METATHESIS

1. Introduction

Olefin metathesis is one of the very few fundamentally novel and one of the most important organic reactions discovered since World War II. The name metathesis comes from the Greek μ ϵ τ α θ ϵ σ ι ζ that means transposition (meta, change and tithemi, place). Indeed, the reaction consists of a unique metal-catalyzed carbon skeleton redistribution in which a mutual exchange of unsaturated carbon–carbon bonds takes place, as shown in equation 1 for the metathesis of propene into ethylene and 2-butene [(*E* and *Z*) isomers]. In other words, olefin metathesis constitutes a catalytic method for both cleaving and forming C=C double bonds. The reaction is generally reversible and limited to an equilibrium. The reacting alkenes need not be identical. Thus, while the forward reaction in equation 1 constitutes an example of self-metathesis, its reverse is accomplished by allowing ethylene and 2-butene to react with each other. In this case, the process is often referred to as a cross-metathesis (CM).

$$2\ H_2C{=}CH{-}CH_3 \xrightleftharpoons{\text{catalyst}} H_2C{=}CH_2 + H_3C{-}CH{=}CH{-}CH_3 \qquad (1)$$

Olefin metathesis is a child of industry and, as with many catalytic processes, it was discovered by accident. The reaction came to light as a serendipitous outgrowth in the systematic study of Ziegler polymerization catalysts with alternate transition metal-based systems. The first catalyzed metathesis reactions were observed in the late 1950s when chemists at DuPont, Standard Oil, and Phillips Petroleum reported the metathesis of propene with catalysts based on molybdenum and tungsten according to equation 1. It was soon established that olefin metathesis (or olefin disproportionation as the reaction was called in these early days) could take place in the presence of various homogeneous and heterogeneous catalysts. Cyclic olefin monomers were also tested under similar experimental conditions and found to produce low yields of amorphous, rubbery polymers with unexpected structures. The first paper by Truett and co-workers (1) detailing what is now recognized as a metathesis polymerization appeared in 1960 and dealt with the ring-opening polymerization of norbornene. The ring-opening metathesis polymerization (ROMP) of cyclobutene into polybutadiene in the presence of titanium tetrachloride, activated with triethyl aluminum (2) and the conversion of cyclopentene into polypentenamer with catalysts based on molybdenum and tungsten (3) were reported, respectively, 2 and 4 years later by Natta and co-workers. Together with a report by Banks and Bailey on the metathesis of acyclic olefins in 1964 (4), these publications are the first mentions of olefin metathesis in the open literature. It took years to recognize that the disproportionