene polymerization in 1953 induced considerable research interest in olefin polymerization reactions and their mechanisms. The first catalyzed metathesis reactions were reported in the late 1950s when industrial chemists at Du Pont, Standard Oil and Phillips Petroleum (H. S. Eleuterio, E. F. Peters, B. L. Evering, R. L. Banks, and G. C. Bailey) reported that propene led to ethylene and 2-butenes when

it was heated with molybdenum [in the form of the metal, oxide, or [Mo(CO)$_6$] on alumina (Fig. 1.1)] (11–16).

The first polymerization of norbornene by the system WCl$_6$/AlEt$_2$Cl was independently reported in 1960 by Eleuterio (11,15) and by Truett et al. (13), but it was recognized only in 1967 by Calderon (9,17) at Goodyear that the polymerization of cyclic alkenes to polyalkenemers and the disproportionation of acyclic alkenes were the same type of reaction, the metathesis. The following year, labeling experiments by Calderon (9,17) at Goodyear and Mol (18) in Amsterdam confirmed this key finding.

## 1.4 UNSUCCESSFUL ATTEMPTS TO SOLVE THE MECHANISTIC PUZZLE

The first mechanistic suggestion to solve the mechanistic puzzle came in 1967 from Bradshaw et al. (19) who proposed a four-centered cyclobutane–metal intermediate. This hypothesis was supported the following year by Calderon (20). No other hypothesis appeared in the United States for three years, and this mechanism seemed to be adopted as being "conventional" by the metathesis community in the United States. Yet, cyclobutanes are not produced by metathesis, and they are not metathesis substrates either. Other mechanistic hypotheses by American chemists appeared only in the early 1970s. In 1971, the brilliant organometallic chemist Pettit (21,22), who had generated the first transition-metal

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History of the olefin metathesis reactions

Ethylene and 2-butenes are found in small amounts upon heating propene at 852 °C: Schneider and Fröhlich (1931)

Heterogeneous metathesis catalysts: M(CO)$_6$ (M = Mo or W) on alumina or silica, or Re$_2$O$_7$ (150–500 °C): Eleuterio (1956) and Bank (1964)

Chauvin mechanism: metal–alkylidene + olefin and metallacyclobutane intermediate, 1971

First stoichiometric metathesis reaction between a metal–carbene and an olefin, Casey (1974)

First isolated metal–alkylidene complex, [Ta=CHBu^t(CH$_2$Bu^t)$_3$]: Schrock (1974)

First catalytic metathesis reaction using a unimolecular catalyst, [LnTa=CHBu^t]: Schrock (1980)

First unimolecular ruthenium–carbene metathesis catalyst, [Ru=C=CHPh(PR$_3$)$_2$Cl$_2$]: Grubbs (1992)

First ruthenium–benzylidene metathesis catalyst: [Ru=CHPh(PCy$_3$)$_2$Cl$_2$]: Grubbs (1995)

Chiral Mo–alkylidene catalyst for enantioselective olefin metathesis: Schrock-Hoveyda (1998)

Second-generation Grubbs-type catalysts with *N*-heterocyclic carbene ligands L [Ru=CHPh(PCy$_3$)(L)(Cl): Grubbs, Nolan, Fürstner-Herrmann (1999) (and chiral version: Grubbs, 2001)

Robust isopropoxybenzylidene Ru catalysts: Hoveyda, Blechert (with NHC), Grela (with NO$_2$), 2000–2002

Figure 1.1 Dates of the history of olefin metathesis.

methylene species $[Fe(\eta^5\text{-}C_5H_5)(CO)_2(=CH_2)][BF_4]$, suggested the possibility of a tetra(methylene)metal intermediate in which the four methylene units were bonded to the transition metal (23–25). Double oxidative addition to a transition-metal center is not possible, however (24,25). Grubbs (26) proposed rearranging metallocyclopentane intermediates and cyclobutane complexed to a carbene (27). Neither of the mechanisms mentioned above (Fig. 1.2) fit the data, and the olefin metathesis mechanism remained rather mysterious in the United States until the mid 1970s.
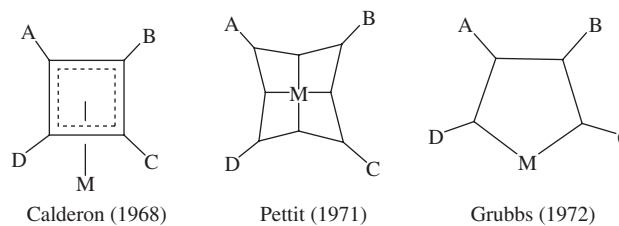

Figure 1.2 Erroneous intermediates proposed around 1970 for the olefin metathesis mechanism.

1.5 THE CHAUVIN MECHANISM: A METATHESIS DANCE

Chauvin from the Institut Français du Pétrole, had three key findings in mind when he envisaged the mechanism of olefin metathesis: the report of Fischer (28) on the synthesis of a tungsten–carbene complex, $[W(CO)_5\{C(CH_3)(OCH_3)\}]$,

that of Natta (29) on the polymerization of cyclopentene by ring-opening catalyzed by a mixture of WCl_6 and $AlEt_3$, and that of Banks and Bailey (14) on the formation of ethylene and 2-butene from propene catalyzed by $[W(CO)_6]$ on alumina. Consequently, Chauvin and his student Hérisson published their proposition of metathesis mechanism in 1971 (Scheme 1.1) (30).
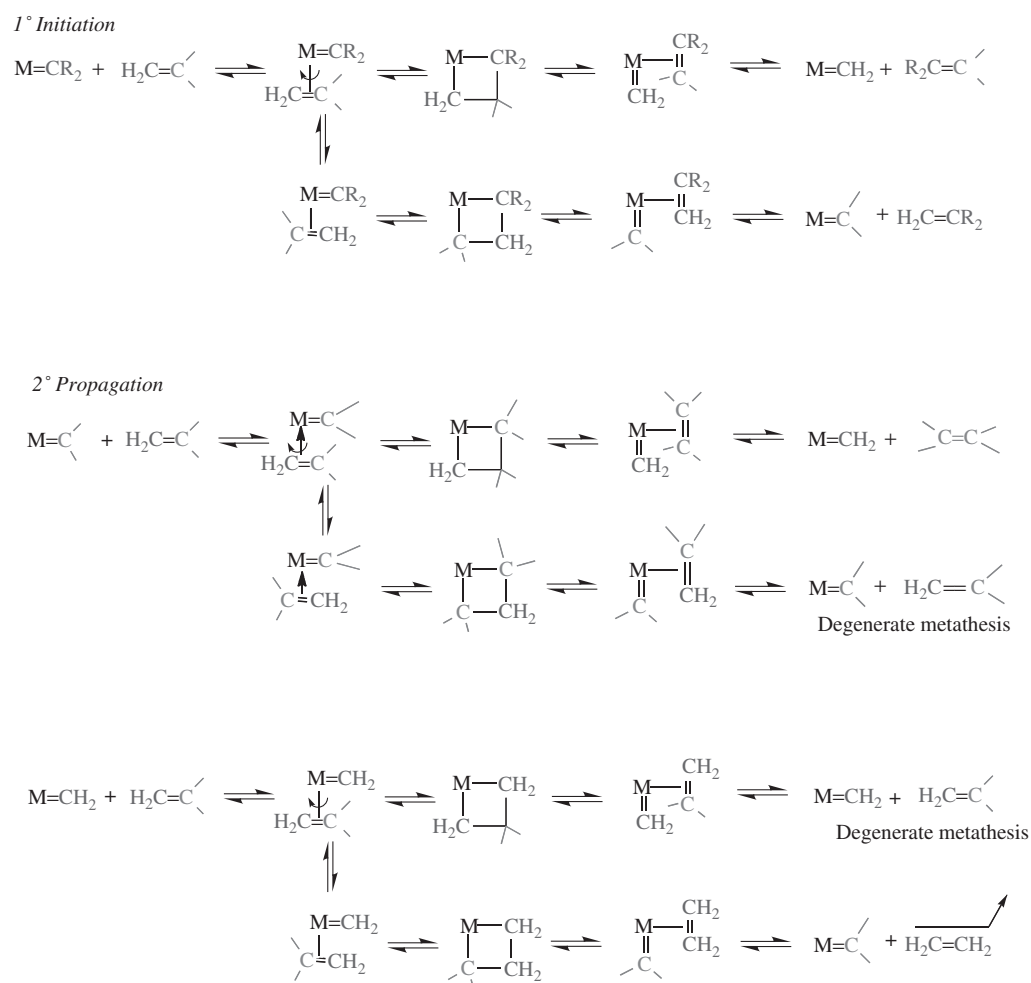
Scheme 1.1 Linear representation of the Chauvin mechanism (including the degenerate metathesis steps).

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 (Schemes 1.1 and 1.2).

In fact, depending on the orientation of the coordinated olefin, the new catalytic cycle can give two different metallacyclobutenes, one leading to the symmetrical olefin and the other leading to the starting olefin. This latter cycle is said to be degenerate olefin metathesis. Thus, the catalytic cycles alternatively involve both metal–alkylidene species resulting from the combination of the metal with each of the two carbenes of the starting olefin (Scheme 1.1).

When the Chemistry Nobel prize was announced on October 5, 2005, Chauvin's metathesis mechanism was compared in a video to a dance in which couples exchange partners, which represents the two carbene fragments of the olefin. The dancers cannot exchange their partner directly, but they have to do the exchange by coupling with a master of ceremony that is the metal center. The master of ceremony also has a partner and, with the entering couple they form a circle so that the master of ceremony can exchange partners within the circle by taking a new partner from the couple. Then with his new partner, he can go to another couple for another exchange, and so on (31).

Chauvin and Hérisson not only suggested the metallacyclobutane mechanism, but also published several experiments to confirm it. For instance, they reported that reaction of a mixture of cyclopentene and 2-pentene led to C-9, C-10, and C-11 dienes in the ratio 1 : 2 : 1. Also, the reaction of a mixture of cyclooctene and 2-pentene led almost exclusively to the C-13 product. The latter reaction, but not the first one, was compatible with Calderon's mechanism. In 1973 and 1976, Chauvin (32,33) published other results showing that the mixture of $WCl_6 + MeLi$ catalyzes the formation of propene by reaction of 2-butene, which was proposed to proceed via methylation of tungsten, followed by the α-elimination in the tungsten–carbon bond of $W-CH_3$ to form a $W(=CH_2)(H)$ species, then metathesis. Here again, Chauvin's intuition was remarkable, because at that time, σ-bond metathesis in d^0 meta-alkyl complexes, that is the only available mechanism to activate such α-C–H bonds, was unknown and was disclosed only more than a decade later by the groups of Watson (Lu) (34), Bercaw (Sc) (35), and Marks (Th) (25,36,37).

The first recognition of Chauvin's valuable mechanism together with an elegant confirmation came from Casey and Burkhardt (38) when they reported that the carbene complex
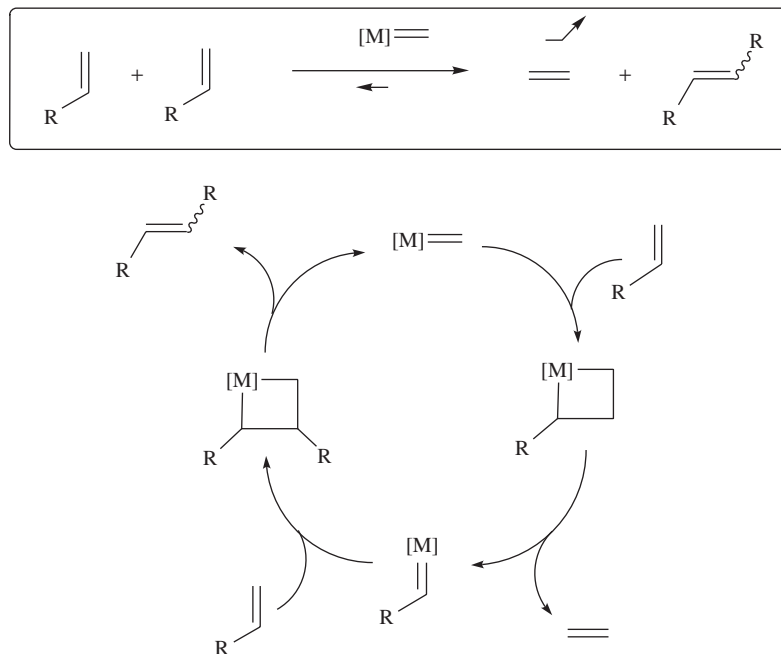
Scheme 1.2   Cyclic representation of the Chauvin metathesis mechanism.

$[W(CO)_5(=CPh_2)]$ reacted with isobutene to form a new olefin, 1,1-diphenylethene (Eq. 1.4), as the major product and that the same complex reacted with $H_2C=C(OCH_3)Ph$ to form 1,1-diphenylethene and the metal−carbene complex $[W(CO)_5\{=C(OCH_3)Ph\}]$ (Eq. 1.5), just as predicted in the Chauvin mechanism.

$$(1.4)$$

$$(1.5)$$
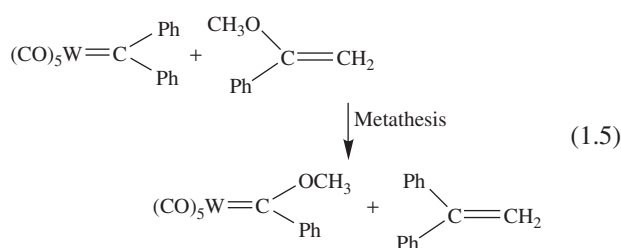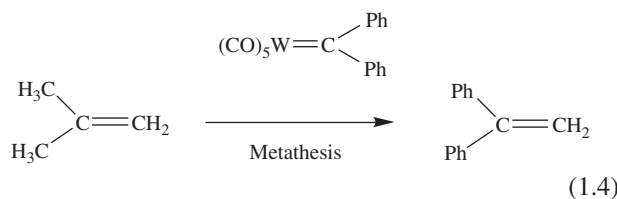
Later, labeling experiments by the groups of Grubbs and Katz (39−41) demonstrated that alkenes underwent non-pairwise exchange as required by the Chauvin mechanism. In particular, Grubbs (39) showed that a mixture of 1,7-octadiene and its analog that was deuterated on both methylene termini underwent metathesis to yield a statistical mixture of d_0-, d_2-, and d_4-ethylene, and that d_0- and d_4-ethylene were not scrambled after their formation. At that point, however, the actual catalytically active species was unknown, because the precatalysts used were 18-electron metal−carbene complexes such as $[W(CO)_5(=CPh_2)]$ or $[W(CO)_5\{C(OMe)Ph\}]$ or eventually metal precursors that did not contain a carbene ligand (38−41). Such complexes cannot bind olefins because the metal valence electron shell does not rise to 20 electrons; hence some decomposition of these pre-catalysts had to occur. Casey had nicely shown that the decomposition was partly limited to a single carbonyl ligand with the former complex, but also half of the starting material decomposed. The second complex that was sometimes used by Katz is more problematic, because carbenes bearing a heteroatom are, like CO itself, singlet carbenes. Thus, contrary to common usage, a double bond between this carbene and the metal should not be used in Fischer-type carbene complexes (28) such as this one (in the same way as the representation of the metal−carbonyl bond that is not written as $M=C=O$). Accordingly, we now know that the Fisher-type metal−carbene complexes are poor metathesis pre-catalysts, and that good tungsten olefin metathesis catalysts systematically have a high oxidation state (4).

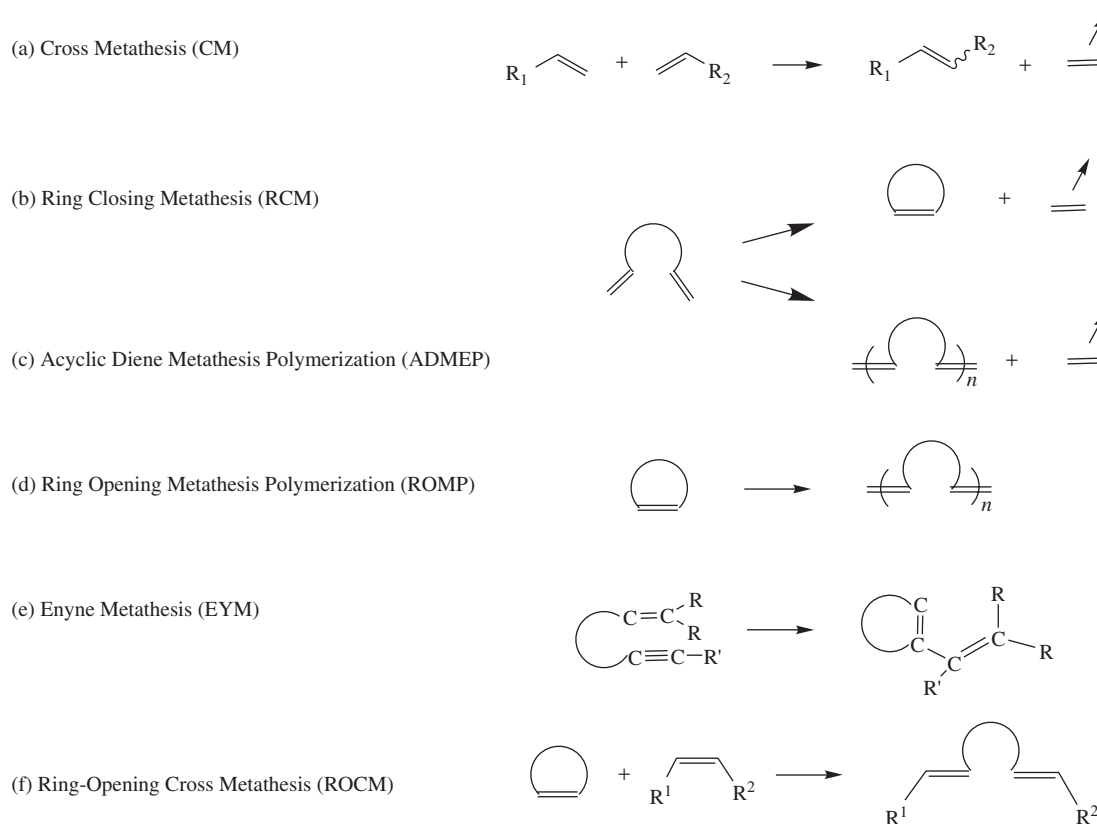## 1.6   THE IMPORTANCE OF THE CHAUVIN MECHANISM FOR OVERALL ORGANOMETALLIC CATALYSIS

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.

Another very important aspect of the Chauvin mechanism concerns the intermediacy of the metallacyclobutane. Such metallocyclobutane complexes are sometimes stable, and some stable metallacyclobutenes have indeed been shown to be involved in metathesis. Elegant studies by Grubbs' group in 1980 showed that Tebbe's complex $[Cp_2Ti(CH_2)(ClAlMe_2)]$, reported in 1978 (42), reacted with olefins in the presence of dimethylaminopyridine to give titanacyclobutanes that slowly catalyze metathesis and could be used to identify all the intermediates in olefin metathesis (43−45).

Chauvin's mechanism applies to the whole range of olefin metathesis reactions, including cross metathesis (CM), ring-closing metathesis (RCM), acyclic diene metathesis polymerization (ADMEP), ring-opening metathesis polymerization (ROMP), enyne metathesis (EYM), and ring-opening cross metathesis (ROCM) (Fig. 1.3) (1−4).

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).

(a) Cross Metathesis (CM)

(b) Ring Closing Metathesis (RCM)

(c) Acyclic Diene Metathesis Polymerization (ADMEP)

(d) Ring Opening Metathesis Polymerization (ROMP)

(e) Enyne Metathesis (EYM)

(f) Ring-Opening Cross Metathesis (ROCM)

Figure 1.3   Various types of olefin metathesis reactions (all proceeding according to the Chauvin mechanism).

1.7   SCHROCK'S HIGH OXIDATION STATE ALKYLIDENE AND ALKYLIDYNE COMPLEXES

From the middle of the nineteenth century to the middle of the twentieth century, chemists believed that metal–alkyl compounds were intrinsically unstable, because of the supposedly too low energy of the metal–carbon bond. Wilkinson (46–48) then synthesized stable binary metal–alkyl complexes that did not contain β-hydrogen, showing that this instability was in fact kinetic, due to β-H elimination, because chemists had been trying to make binary metal–ethyl complexes. Organometallic chemists could then synthesize a whole series of thermally stable binary (and other) metal–alkyl complexes with alkyl groups lacking β-hydrogens, such as methyl, benzyl, neopentyl, trimethylsilylmethyl, and mesityl, even if the metal had less than 18 valence electrons in the valence shell (47,48). Such binary metal–poly(alkyl) complexes have indeed a low number of valence electrons in conflict with the 18-electron rule (49).

Richard Schrock was a PhD student at Harvard of John Osborn, who had been a PhD student of Geoffrey Wilkinson, who was at Imperial College, London, after Harvard had turned down his promotion for tenure. The influence of Wilkinson on his scientific grandson Schrock is seen clearly.

Also inspired by Schmidbauer' synthesis of pentaalkyl phosphorous and arsenic derivatives, Schrock, then at Du Pont, synthesized [TaMe$_5$], [Ta(CH$_2$Ph)$_5$] (47) and tried to synthesize [Ta(CH$_2$CMe$_3$)$_5$], 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(CH$_2$CMe$_3$)$_3$(=CHCMe$_3$)] that was reported in 1974 (Scheme 1.4) (50).

Schrock's group subsequently showed that the α-elimination reaction was quite general when the coordination sphere became crowded in these Ta and Nb complexes. This yielded a rich family of high oxidation state Ta and Nb alkylidene complexes in which the carbenic carbon is nucleophilic, somewhat resembling phosphorus ylids (51,52). At the time of this finding, the detailed mechanism of this reaction was unknown, but as stated above, the σ-bond metathesis that takes the α-elimination reaction into account was recognized 8 years later (34–37). Neither the 18-electron Fischer-type metal–carbene complexes (see above) nor the 10-electron Schrock-type Ta- or Nb-alkylidene complexes gave olefin metathesis upon
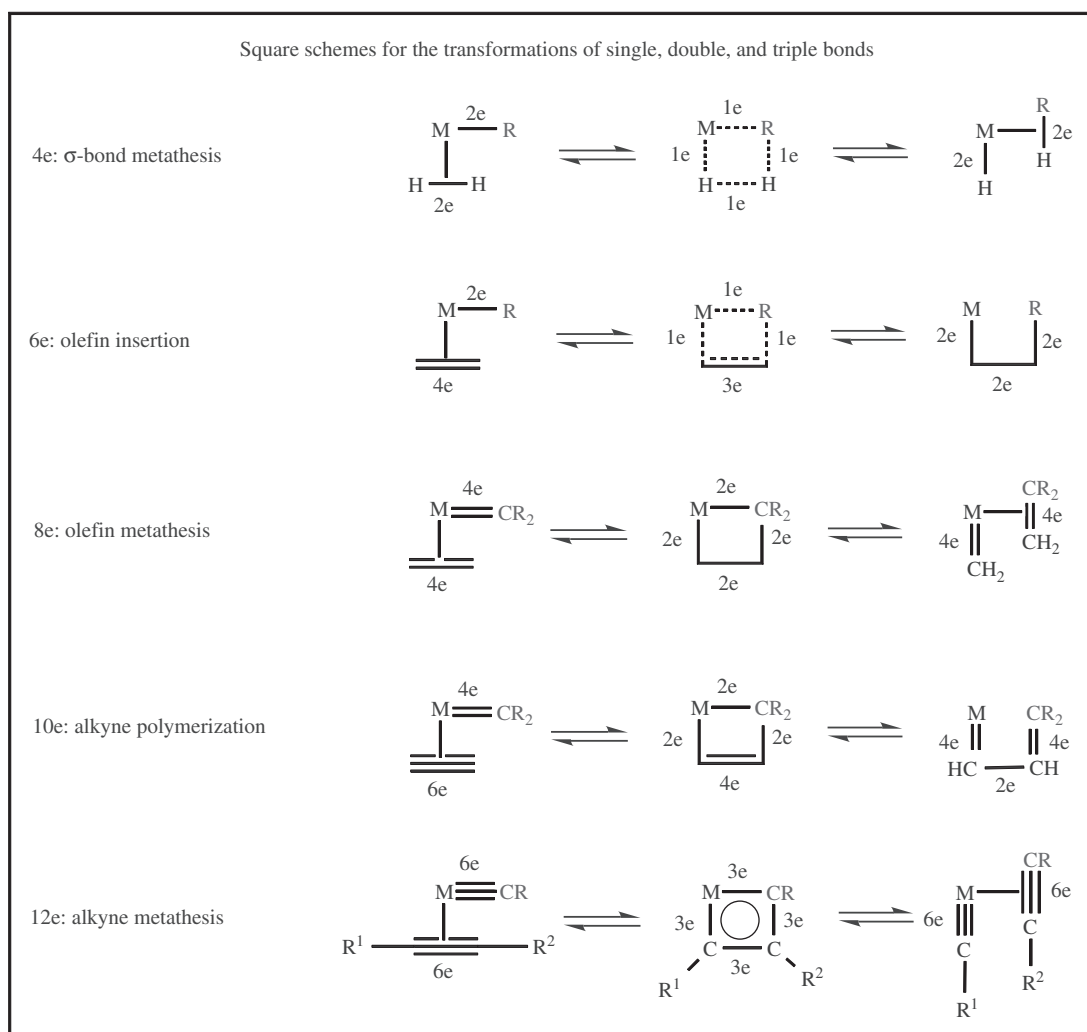
Scheme 1.3   Square schemes involved in the mechanisms of catalytic organometallic reactions (the metallosquares can eventually have puckered shapes).
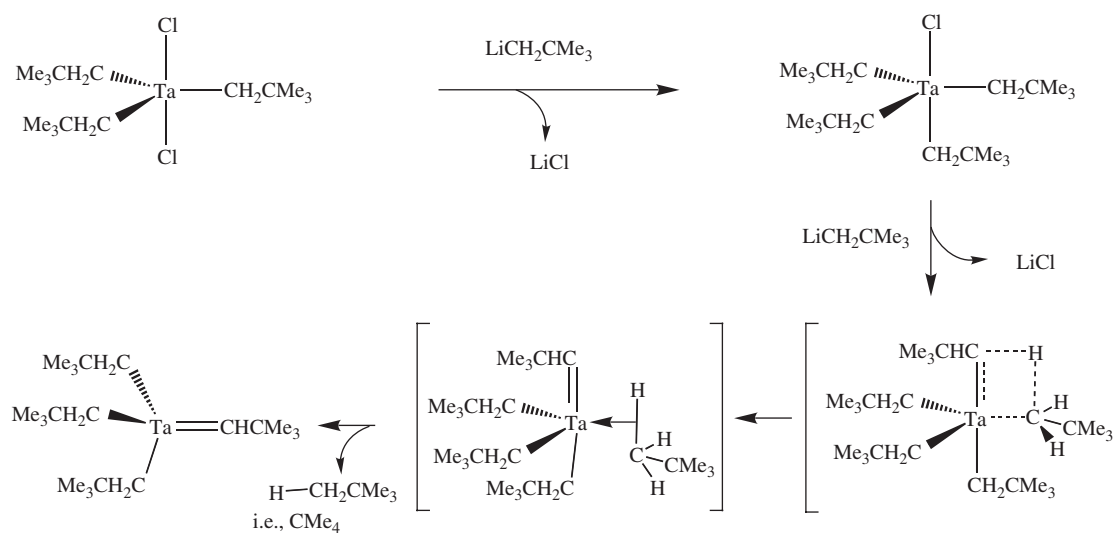
Scheme 1.4   σ-bond metathesis mechanism in the formation of Schrock's first neopentylidene complex.
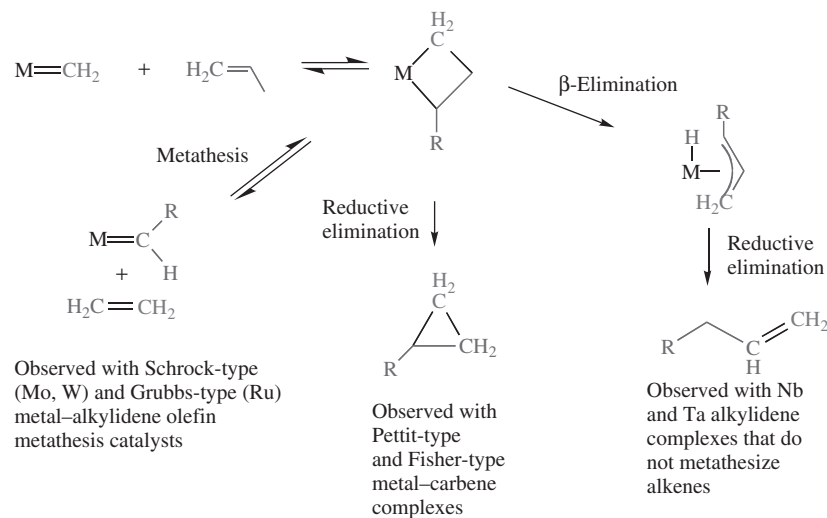
Scheme 1.5   The three modes of evolution of metallacyclobutanes formed by reaction between a metal–carbene complex and an olefin.

reaction with olefins, however, because the metallocyclobutane intermediates gave other products. Fischer-type metal–carbene complexes react with some olefins to give cyclopropanes eventually (but not always) by reductive elimination of intermediate metallacyclobutanes (53), whereas metallacyclobutanes resulting from the reaction of olefins with Schrock-type complexes gave β-H elimination, because they had less than 18 electrons in the Ta valence shell (Scheme 1.5).

The metal–alkenyl hydride species formed in the latter case gave reductive elimination. Then, the free coordination sites allowed reaction with 2 mol of olefins giving tantalacyclopentane intermediate that also underwent β-H elimination followed by reductive elimination to yield for instance 1-butene, when the olefin was ethylene. The metal species thus catalyzed olefin dimerization. Interestingly, Chauvin (54,55) also discovered extremely efficient and selective titanium-based olefin dimerization catalysts that are used industrially. In 1975, Schrock (56) also synthesized at Du Pont the first stable transition-metal–methylene complex, [TaCp$_2$(CH$_3$)(=CH$_2$)] by deprotonation of the cationic Ta-methyl precursor [TaCp$_2$(CH$_3$)$_2$][BF$_4$], and this methylene complex was characterized *inter alia* by its X-ray crystal structure.

It was only in 1980 that Schrock's group at MIT reported a tantalum–alkylidene complex, [Ta(=CH-*t*-Bu)(Cl)(PMe$_3$)(O-*t*-Bu)$_2$], **1** (Fig. 1.4, also Nb and W complexes), that catalyzed the metathesis of *cis*-2-pentene (57).

After Casey's finding in 1974 and stereochemical arguments from the Grubbs and Katz groups, this provided another evidence for Chauvin's mechanism of olefin metathesis with well-defined high oxidation state alkylidene complexes, almost a decade after Chauvin's proposal.

The reason that these complexes catalyzed the metathesis reaction, whereas the other members of the family of niobium– and tantalum–alkylidene complexes failed to do so, was the presence of ancillary alkoxide ligands in the catalysts. Molybdenum and tungsten, however, were obviously the most active metals in alkene metathesis and, around 1980, Schrock and his group considerably increased their efforts in the search for stable molecular alkylidene and alkylidyne complexes of these metals including alkoxide ligands that would catalyze the metathesis of unsaturated hydrocarbons. This search was successful (58) and eventually produced a whole family of molybdenum– and tungsten–alkylidene complexes of the general formula [M(=CHCMe$_2$Ph)(N–Ar)(OR$_2$], R and Ar being bulky groups. In these complexes, the imido ligand is supposed to be a four-electron ligand, because the lone pair of the nitrogen atom is engaged in a vacant tungsten orbital, so that these four-coordinate pseudo-tetrahedral complexes are best considered as 14-electron complexes. These compounds presently are the most active alkene metathesis catalysts (Fig. 1.4). Their metathesis mechanism involves direct (weak) coordination of the olefin to provide 16-electron M(=CH-*t*-Bu)(olefin) intermediates, presumably of trigonal bipyramidal structure that form 14-electron metallacyclobutanes according to the Chauvin (59–61) mechanism and further continue to give olefin metathesis.

Other chemists such as John Osborn in Strasbourg (26) and Jean-Marie Basset (27) in Lyon played an important role in the history of olefin metathesis by reporting tungsten complexes that were active as olefin metathesis catalysts in the 1980s. Osborn reported a well-defined W(VI) alkylidene metathesis catalysts, **2** (Fig. 1.4) and showed the living character of the polymerization system and the intermediacy
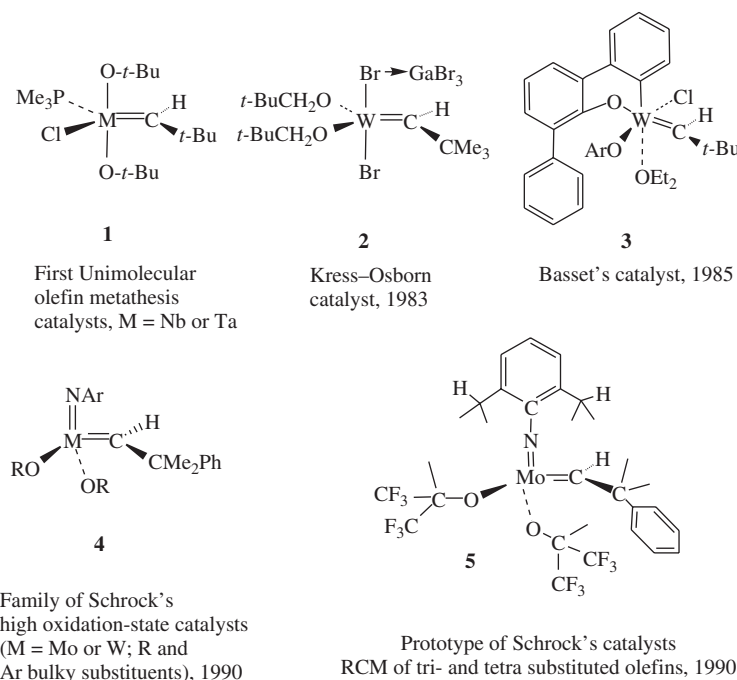
Figure 1.4   Early and optimized "unimolecular" Nb, Ta, Mo, and W metal–alkylidene catalysts of olefin metathesis.

of a tungstacyclobutane by ^{1}H NMR spectroscopy (62–65). Basset (66–68) reported aryloxoalkoxoalkylidene W(VI) catalysts and one of the first examples of Lewis-acid-free initiators, **3** (Fig. 1.4) that allowed the polymerization of substituted norbornenes following the ROMP mechanism.

The advantage of Schrock's (59–61) catalysts, whose most efficient members **4** and **5** (Fig. 1.3) were reported in 1990–1991, was that even though they are extremely active, they are molecular (without additives) and also provided a commercial catalyst and chiral versions for the first examples of asymmetric metathesis catalysis (69–76).

In 1975, Schrock (77) also reported the first high oxidation state alkylidyne complex, [Ta(C-t-Bu)(CH$_2$$t$-Bu)$_3$]. As its alkylidene analog and the Fischer-type carbyne complex [W(CO)$_4$(Br)(C–Ph)], however, this Ta complex was inactive in metathesis. Schrock (78) applied the same principles as with olefin metathesis and thus turned to W complexes with alkoxide ancillary ligands. In 1982, his group reported a very active catalyst, [W(C-t-Bu)(O-t-Bu)$_3$] for the metathesis of internal alkynes. Schrock's W-alkylidyne complexes do not react with olefins, but they selectively and efficiently metathesize alkynes without the need for a co-catalyst. For instance, the prototype [W(CCMe$_3$)(O-t-Bu)$_3$] effects several hundred turnovers per minute of 2-heptyne metathesis under mild conditions. Some reactions even proceed at 25 °C. Here again, the alkoxide ligands are indispensible for the catalysis of the metathesis reactions.

1.8   GRUBBS' APPROACH AND THE RU OLEFIN METATHESIS CATALYSTS

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 (26,27) had been interested for a long time in the metathesis reaction, as indicated by his mechanistic proposals early on. He had eventually noticed Natta's 1965 publication on the catalysis by RuCl$_3$ of the polymerization of cyclobutene and 3-methylcyclobutene by ring opening (79). This process (in butanol) had been developed by Norsorex. In this context, the Ziegler–Natta polymerization of olefins under mild conditions obviously had a considerable

impact on polymer chemistry (80). The delineation of a new polymerization mechanism, however, was not a simple task. Greatly inspired by this approach, Grubbs published in 1988 the polymerization of 7-oxanorbornene into a high molecular weight monodisperse polymer ($M_w = 1.3 \times 10^6$ g mol^{-1}; $M_w/M_n = 1.2$) by $RuCl_3 \cdot xH_2O$ or $[Ru(H_2O)_6](OTs)_2$ (OTs = toluene sulfonate), 6 (Fig. 1.5).

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 reactions and other metathesis reactions such as those involving ring closing of terminal diolefins (83,84).

Interestingly, Noels' group (85) reported, also in 1992, the Ru-catalyzed ROMP of cycloolefins initiated by diazoesters. In 1995, this group showed that addition of such diazoesters to $[Ru(\eta^6\text{-cymene})PR_3]$ (R = Cy or t-Bu) produces very active arene-free ruthenium–carbene catalysts in which the carbene proton could be observed by ^{1}H NMR, shedding light onto the catalyst structure (86). In 1995, the new molecularly well-defined catalysts $[Ru(=CHPh)Cl_2(PR_3)_2]$, R = Ph or Cy, whose structures are closely related to the vinylidene ones published 3 years earlier, were reported by the Grubbs group and commercialized with R = Cy. 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).

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) (Fig. 1.5). The complex **10**, and the third-generation of 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).

In the late1990s, other ruthenium olefin metathesis catalysts were reported (108–113) including that of Peter Hofmann. The latter, also very active, was obtained by chloride abstraction providing a dicationic dimer from a ruthenium analog bearing a *cis*-diphosphine (108–110).

Hoveyda (114,115), Grela (116,117), Buchmeiser (118), Misutani (119), and Blechert (120–122) reported other related, very active, stable, and functional group-tolerant ruthenium metathesis catalysts of this family in the early 2000s. Some of the best catalysts are represented in Figure 1.4. The first Hoveyda metathesis catalyst **12** is derived from Grubbs' first-generation catalyst **8**, and the chelating benzylidene ligand improved the stability compared to **8**. It bears only one phosphine and a chelating carbene ligand. In 2000, Blechert and Hoveyda independently reported a more active and more stable complex **13**, also bearing a NHC ligand instead of the phosphine. Both catalysts are now commercially available, although expensive. Grela reported variations of the Hoveyda catalyst with increased efficiency (active even at 0 °C) when the aryl group of the benzylidene ligand bears a nitro group in the meta or para positions or two methoxy substituents (**14**, Fig. 1.5). Grela's successful idea was to destabilize the Ru–O(ether) bond in order to favor the ether decoordination that generates the catalytically active 14-electron species (116,117). This key finding was further confirmed by Grela's group upon reporting the poorer catalytic performances of this catalyst in which the nitro group was replaced by the electron-releasing NEt_2 group at the para position, whereas the introduction of the related electron-withdrawing diethyl methyl ammonium substituent brought about a remarkably excellent activity. This family of Grubbs–Hoveyda–Grela catalysts, whose
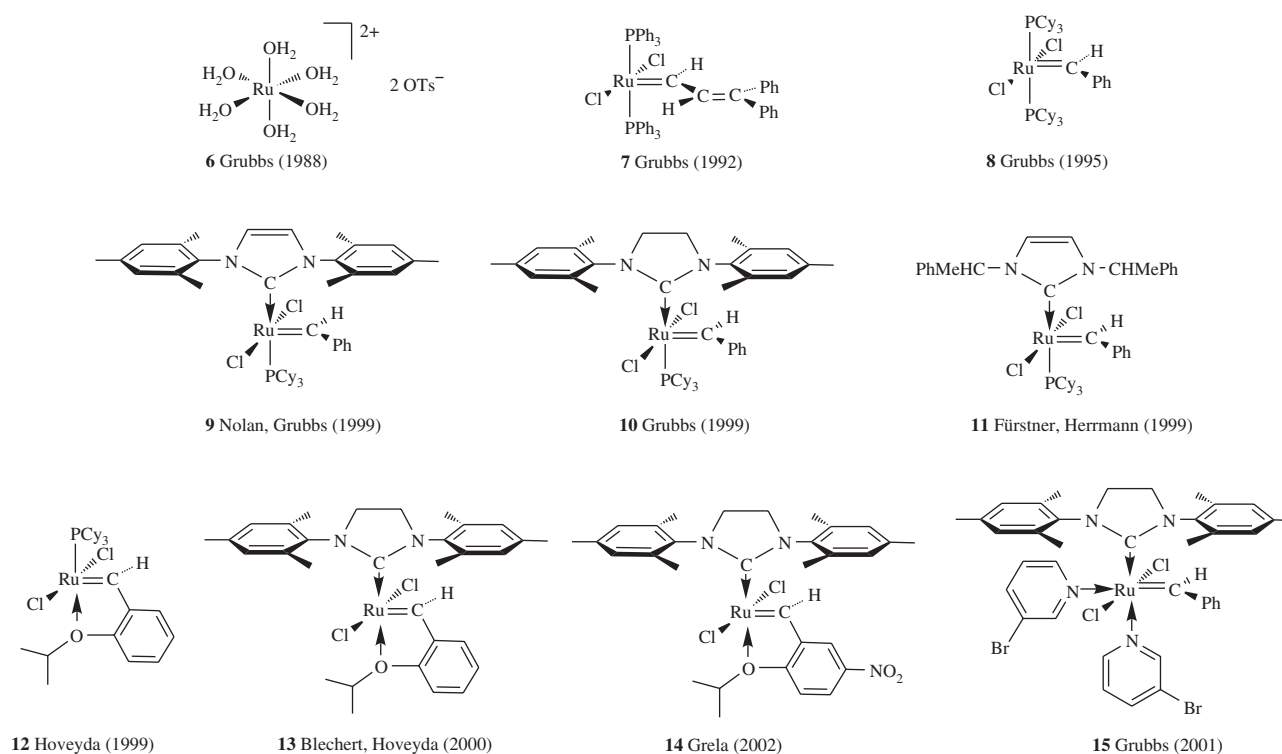
**Figure 1.5** Key steps in the discovery and improvements or variations of ruthenium metathesis catalysts.

activity compares with that of the second-generation Grubbs catalyst, are especially useful for difficult cases of metathesis of polysubstituted olefins and selective CM in which homo-coupling needs to be avoided (114,115,123,124). A successful variation of these Ru-benzylidene catalysts so far has been reported by Blechert (120–122), whose strategy to sterically destabilize the Ru–O(ether) bond consisted of the introduction of an aryl (phenyl or naphthyl) substituent on the benzylidene aryl in the ortho position relative to the O(ether). The catalytic efficiency and stability of these Grela (116,117) and Blechert (120–122) complexes reported in the early 2000s surpasses those of many other Ru catalysts, although it has been shown several times that the catalytic efficiency depends on the type of metathesis reaction examined and the tolerance toward the required functional group.

Since the mid 2000s, the introduction of the NHC ligands and their chelate forms have led to myriads of structural variations of the ruthenium–NHC carbene–benzylidene complex structures toward the optimization of catalytic activities and recyclability in the various metathesis reactions. This very rich design research has been all the more attractive as these complexes are air- and water stable and of very practical use in organic chemistry, and this area has been the subject of excellent reviews (125–131). In-depth comparison of the catalytic efficiencies among various benzylidene and

indenylidene ruthenium complexes conducted by Grela's group showed that different catalysts proved to be optimal for different applications, and that no single catalyst outperforms all others in all cases. A strong temperature effect was noted in all the reactions tested, and the authors suggested that difficult metathesis transformations should be conducted at 70 °C in toluene, rather than simply by increasing the catalyst loading at ambient temperature (127). For instance, under such conditions, Fürstner's and Nolan's (131–137) robust and readily accessible indenylidene complexes were shown to be in many cases fully equivalent to the second-generation Grubbs and Grubbs–Hoveyda complexes (although their activities under ambient conditions were lower, their practical and easy synthesis makes them interesting; Scheme 1.6) (126).

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 (138–141) has isolated remarkable 14-electron ruthenium phosphonium–alkylidene complexes that are all better
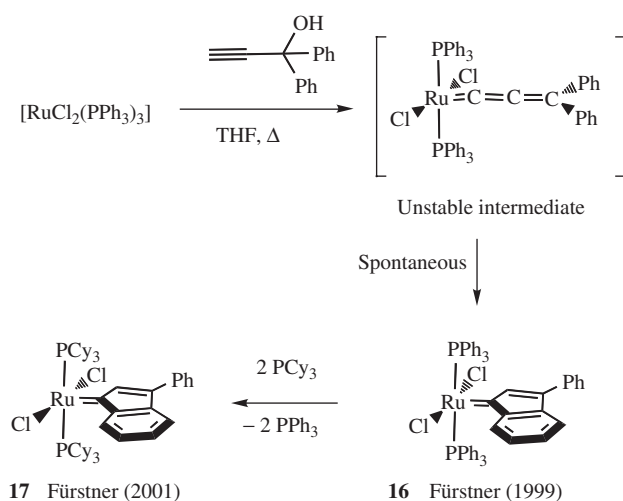
Scheme 1.6 Synthesis of the indenylidene Ru metathesis catalysts.
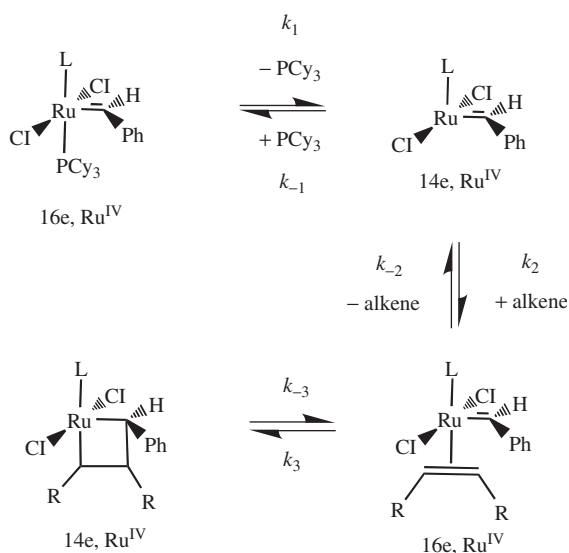
Scheme 1.7 General mechanism of the olefin metathesis reaction with the Ru catalysts. With L = PCy_3 (complex **8**), $k_1 = 10^2$; $k_2/k_{-1} = 10^{-4}$; with L = saturated NHC (complex **10**), $k_1 = 1$; $k_2/k_{-1} = 1$. It is the faster complexation of olefins by the 14e intermediate that makes the catalyst **10** more active than **8** (not the phosphine decoordination step) (107).

metathesis catalysts as they do not require ligand decoordination before olefin binding, which results in very low olefin binding energy, high catalytic activity in model RCM reactions, and direct relevant observation of ruthenacyclobutane intermediates resulting from olefin coordination (139–141).

An opposite strategy reported by the Lemcoff and Grela groups consisted in synthesizing ruthenium–NHC complexes that were thermo-switchable latent metathesis catalysts with a chelating benzylidene thioether, sulfoxide, or sulfone ligand. These robust complexes are not catalytically active under ambient conditions but show very good RCM and EYM catalytic activity upon heating (Fig. 1.6) (141–145).

Among the multiple ligand variations, Grubb's third-generation metathesis catalysts are especially remarkable five- and six-coordinate mono- and bis-pyridine complexes (see for instance the structure of the most active catalyst of this series, **15**, Fig. 1.4). The *cis*-bis(pyridine) complexes, simply prepared by adding an excess of the appropriate pyridine to Grubbs' second-generation catalyst **10** (146,147) are efficient in the challenging CM of acrylonitrile (147) and are among the fastest initiating ruthenium catalysts known, which, for instance, with 3-bromopyridine in **15** proved extremely useful for the synthesis of polymers with very narrow polydispersity and for the synthesis of block copolymers (148). The corresponding mono(pyridine) complexes are obtained from the bis(pyridine) complexes under vacuum and many structural variations are also known in this series of Grubbs' third-generation catalysts (129).

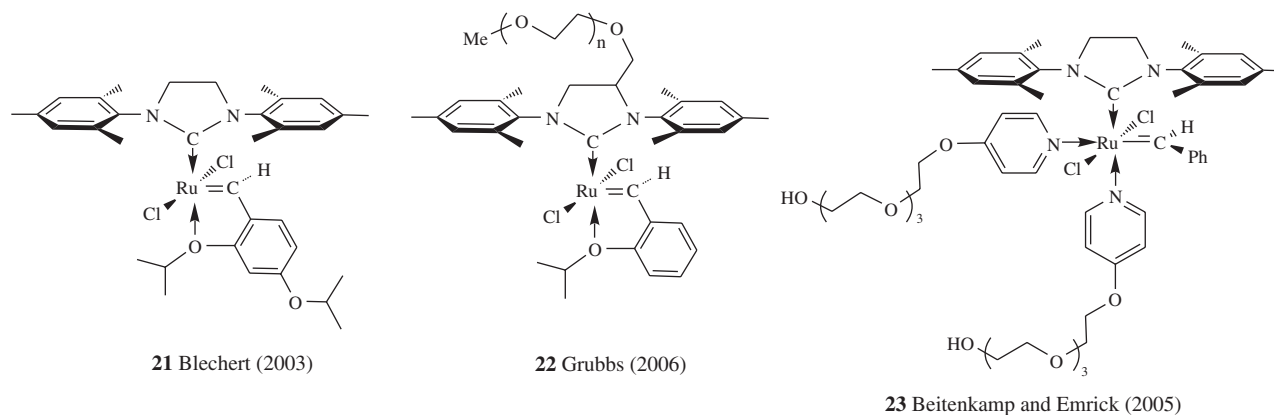## 1.9   OLEFIN METATHESIS IN AQUEOUS SOLVENTS AND WATER

Water obviously is the greenest solvent, due to its abundance and lack of toxicity and risks. The ruthenium molecular metathesis catalysts withstand water, and often even benefit from its presence in the medium. Early studies by Grubbs (82) involved the ROMP of 7-oxanorbornene catalyzed by $RuCl_3$(hydrate) in which water acted favorably, and further studies conducted in water as the only solvent produced a larger polymer and with a better polydispersity index (PDI) than in organic solvents (82). Later, this catalyst and method was applied to neoglycopolymers (149). Since then, ruthenium benzylidene catalysts have been widely used as olefin metathesis catalysts in aqueous solvents or water only under homogeneous or heterogeneous conditions, water-soluble ruthenium catalysts have been synthesized and efficiently used, and the area of aqueous olefin metathesis has been the subject of an excellent review (150).

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).

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

18 Lemcoff (2008)   **19** Grela (2009)   **20** Grela (2009)

isomers
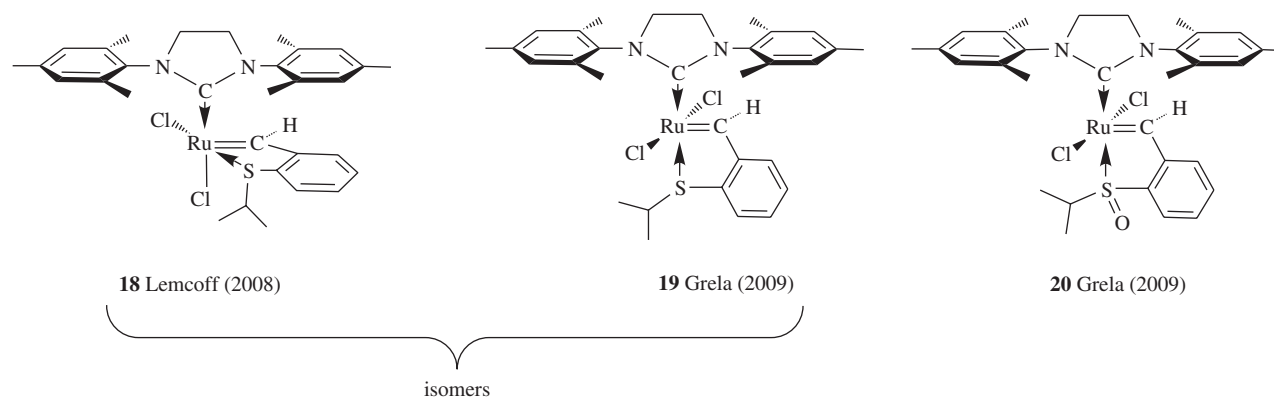
Figure 1.6 Thermo-switchable latent ruthenium metathesis catalysts with chelating benzylidene–thioether and benzylidene–sulfoxide ligands. A whole family of Lemcoff's metathesis catalysts related to **18** was also synthesized with various sulfur substituents (129).

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).

surfactant has been broadly applied to polymer syntheses by ROMP metathesis reactions using hydrophilic or hydrophobic norbornene derivatives (150,154–158). Then this strategy was first applied by Sinou's group (159) to RCM and CM metathesis in water with and without a sodium dodecyl sulfate (SDS) surfactant using Grubbs' commercial catalysts **8** and **10**. Lipschulz's group (160,161) reported the use of a nonionic PTS amphiphile derived from vitamin E as an efficient surfactant for the metathesis of CM reactions in water 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 Grubbs catalysts were occluded in a slab of polymethylsiloxane for CM and RCM metathesis reactions of substrates that are soluble in aqueous methanol (164). Another classic approach involves the modification of the ruthenium metathesis catalyst with a small (most often ionic) or hydrophilic polymer (polyethylene glycol (PEG) type) group on one of the ligands (phosphine, NHC carbene, or benzylidene) in order to render it water soluble. This method is applied to water-soluble substrates for metathesis in a homogeneous aqueous solution (Fig. 1.7) (150,165,166). It has also been applied in the outer aqueous phase of 1–4 μm liposomes for ROMP reactions by Maingotaud's group to heterogeneous mixtures of ruthenium catalysts that are in the same time-surfactants ("inisurf") via a polyalkyl or polyfluorinated alkyl tag (167,168). The use of ammonium substituents in ruthenium–benzylidene–isopropyl ether chelate catalysts such as **24–26** has proved very efficient, not only

24   Grela (2002)   Grela, Mauduit and Clavier (2006)   Grela, Mauduit and Clavier (2006)
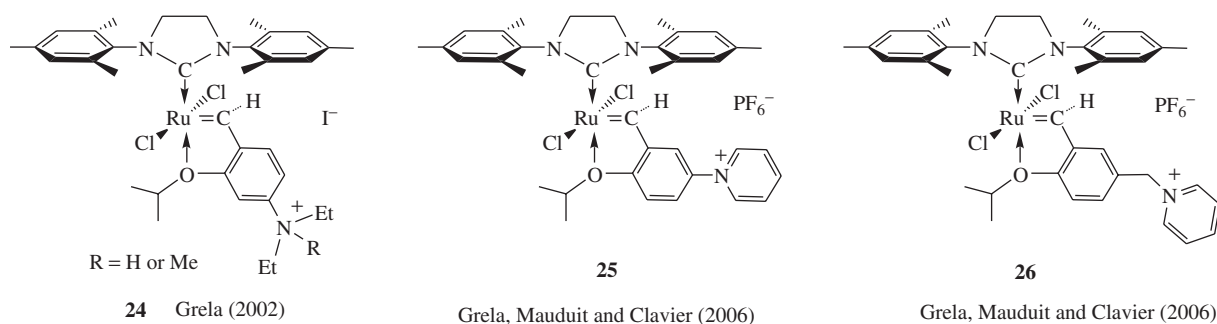
Figure 1.8   Examples of Grela's cationic ruthenium benzylidene–isopropyl ether complexes **24–26** that catalyze RCM, CM, and EYM reactions in water. The ammonium substituent also serves as a non-covalent anchoring group for the fixation of anionic tags (150).

for metathesis catalysis in water, but also as a viable strategy to introduce tags noncovalently (Fig. 1.8).

In conclusion, metathesis in water is extremely attractive, using water- and oxygen-stable very active ruthenium catalysts, which, for instance, enables applications of metathesis in biological molecules (150,169).

1.10   OLEFIN METATHESIS IN OTHER "GREEN SOLVENTS": IONIC LIQUIDS AND sCO$_2$

The concept of the use of ionic liquids in catalysis (170–173) was raised by Chauvin and Olivier-Bourbigou (170,171) in 1995 when they efficiently used [bmin]Cl-AlCl$_3$-EtAlCl$_2$ ionic liquid as a solvent for the metathesis of pentene catalyzed by [W(OAr)$_2$Cl$_4$] (ArH = 2,6-diphenylphenol or 2,4,6-trimethylphenol). Many advantages are provided by their use, including high chemical and thermal stability, extremely low vapor pressure, insolubility, or immiscibility with aqueous and organic reaction media, and good ability to solvate both polar and nonpolar compounds. Since this first report, more than 50 publications have appeared on this specific subject that was reviewed in 2008 (172). The studies concerned, almost exclusively, ruthenium catalysts (173), the first example of which was reported by Buijsman (174), with the synthesis of hydantoin using Grubbs' catalysts. Indeed, in the early 2000s, commercial Grubbs's catalysts were used as such in ionic liquids without a tag. Our group reported several reactions in [bmim]PF$_6$ including the multiple RCM reaction of a nona-allyl dendritic core to a tetracyclic aromatic in 75% yield (175). Occasionally, microwave irradiations were efficiently used to accelerate reactions, but without catalyst recovery (176,177), and a biphasic catalyst composed of ionic liquid and scCO$_2$ was astutely applied to the macrocyclization of pharmaceutical precursors (178). Charged allenylidene ruthenium catalysts were also efficiently used in biphasic [bmim]BF$_4$–toluene at 80 °C (179). A step forward in the area was accomplished with the introduction of ruthenium catalysts incorporating the imidazolium motif of

the ionic salt as a tag (180–185). In particular, the use of the biphasic system [bmim]PF$_6$–toluene at 25 °C allowed the formation of tri- and tetra- substituted olefins together with catalyst recycling and low ruthenium contamination (1–22 ppm, Fig. 1.9) (181). Alternatively, the introduction of pyridinium group in the tag instead of imidazolium brought about promising results (Fig. 1.8) (186,187).

Another "green" solution consists of conducting the metathesis reaction in supercritical carbon dioxide (scCO$_2$), rendering catalyst recovery easier than with organic solvents (126,188,189). Combined use of ionic liquid and scCO$_2$ has already been involved (see above) (178). This field was pioneered by DeSimone (190) with the ROMP of norbornene catalyzed by [Ru(H$_2$O)$_6$][OTs]$_2$ (Ts = *para*-toluenesulfonate), then by Fürstner and Leitner (112,191) with Schrock's and Grubbs' metal–carbene catalysts. Using the Grubbs–Hoveyda-type catalysts covalently immobilized on solid supports, Bannwarth et al. (192) obtained excellent recycling of the catalysts.

1.11   SOLID CATALYST SUPPORTS

Solid catalyst supports allow, in principle, to recover the solid catalyst simply by filtration and thus remove it from the substrate solution after the reaction. The solid support must be attached to one of the ligands. In the ruthenium catalysts, there is the choice between anionic ligands (by substitution of one or two Cl ligands in the Ru catalysts), phosphines (first-generation Grubbs catalysts), NHC carbenes (second and third-generation Grubbs catalysts), pyridines (third-generation Grubbs catalysts), arenes (Fürstner catalyst), or most commonly benzylidenes (Grubbs–Hoveyda catalysts). In the Schrock-type catalysts, the Basset group has replaced an alkoxide ligand by silica in Mo, W, and Re catalysts. The area has been reviewed several times, in particular by Buchmeiser (165,193), Basset (194–197), Weck (198), Toma (199), and in the review on sustainable concepts in olefin metathesis by Clavier et al. (126).
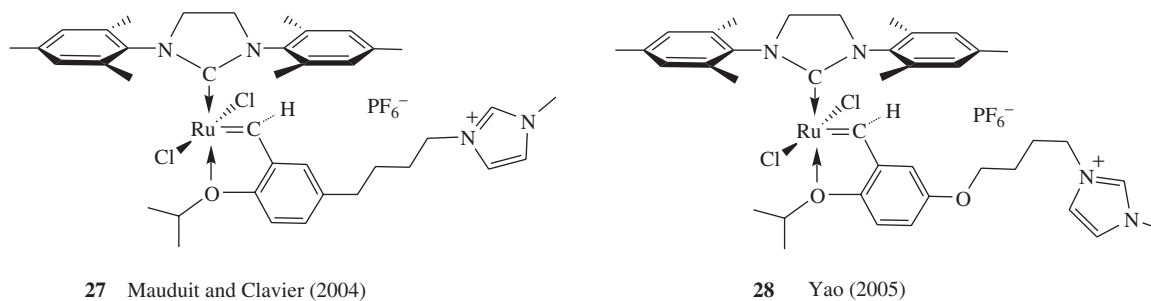
27   Mauduit and Clavier (2004)

28   Yao (2005)

Figure 1.9   Examples of the ruthenium metathesis catalysts **27** and **28** derivatized with imidazolium tags used in biphasic medium dichloromethane/[BMI][PF$_6$] or toluene/[BMI][PF$_6$] and displaying high recyclability for the RCM of tri- and tetra-substituted olefins at room temperature with very low Ru contamination (1–22 ppm over several cycles) (181,182).

1.11.1   High Oxidation-State Mo, W, and Re Silica-Bonded Catalysts

Basset's group has provided well-defined heterogeneous catalysts for olefin metathesis upon coordinating active metal centers (Mo, W, and Re) to silica, with the metal-bearing ligands that have already proved useful in homogeneous catalysis and with silica as an additional ligand (60). Recall that Schrock had turned metathesis-inactive alkylidene complexes into active ones by the introduction of alkoxy groups. In Basset's catalysts, this beneficial role is played by a siloxide ligand from silica. Thus, the catalysts [(SiO)M(=CH-*t*-Bu)(CH$_2$-*t*-Bu)$_2$], M = Mo or W (200), and [(SiO)Mo(=NH)(=CH-*t*-Bu)(CH$_2$-*t*-Bu)] (200,201) are active at 25 °C, unlike previously reported ill-defined heterogeneous catalysts and the early Mo and W oxides on silica or alumina. The only oxide that had catalyzed olefin metathesis at 25 °C was Re$_2$O$_7$/Al$_2$O$_3$, but it suffers from a low number of active sites, side reactions caused by the acid support, and deactivation of the catalyst (193). On the other hand, Basset's silica-supported rhenium catalyst [(SiO)(Re(C-*t*-Bu)(=CH-*t*-Bu)(CH$_2$-*t*-Bu)], **29** (Fig. 1.10) catalyzes the metathesis of propene at 25 °C with an initial rate of 0.25 mol per mol Re per second.
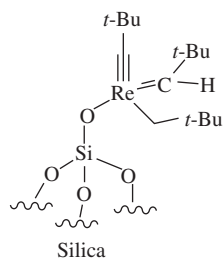
The formation of 3,3-dimethylbutene and 4,4-dimethylpentene in a 3 : 1 ratio results from cross metathesis between propene and the neopentylidene ligand, and the ratio of cross metathesis products matches the relative stability of the metallacyclobutane intermediates. Cross metathesis of propene and isobutene and self-metathesis of methyl oleate can also be achieved, and TON reaches 900 for the latter reaction, which is unprecedented for heterogeneous and most homogeneous catalysts (202,203). In his recent *Chemical Review* article on high oxidation state Mo and W imido alkylidene complexes, Schrock (204) has included a review on Mo and W metathesis catalysts supported on silica. In addition to the advantage of separating the solid catalyst from the products, Schrock has emphasized that another advantage of the support is to minimize bimolecular alkylidene coupling by retaining the metal centers far apart on the solid support. Finally, Basset's (205) work has produced silica-supported Schrock-type metathesis catalysts that are sometimes, as for [Mo(NAr)(CHCMe$_2$R)(O-*t*-Bu)(OSi700)], dramatically more active in metathesis with their siloxide ligand than their soluble version with the *t*-BuO ligand, although it is difficult to deconvolute the various reasons for increased catalytic activity.

1.11.2   Ruthenium Benzylidene Olefin Metathesis Catalysts on Solid Supports

Anchoring catalysts on solid supports allows easy removal of catalysts and their re-use. As the subject has been reviewed (128–131,165,193,197–199), only some of the main representative examples are given here. Buchmeiser (197) has reported perfluoroalkylcarboxylate ligands that result in less than 0.015 ppm Ru contamination, but these supported catalysts have not been recycled. Air-stable supported pyridine complexes, active in CM and RCM, could be recycled five time with almost no yield decrease, but no Ru contamination was reported (206), as for polymer-supported

29   Basset (2001)

Figure 1.10   Example of Basset's highly active silica-supported alkene metathesis catalysts (196).

Ru–arene–allenylidenes complexes that catalyzed RCM upon recycling three times (207). An NHC ligand derivatized with a poly(norbornene) support provided a ROMP and RCM catalyst with only 70 ppm ruthenium leaching (208). However, silica-supported NHC ligand-containing catalysts were also efficiently recycled multiple times, and they did not leach ruthenium (<5 ppb by ICP-MS) (209). Anchoring the metathesis catalyst to a solid support via the benzylidene ligand is the most widely used method, because the benzylidene ligand with its support is released at the beginning of the metathesis mechanism, allowing catalysis to proceed homogeneously in solution, but is recovered at the Ru center according to the "boomerang" process of the chelate carbene ligand at the end of the reaction (126,165). The Grubbs–Hoveyda catalyst with the chelating benzylidene–ether ligand is particularly efficient for this

strategy and has been developed with various supports (Scheme 1.8 and Fig. 1.11), but contamination usually reaches several hundred ppm, which is an inconvenience because of the re-anchoring of the active Ru species to the support at the end of the reaction (165). With a Wang resin attached to the benzylidene ligand, however, the ruthenium catalyst could be recycled up to five times (210). Likewise, the dendrimer technique (211) did not prove to be productive, as recycling failed (212).

1.12 METAL CONTAMINATION OF THE METATHESIS REACTION PRODUCTS

The preceding sections have summarized the efforts to recover and recycle the metathesis catalysts in the spirit
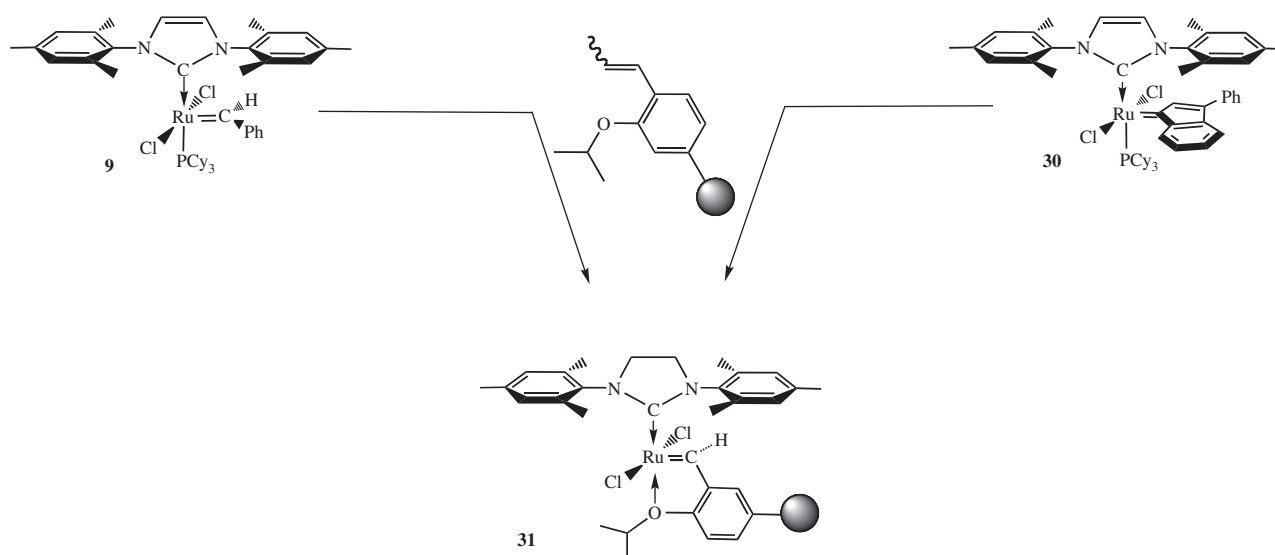
Scheme 1.8 Boomerang synthesis of Ru metathesis catalysts **31** derivatized on solid supports starting from the catalyst **9** or **30** (165).

32 Blechert (2001)   **33** Dowden (2001)   **34** Grela (2002)
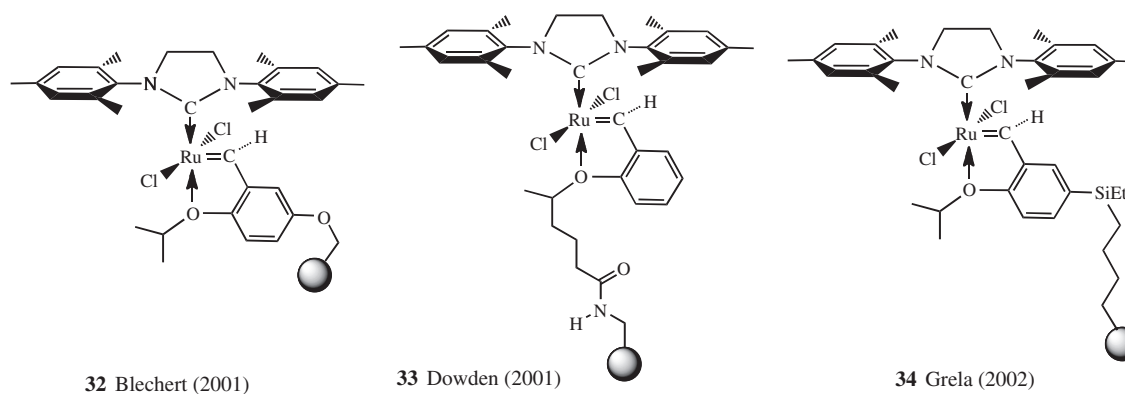
Figure 1.11 Examples **32**–**34** of ruthenium metathesis catalysts anchored on solid support and recycled several times with high yields. The isopropyl benzylidene-chelating ligand allows the so-called "boomerang" recycling that is allegedly efficient.
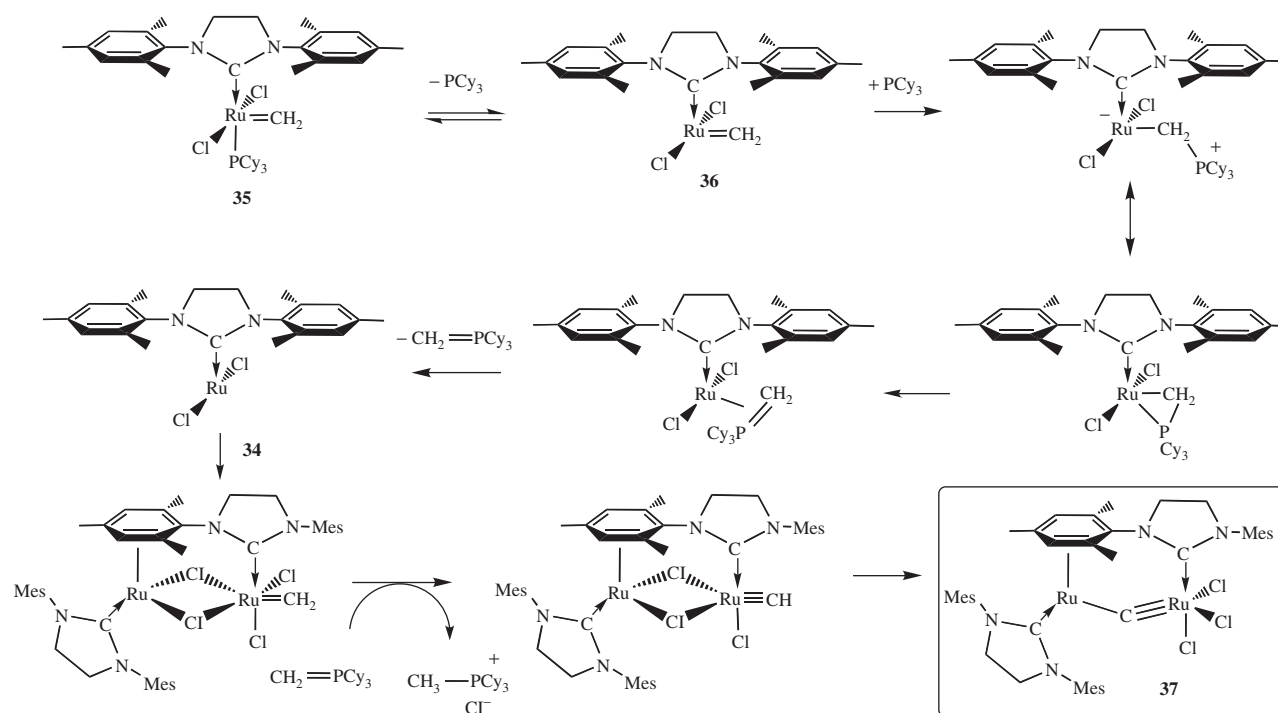
Scheme 1.9 Proposed mechanism for the decomposition of the second-generation Grubbs ruthenium−methylene complex **35** to the carbide-bridged diruthenium complex **37** (100).

of "green chemistry." Ruthenium catalysts have concentrated most studies on metal contamination of the products, although immobilization of Mo and W catalysts is also well known (165,193–196,200–204,213). Metathesis chemistry requires a rather large amount of catalyst due to the high reactivity of the metal–methylene species involved in the metathesis of terminal olefins. For instance, many metathesis steps in total synthesis use 20 mol% ruthenium (126,214,215). Yet, the acceptable limit for pharmaceutical industries concerning ruthenium contamination is 10 ppm. Thus, considerable efforts have been devoted to the removal of metal contamination either by chromatographic purification or by tagging the catalyst to separate it from the products. The most classic and efficient tag is a solid phase involving attachment of the catalyst to an insoluble organic or inorganic polymer as indicated in the above section, but water (Section 1.9), ionic liquids, or perfluorinated solvents (Section 1.10) are alternative media attracting tags that have specific affinities for these solvents and allow separation from organic products. A simple example is the derivatization of an NHC carbene ligand with PEG of the Grubbs–Hoveyda complex that catalyzes RCM, followed by extraction of the reaction mixture with water, leading to a contamination level of 41 ppm, which was decreased to 0.04 ppm (ICP-MS) by treatment with activated carbon (216). Other published strategies to decrease Ru contamination down to 60–200 ppm involve purification of

the products on silica gel followed by treatment with activated carbon, use of DMSO, $Ph_3P=O$, or lead tetra-acetate as Ru scavengers in combination with chromatography and treatment with isocyanide $CNCH_2CO_2K$ (130). As the decomposition of Grubbs' dichlororuthenium catalyst **10** was shown to yield (via the methylene complex **35**) the neutral carbide-bridged organo-diruthenium complex **37** (Scheme 1.9) (100,217,218), an additional potential solution to remove them from the organic metathesis products might be to oxidize them.

A drawback of a large number of publications on metathesis catalysis is the lack of reports of the metal contamination of the reaction products, although inductively coupled plasma mass spectrometry (ICP-MS) is an ideal tool for this purpose. This issue is the key to the awaited industrial development of drugs involving olefin metathesis steps in their synthesis.
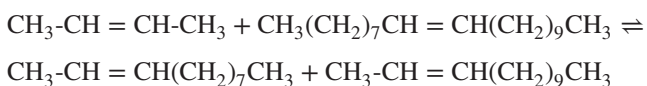
1.13 INDUSTRIAL APPLICATIONS

1.13.1 Simple Alkenes

Some simple alkenes are produced on an industrial scale. Although propene is mainly produced from naphtha steam crackers, strong demand has led to the development of the Phillips tri-olefin process from ethylene and 2-butene, using heterogeneous metathesis catalysts such as WO_3/SiO_2 at

>260 °C and 30–35 bar. 1-Butene can be used in such a process with MgO as a catalyst for isomerization to 2-butene. This process has been developed in Texas by Lyondell Petrochemical Co. and BASF Petrochemical, in Osaka by Mitsui Chemicals, in Singapore by Shell Chemicals and Sumitomo Chemical and in Caojing, China, by Shangai Secco Petrochemical. The Institut Français du Pétrole and the Chinese Petroleum Corporation at Kaoshiang, Taiwan, have also developed the Meta-4 process in liquid phase using Re_2O_7/Al_2O_3 at 35 °C and 60 bar (219).

Neohexene (3,3-dimethyl-1-butene), an intermediate in the synthesis of Tolalide, a synthetic musk perfume, and Terbinafine, an antifungal agent, is produced by metathesis of ethylene and the dimer of isobutene (a mixture of 2,4,4-trimethyl-2-pentene and 2,4,4-trimethyl-1-pentene).

In the Shell Higher Olefin Process (SHOP), lighter (<C6) and heavier (>C18) terminal alkenes produced by nickel-catalyzed oligomerization of ethylene are isomerized over a potassium metal catalyst, then metathesized over a MoO_3/Al_2O_3 catalyst at 100–125 °C and 10 bar to a statistical distribution of C_{11}–C_{14} linear internal alkenes sold by Shell Chemical as Neodene (>1,000,000 t per year) (220).

$$CH_3\text{-}CH = CH\text{-}CH_3 + CH_3(CH_2)_7CH = CH(CH_2)_9CH_3 \rightleftharpoons$$

$$CH_3\text{-}CH = CH(CH_2)_7CH_3 + CH_3\text{-}CH = CH(CH_2)_9CH_3$$

1.13.2   Polymers

The three main cycloolefins that have been transformed to polymers using the ROMP reaction in industrial processes are norbornene (the classic example), dicyclopentadiene, and cyclo-octene (221,222). Cyclopentene, however, was also polymerized to *trans*- and *cis*-cyclopentenamer for the rubber industry soon after the discovery of olefin metathesis (Scheme 1.10) (221–224).
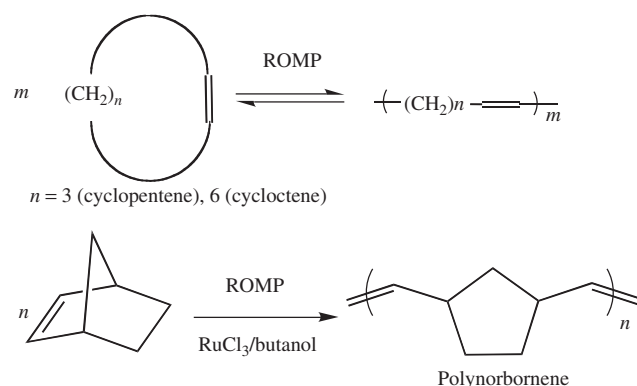
Scheme 1.10   Main cycloalkenes (together with dicyclopentadiene) utilized for ROMP reactions in industry.

In 1976, CdF Chimie and Elf Atochem in France started to produce norbornene polymers. The ROMP reaction of 2-norbornene catalyzed by $RuCl_3/HCl$ in butanol operating in air gives a 90% trans polymer of molecular weight $>3 \times 10^6$ g/mol, Norsorex, produced by Atofina and developed by Nippon Zeon as Zeonex (225,226).

The ROMP reaction of endo-dicyclopentadiene (obtained from naphtha crackers) leads to opening of the strained norbornene ring, yielding linear polymers. Under certain conditions, however, the cyclopentene double bond also opens, giving cross linking. The catalyst can be WCl_6 + $WOCl_4$, with the $EtAlCl_2$ co-catalyst and additives, a tetrakis (tridodecylammonium)octa-molybdate activated with a mixture of Et_2AlCl, propanol and $SiCl_4$ or a Grubbs-type ruthenium catalyst. These polymers are largely used for heavy-vehicle applications (220).

Degussa has been producing Vestenamer 8012 by ROMP of cyclooctene since 1980. The reaction proceeds in hexane using WCl_6 as the catalyst. The trans double bond content is 80% and the molecular weight is 75,000. A minor fraction of the product results from cyclization of short oligomers. Vestenamer 8012 is hard at 20 °C and has an exceptionally high viscosity, then becomes fluid above 60 °C. It is useful in blends (225).

1.13.3   Fine Chemicals

The availability of highly chemo-selective catalysts is now developing applications in oleochemistry, agrochemicals (insect pheromones, etc.), fragrances, drugs, pharmacy, and so on (see Sections 1.14 and 1.15) (227).

1.14   APPLICATIONS TO ORGANIC SYNTHESIS

Metathesis reactions have a huge impact on the possibilities of transformation of organic molecules and are systematically thought of and involved in organic strategies, including those concerning complex structures and total syntheses (1,214,215). This area is well developed in the second volume of Grubbs' (1) metathesis handbook, and a book on metathesis in natural product synthesis edited by Janine Cossy (215) that has recently appeared. Several Grubbs-type and Schrock-type catalysts and derivatives are commercial and now of common use in organic synthesis. A study of the tolerance of Mo metathesis catalysts has indicated that Schrock's Mo catalysts, although air- and moisture-sensitive, are effective in the presence of phosphanes, thioethers, nitriles (whereas the Ru catalysts are decomposed by these substrates), sterically protected free alcohols, metal carbonyls and, in many cases, in the presence of amines (even giving unparalleled enantioselectivity with the latter groups) (4). Grubbs and the family of Grubbs-type catalysts benefit from the largest use in organic synthesis, because

they are stable in air and moisture, and metathesis reactions can be conducted in water or aqueous solvents (Section 1.8). The main type of metathesis used in organic synthesis is olefin RCM, despite unpredictable and problematic *E/Z* selectivity (a problem that is avoided in alkyne RCM, see below Section 1.14), because complex rings are of great value in pharmaceuticals. CM and EYM are also largely used (228). Ethylene (or 2-butyne) is lost in RCM and CM reactions of terminal dienes (or diynes terminated by ethylidyne fragments), which displaces the thermodynamic equilibrium toward the formation of the metathesis products. On the other hand, EYM is "greener" in the sense that no carbon is lost in the metathesis reactions.

Remarkably, RCM metathesis allows the synthesis of small, medium, and large rings. The easiest RCM reactions are those affording synthesis of 5-membered rings (carbocycles and a large variety of heterocycles), and the entropic and enthalpic factors become less favorable as the ring size increases (229–231). Many eight-membered rings have been synthesized by metathesis, however. Large macrocycle formation (calixarenes, cyclodextrins, macrolactones, macrolactams, and catenanes) usually requires high dilution (to minimize oligomerization), high catalyst content, and higher reaction temperatures because of competition with catalyst decomposition (228). Tandem or domino reactions, that is, successive one-pot reactions involving RCM and another reaction such as ring-opening metathesis (ROM), CM, or a non-metathesis reaction are particularly elegant, ecologically advantageous, and useful, because they allow the rapid construction of complex structure from relatively simple precursors (228,232,233). Optically pure cyclic compounds are accessible from an optically pure precursor diene upon treatment with an achiral RCM catalyst or alternatively a racemic RCM product can be resolved using an enantiomerically pure catalyst, such as one of Schrock's or Grubbs' chiral catalysts (Eqs 1.6, 1.7) (3,4,234).

(1.7)

(1.8)
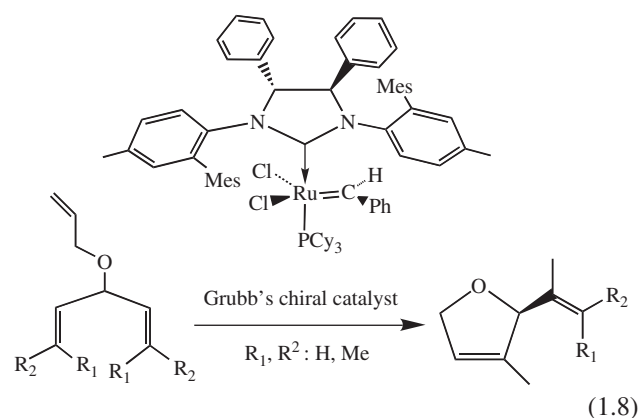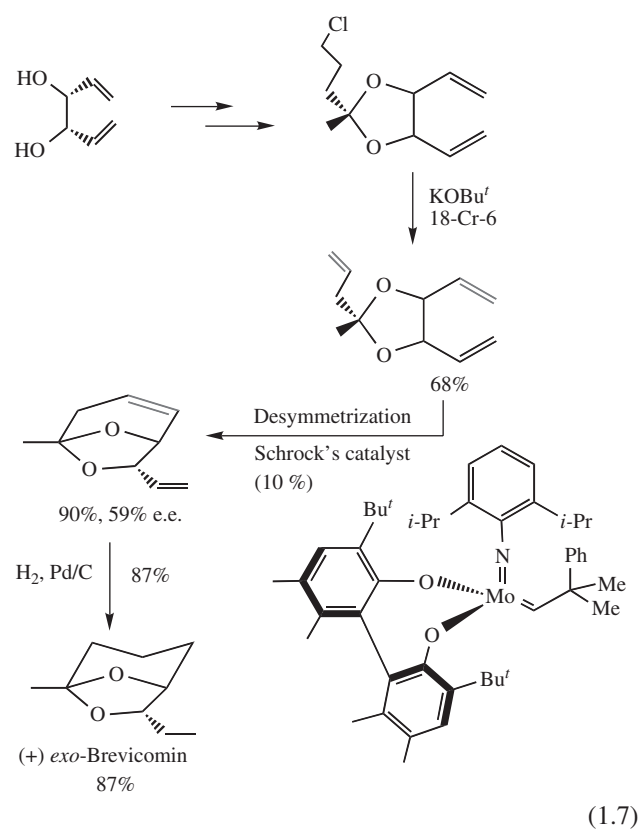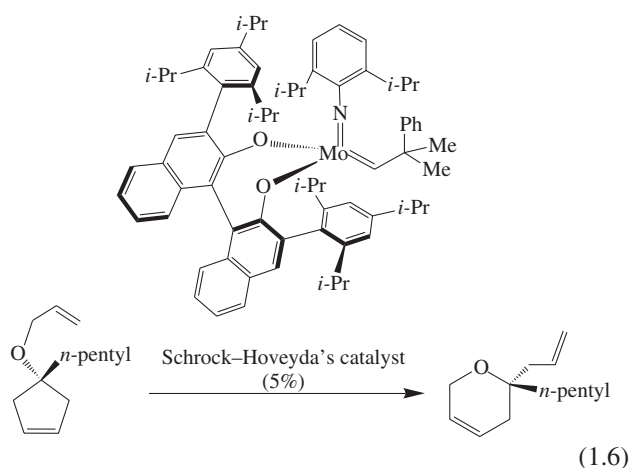
A plethora of RCM reactions have been reported for the synthesis of bioactive compounds, including total syntheses (233–236). As an example, the macrocyclic hepatitis C virus (HCV) S3 protease inhibitor-labeled BILN 2061 (Ciluprevir™), **39**, was synthesized via RCM (237). This RCM reaction gave the best results with Grela's (238) catalysts (in particular **14**), yielding the macrocycle **38** with the desired *Z* selectivity using an RCM reaction that has then been scaled-up to 400 kg (Scheme 1.11) (239).

Cross metathesis is another currently used metathesis reaction for the synthesis of a wide variety of biologically active compounds and organic materials, although it also suffers from the lack of *E/Z* selectivity with many olefins (Eq. 1.8) (239).

(1.6)
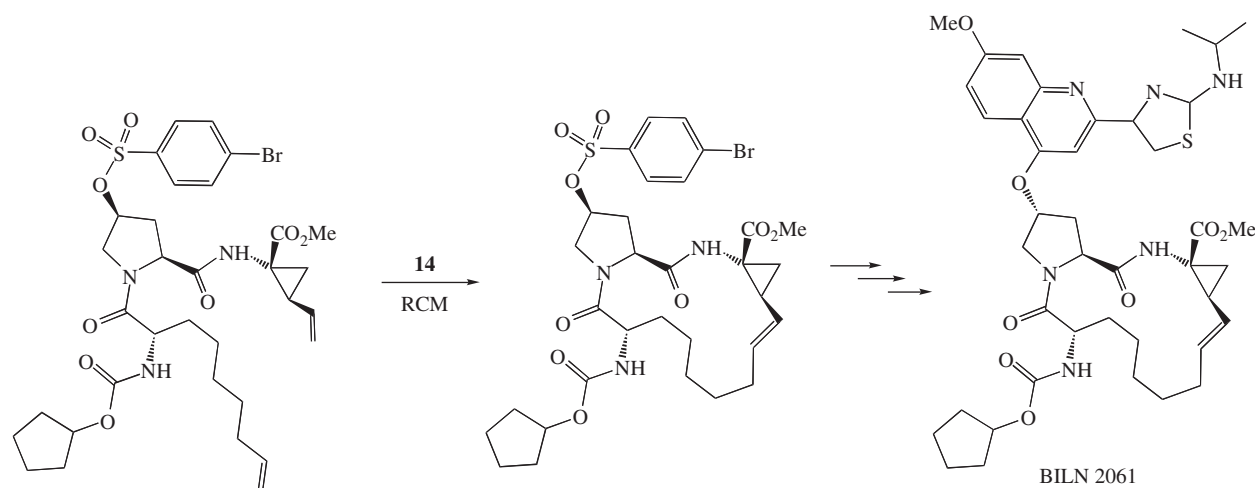
Scheme 1.11 Synthesis of BILN 2061 involving a stereospecific RCM step most efficiently catalyzed by Grela's complex **14** (238).

$$(1.9)$$
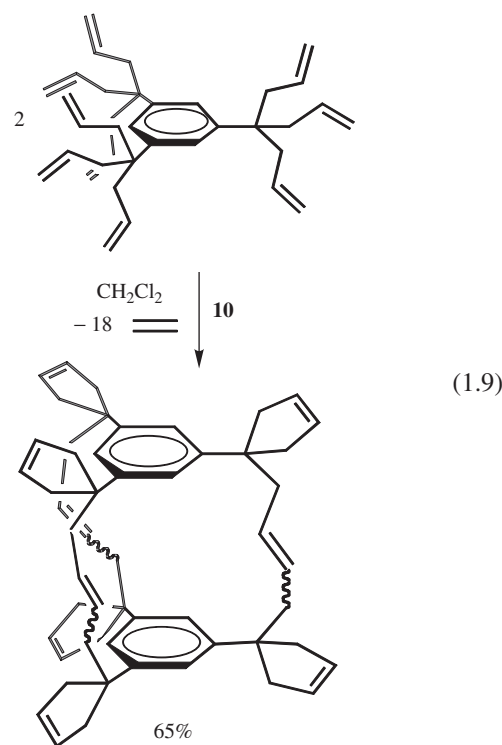
The problem of the lack of *Z* selectivity has been recently solved by Grubbs' and Schrock's groups (240) with new catalysts bringing about *Z* selectivity based on kinetic control in the metathesis products. When one of the olefin bears an electron-withdrawing or bulky substituent, however, excellent *E* selectivity can be obtained as a result of thermodynamic control (241–243). For instance, CM also is a key step in the synthesis of *E*-stilbenes that are precursors of anticancer compounds also useful for cardiovascular properties such as resveratrol, piceatanniol, and pinostilbene (244,245).

CM has been used for the total synthesis *inter alia* of plastensimycin (and carbaplatensimycin) and analogs that attract considerable interest due to their pharmaceutical properties related to strong activity against many drug-resistant bacteria. A CM step is a crucial common point in their total syntheses (236,246,247).

EYM is largely applied to the cyclization of enynes producing cyclic conjugated dienes, although intermolecular metathesis between an alkyne and an olefin (enyne cross metathesis) is almost limited to ethylene and thus much less applied in organic chemistry (particularly in total synthesis) to produce acyclic conjugated 2,3-disubstituted dienes due to selectivity problems. This metathesis reaction between internal alkynes and ethylene (1 atm) to produce such dienes, however, was introduced by Mori's group for the synthesis of anolignan A. High yields for cross EYM under 1 atm ethylene are usually obtained with the catalyst **10** (248). Earlier, in the mid 1990s, it was Mori who had pioneered intramolecular EYM using the first-generation Grubbs catalyst, and rapidly applied it to total synthesis, a field that has been considerably expanded (235,249).

Many applications of alkyne metathesis to total syntheses have also been elegantly developed by Fürstner's group (Section 1.15).

1.15   ALKYNE METATHESIS

Although the metathesis of internal (and sometimes terminal, see below) alkynes proceeds according to the same Chauvin-type mechanism (2) as olefin metathesis (250), via metallacyclobutadiene intermediates (that can be isolated and also serve as alkyne metathesis catalysts (78,251,252)), it is remarkable that olefin metathesis catalysts do not metathesize alkynes (except enynes), and alkyne metathesis catalysts do not metathesize olefins.

Besides the unpractical heterogeneous mixture of tungsten oxide and silica that was found in the late 1960s to metathesize alkynes at 200–450 °C (253), the first useful internal alkyne metathesis catalysts were reported by Mortreux and Blanchard (254) in 1972 and consisted of a mixture of $[Mo(CO)_6]$ and a simple phenol derivative in high boiling solvents. In 1998, Bunz's group (255,256) reported that phenols bearing electron-deficient substituents such as *p*-chlorophenol, a temperature of 130 °C, and purging 2-butyne with a N_2 stream gave optimized yields and rates, which proved to be synthetically valuable, and other groups indicated that microwave assistance was also helpful (257,258). Improvement of the $[Mo(CO)_6]$ catalyst with 2-flurorophenol was reported in 2002 by Grela and Ignatowska (117,259). In 2003, Lavigne and Chauvin's group (260) found that the temperature could be decreased to 50 °C in the presence of 1,2-diphenoxyethane and molecular sieves.

Schrock's high oxidation state Mo and W alkylidyne complexes bearing the key alkoxide ligands (as in olefin metathesis) are well defined, unimolecular catalysts that are more reactive than Mortreux' catalyst and had been disclosed in the early 1980s (78,252,261,262). For instance, the prototype of this family, $[W(C\text{-}t\text{-}Bu)(O\text{-}t\text{-}Bu)_3]$, **42**, was obtained in a remarkable metathesis reaction between a triply bonded tungsten–tungsten dimer **40** (an alkyne metathesis catalyst (78,263)) and neoheptyne (or also conveniently with *t*-BuCN) via the W_2C_2 tetrahedrane intermediate **41** (Scheme 1.12) (264,265).

It is an efficient catalyst at ambient temperature for 3-heptyne that is equilibrated with the metathesized alkynes

in 5 min at 20 °C (260). In the light of the structure and efficiency of Schrock's catalysts, it appears probable that in Mortreux's improved system the phenol molecules are turned into phenoxide ligands, diphenoxyethane eventually serves as a bulky stabilizing chelate ligand, and the carbyne ligand comes from the same metathesis reaction as that involved in the synthesis of Schrock's catalyst.

In the late 1990s, Fürstner discovered even more active alkyne metathesis pre-catalysts such as the binary compound $[Mo\{N\text{-}t\text{-}Bu(2,4\text{-dimethylphenyl})\}_3]$, **43** (Fig. 1.12) producing $[MoX\{N\text{-}t\text{-}Bu(2,4\text{-dimethylphenyl})\}_3]$, X = Cl or Br upon reaction with a halogen source, in particular CH_2Cl_2.

These complexes do not contain a carbyne ligand, and the X-ray crystal structure of the Mo–Cl derivative showed considerable shielding of the metal by the bulky ligands (266,267). These precatalysts could even initiate (presumably also through a high oxidation-state catalytically active
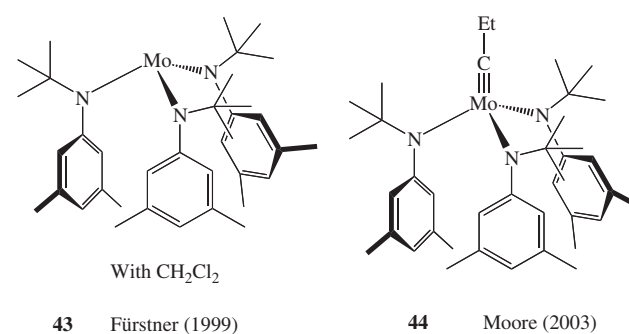
Figure 1.12   Fürstner's and Moore's efficient Mo alkyne metathesis initiators.
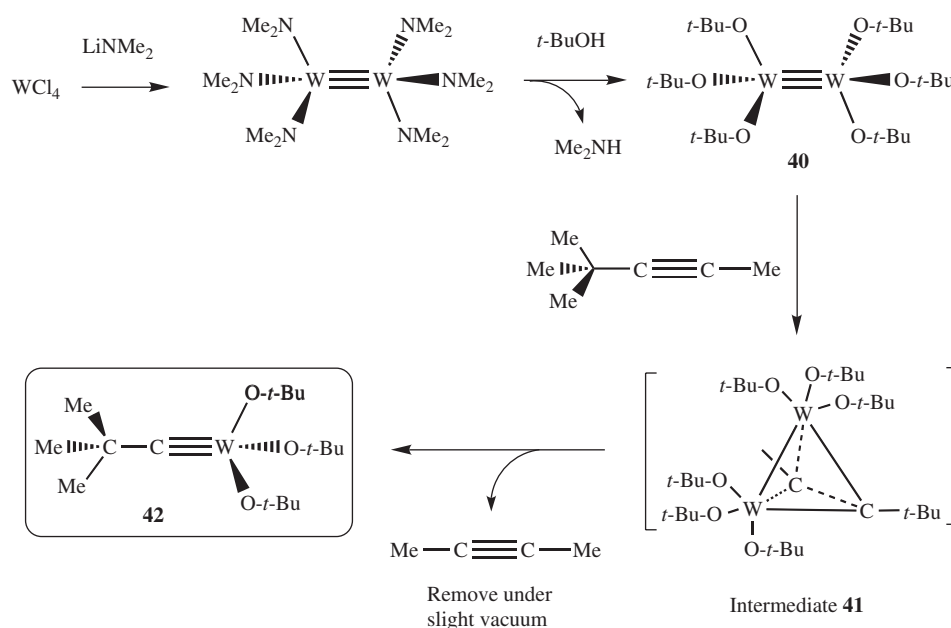
Scheme 1.12   Synthesis of Schrock's prototype alkyne metathesis catalyst **42** (264,265).

metal–carbyne species (268)) the metathesis of alkynes containing a thioether, amine, or crown ether fragment that could not be metathesized using Schrock's catalysts. The complex [Mo(Cl){N-t-Bu(2,4-dimethylphenyl)}$_3$], formed by reaction of **43** with CH$_2$Cl$_2$ is the pre-catalyst that was conveniently used in the metathesis reactions in this solvent.

Moore (268–270) has reported the use of [EtCMo {NAr(t-Bu)}$_3$], **44** (Fig. 1.12) for the remarkable synthesis of arylene ethynylene macrocycles by precipitation-driven alkyne metathesis. Discrete alkylidyne W and Mo complexes on silica prepared by Basset's group (271) also produce useful catalysts that are intermediate between homogeneous and heterogeneous, with the advantages of both types. Metathesis of 2-pentyne by the silica-supported alkylidyne–alkylidene complex [(SiO$_x$Re(C-t-Bu)(=CH-t-Bu)(CH$_2$-t-Bu)], **29** (Fig. 1.10) has been reported.

Applications of alkyne metathesis catalysis have been greatly developed using the improved Mortreux-type-, Schrock-type-, and Fürstner-type catalysts. The categories of metathesis reactions that have been exploited are the RCM, CM, and acyclic diyne metathesis (ADIMET). Although the metathesis of terminal alkynes is successful (272–275) using Schrock's catalyst [W(C-t-Bu)(O-t-Bu)$_3$] in the presence of quinuclidine, it has not been exploited in organic synthesis. However, 80% of the metathesis compounds were obtained from terminal alkynes at 80 °C within 1 min using 4 mol% catalyst. Even phenylacetylene that was earlier found to polymerize more easily than other terminal alkynes gave several turnovers of carbyne exchange metathesis (273,274). Besides, one can also find a literature report of an heterogeneous catalyst, CoO–MoO$_3$–SiO$_2$, for the carbyne exchange metathesis of terminal alkynes such as 1-heptyne (276). Terminal alkynes, however, polymerize in the presence of ordinary transition-metal initiators (such as [W(CO)$_6$]) to yield polymers according to the Katz mechanism that starts with the well-known isomerization of the terminal alkynes to a metal–vinylidene complex followed

by coordination of another terminal alkyne molecule that forms a metallocyclobutene intermediate (41,250).

Thus, organic strategies involving alkyne metathesis use molecules terminated by a propynyl group for CM or two propynyl ends for diyne RCM. The byproduct of these alkyne metathesis reactions, 2-butyne, is volatile and removed from the reaction medium in the course of the reactions (a slight vacuum is necessary), which shifts the metathesis equilibrium toward the metathesis products. Owing to the ring strain of the cycloalkyne, no macrocycle smaller than 11 or 12 members can be obtained. A key point is the stereoselectivity that is obtained using alkyne metathesis, whereas the E/Z selectivity is a major drawback of many olefin RCM reactions. Lindlar reduction of alkynes gives Z olefins, whereas Birch reduction yields E olefins (Scheme 1.13).

This is exemplified here in the problem of the total synthesis of epothilone C. Several previous total syntheses of epothilone C using nonsteroselective olefin RCM had been less attractive than conventional methods. The total synthesis of epothilone C, **45**, was subsequently elegantly achieved by Fürstner's group via alkyne RCM followed by stereospecific Lindlar reduction to give the precursor yielding epothilone C in only one more step (Scheme 1.14). In this alkyne RCM metathesis reaction, Fürstner's pre-catalyst [MoCl{N-t-Bu(2,4-dimethylphenyl)}$_3$], **43**, in CH$_2$Cl$_2$/toluene was used whereas Schrock's catalyst [W(C-t-Bu)(O-t-Bu)$_3$] was not efficient due to the incompatible presence of sulfur and nitrogen atoms in the thiazole ring (277).

An impressive example of alkyne CM is the total synthesis of (+)dehydrohomoancepsenolide reported by Fürstner and Dierkes in 2000. It involves an alkene RCM catalyzed by the first-generation Grubbs' catalyst leaving the alkyne bond unreacted, followed by alkyne CM using Schrock's catalyst [W(C-t-Bu)(O-t-Bu)$_3$] (10%) at 100 °C leaving the olefinic bond unreacted, and finally stereoselective Lindlar reduction (277).
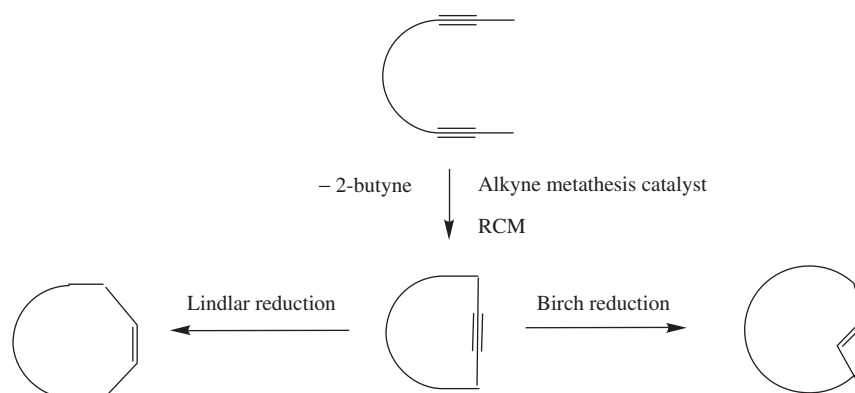
Scheme 1.13   Selective access to E and Z olefins initiated by Fürstner via alkyne RCM (131).
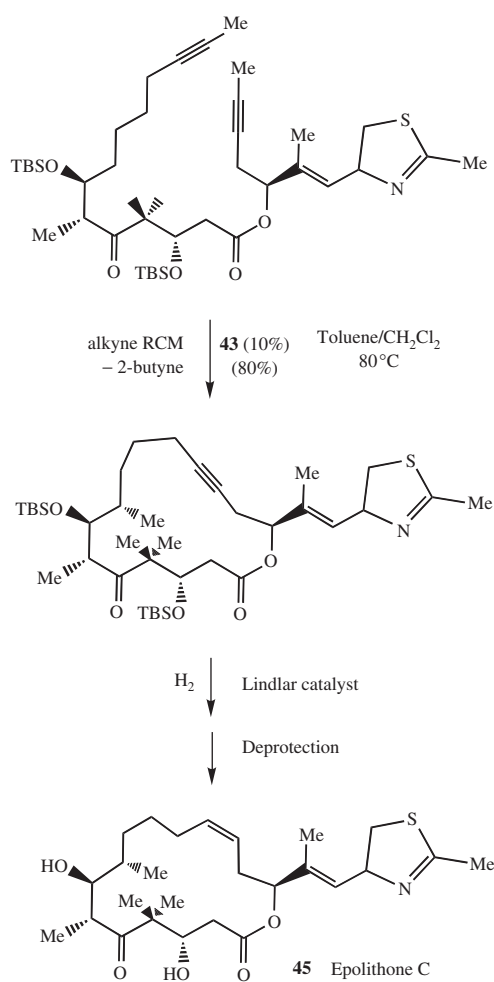
Scheme 1.14 Synthesis of epothilone C: Fürstner's stereospecific synthesis via alkyne RCM followed by Lindlar semi-hydrogenation (277).

The alkyne CM reaction has also been largely developed by Bunz's group with the simple catalyst [Mo(CO)$_6$] + p-ClC$_6$H$_4$OH for the synthesis of poly(dialkylparaphenyleneethynylene)s that are conjugated cyclic molecular nanostructures (256,279) and polymers with high molecular weights (with particularly interesting optical and liquid-crystalline properties) resulting from the metathesis of dipropynylated dialkylbenzenes (255,256).
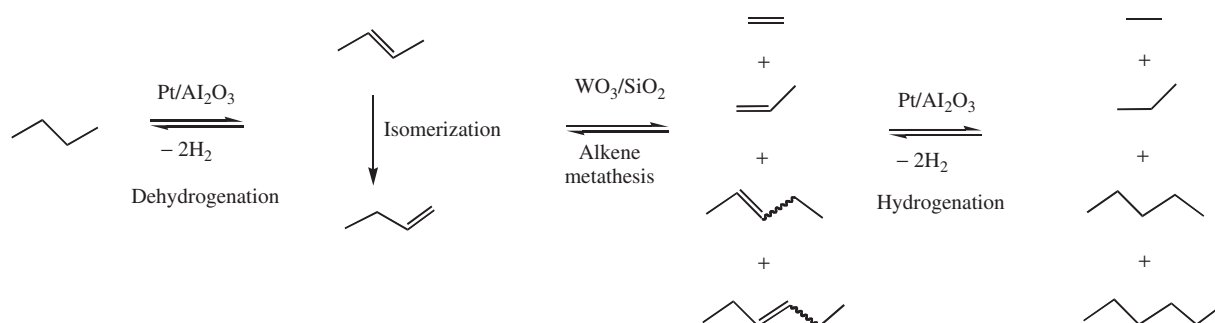
1.16   ALKANE METATHESIS

The metathesis of alkanes was first reported by Burnett and Hugues (280) at the Chevron Company in 1973. When butane was passed at 400 °C on a heterogeneous Pt–Al$_2$O$_3$ mixture, a deshydrogenation catalyst, and WO$_3$–SiO$_2$ mixture, an olefin metathesis catalyst, the direct metathesis products propane and pentane were predominantly formed,

together with lower and higher molecular weight alkanes (Scheme 1.15).

Basset's group reported a family of well-defined single-site heterogeneous Ta and W–alkylidene catalysts containing siloxy ligands that metathesize alkanes. These catalysts resulted from the reactions of silica with Schrock's high oxidation-state olefin metathesis catalysts. The siloxy ligand brought by silica played the role of alkoxy ligands in favoring metathesis activity with even an improved reactivity with the siloxy ligand resulting from the increased metal electrophilic properties compared to alkoxy complexes. The strategy was thus clearly to metathesize olefins resulting from alkane dehydrogenation (196,281–287). In particular, Basset et al. also noticed that propane and propene gave similar C$_{n+1}$/C$_{n+2}$ ratio of cross-metathesis products on silica-supported Ta-neopentylidene catalysts at 150 °C. The complexes [(SiO)$_x$Ta(=CH-t-Bu)(CH$_2$-t-Bu)$_{3-x}$] (x = 1 or 2 catalyzed the metathesis of alkanes into a mixture of higher and lower alkanes at 150 °C, as did the hydride complex [(SiO)$_x$Ta–H]. For instance, ethane reversibly yielded methane and propane. The mechanism was suggested to proceed by a composite series of σ-bond metathesis of C-H bonds and α and β-eliminations (rather than direct σ-bond metathesis of C–C bonds). The α-elimination from d^2 metal–methyl or metal–alkyl species formed, respectively HTa=CH$_2$ or HTa=CHR, and the mechanism was proposed to then follow an alkene metathesis pathway with olefins generated by β-elimination (including metallacyclobutane intermediates as in the Chauvin mechanism; Scheme 1.16) (194–196).

What is most elegant and original in this strategy is the multiple activation by a single site, and the in-depth characterization techniques of surface organometallic species that resulted in very efficient, well-controlled, and robust heterogeneous metathesis catalysts for alkanes, alkenes, and alkynes.

With this background in mind, Goldman and Brookhart also recently directly mimicked the system of the Chevron company (280), using well-defined homogeneous catalysts for alkane metathesis. The challenge was the compatibility between the alkane dehydrogenation catalyst and the olefin metathesis catalyst operating separately in solution. Successful "tandem" catalytic activation using homogeneous catalysts for both alkane dehydrogenation and olefin metathesis types was thus reported in 2006 (288,289). The dehydrogenation catalysts are Ir pincer complexes nicely designed and improved by Goldman (290–292) and further optimized by both research groups (293–297), and the olefin metathesis catalyst is a Schrock-type complex such as [Mo(NAr)(=CHCMe$_2$Ph)(OR$_{F6}$)$_2$] or a heterogeneous catalyst, Re$_2$O$_7$ on Al$_2$O$_3$. Reactions in neat octane or decane require heating for several days at more than 125 °C to approach alkane metathesis equilibrium, but the reaction is limited by the decomposition of the Mo–alkylidene catalyst.

Scheme 1.15   Alkane metathesis: the Chevron process at 150 °C involving alkane dehydogenation followed by alkene metathesis and hydrogenation of the metathesized alkenes (280).
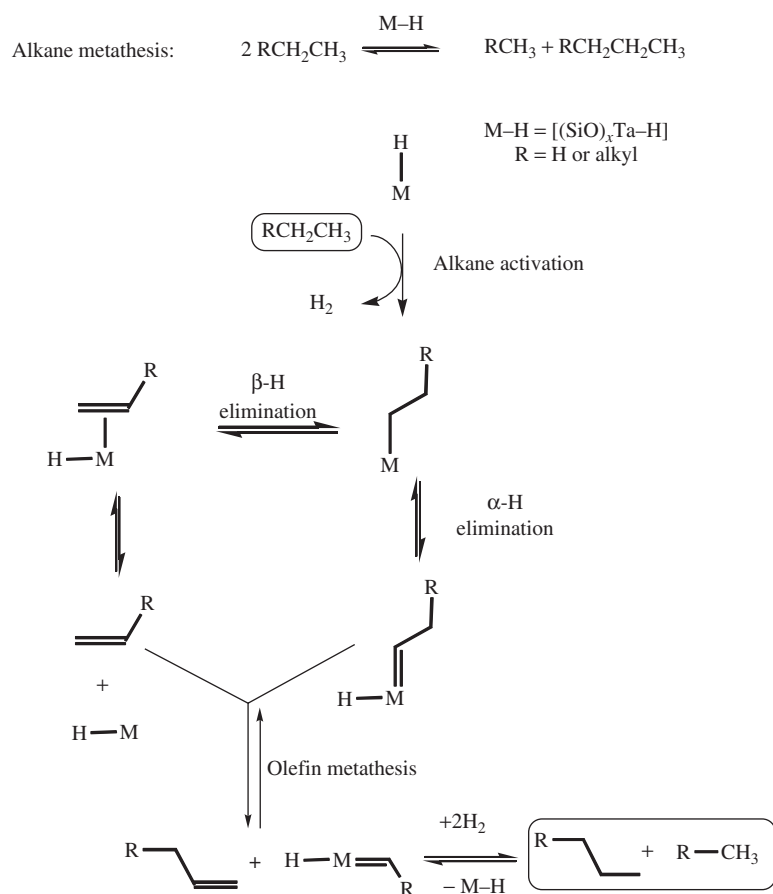
Scheme 1.16   Alkane metathesis at 150 °C on Basset' single-site early transition-metal catalysts containing siloxy ligands and its mechanism. The alkane activation step involves σ-bond metathesis between the M−H bond and an alkane C−H bond (196,281).

More than 40 Mo and W alkylidene catalysts were tested, W catalysts outperforming Mo ones, and the greatest activity was obtained using [W(NAr)(=CHCMe$_2$Ph)(OSiPh$_3$)$_2$] (297). Indeed, as in Basset's catalyst (see above), the siloxy ligand brings an advantage over the alkoxy ligand because it presumably reduces the donation of π electron density to the metal.

1.17   POLYMERIZATION METATHESIS AND POLYMER MATERIALS

Several types of metathesis reactions produce polymers and the polymer field occupies a major part of the overall activities in metathesis research. For instance, the entire third volume of Grubbs' (1) handbook on metathesis is devoted
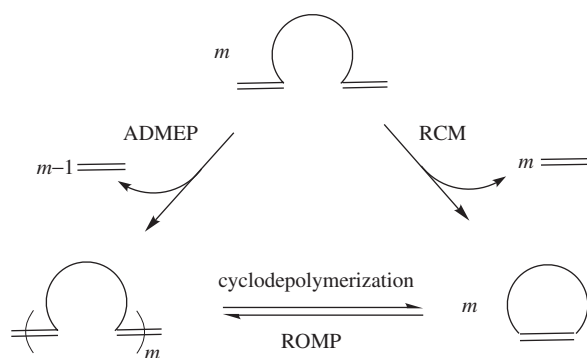
Scheme 1.17 Relationships between ring-closing, ring-opening, and polymerization/depolymerization processes in metathesis reactions initiated by metal–carbene complexes (301).

to polymers. The best known metathesis reaction leading to polymers is the ring opening metathesis polymerization (ROMP) that is mostly used for norbornene derivatives (the other cyclo-olefins undergoing ROMP are those that are also subjected to release of ring strain upon opening, which provides the driving force of the reaction, that is, in particular, cyclobutene, cyclopentene, cyclo-octene, and dicyclopentadiene), including industrial developments (Section 1.8 and Scheme 1.10).

The acyclic diene metathesis (ADMET) polymerization is also well known to proceed when the RCM of the terminal diene is sterically inhibited (298). Its equivalent with aromatic methyl-terminated diynes (ADIMET) produces, as indicated in Section 1.15, poly(dialkylparaphenyleneethynylene)s in addition to sacrificial 2-butyne (256). Terminal alkynes polymerize according to the Chauvin–Katz metathesis mechanism subsequent to alkyne coordination and isomerization to metal–vinylidene complexes upon catalysis by tungsten carbonyl (41) and other simple organometallic compounds (299). This mechanism is different from the Ziegler–Natta-type polymerization of alkynes resulting from alkyne coordination followed by insertion into a metal alkyl bond (300). Finally, a unifying view should be highlighted by recalling that the ROMP and ADMET (or ADMEP) are also connected to the RCM, and that the reverse reaction of ROMP, cyclodepolymerization, is also known (Scheme 1.17). The equilibrium between RCM and its reverse leading to oligomerization, and the ring-chain equilibriums in ROMP have been emphasized and analyzed in depth in an excellent review by Monfette and Fogg (301) in 2009.

During the last decade, the stereo-control among the monomer units introduced by ROMP has been addressed, involving cis/trans configuration of the exo-cyclic double bond, configuration of the allylic bridgehead carbons, and linkage of unsymmetrically substituted monomers (302,303). For instance, a Schrock-type Mo initiator with hexa(isopropyl)terphenoxide and monopyrrolide ligand allowed cis selectivity in the ROMP of norbornadiene and

cyclooctene derivatives, although these initiators suffered from high sensitivity toward moisture and oxygen (304). Another example is the alternative polymerization of cyclooctene and norbornene that was achieved with Ru initiators based on the different insertion rates for norbornene and cyclooctene that depend on the previous monomer inserted (305–310).

Most advances in polymer materials synthesized by ROMP have involved Grubbs' first-, second-, and third-generation catalysts and the indenylidene ruthenium catalysts (310,311). The ruthenium-based initiators are usually chosen for ROMP because of their functional-group tolerance and allowance to achieve copolymer syntheses (312,313). Highly functionalized polynorbornene homopolymers have been synthesized by ROMP, for instance, with radical moieties (TEMPO, 2,2,6,6-Tetramethylpiperidinyloxy) for applications as cathode-active materials in organic radical batteries (314). Random co-polymer synthesis allows to incorporate, for instance, optical sensors (309). Well-defined block copolymers with narrow size distributions have been reported (307). End-group functionalization can be implemented using a carbene-functionalized initiator, a chain-transfer agent during polymerization, or a terminating agent and is a valuable means for combining different polymerization techniques (reversible addition–fragmentation chain transfer (RAFT), atom transfer radical polymerization (ATRP), etc.) (315). The structural diversity that can be reached involves grafted, dendronized, and hyperbranched polymers with various material applications (resistant plastics, antifouling coating, thermoplastic elastomers, and emulsifiers) (316) and liquid crystals (317), porous polymers (318), and self-healing materials (310). Finally, implications of polymers in green chemistry often involve natural products (319) and water-soluble polymers (Section 1.7) (310).

1.18 CONCLUDING REMARKS

From the Chauvin mechanism, alkene, alkyne, and alkane metathesis reactions are rather well understood. All viable olefin metathesis catalysts proceed by olefin coordination of a 14-electron transition-metal species to produce 14-electron metallocyclobutane intermediates that can sometimes be isolated and shown to also be good metathesis catalysts. The various types of metathesis reactions lead to numerous applications in pharmacologically important drugs (alkene and alkyne RCM, and EYM) and polymer materials (ROMP, ADMET, and ADIMET) (1,320). The metathesis reactions are greener than many other bond forming reactions, because they do not require a base or product salt as in Pd-catalyzed cross carbon-carbon and carbon-element forming reactions. Yet there are a number of key challenges to address before metathesis catalysis can be extensively adopted in industrial

processes. The present drawbacks are the metal contaminants related to the rather high loading of catalysts in reactions (from a few % to sometimes up to 50% in some steps of total syntheses) (321). Thus the robustness of the catalysts must still be improved, as well as the turnover numbers (322). Metathesis catalyst decomposition or aerobic sensitivity due to the intermediacy of fragile metal–methylene species intermediates in the catalytic cycles of common terminal olefin metathesis reactions remains a crucial problem. The definition and prevention of decomposition pathways is therefore a difficult challenge that remains to be faced. Olefin metathesis catalysts should be designed to reach (particularly) Z selectivity (323,324). The synthesis of large rings still requires the use of high dilution to minimize the formation of oligomers. This trend cannot be presently extended to large scales. This stereochemistry is especially challenging for the formation of di- and trisubstituted olefins. The design of chiral catalysts to produce highly enantioselective reactions is also called for (325–327). The progress that has been accomplished in the last thirty years is formidable and has brought the metathesis reactions to the forefront of organic synthesis and materials science. There is no doubt that the present exciting challenges to bring metathesis of current use in industry will encourage researches to make decisive new discoveries in the area (331–335).

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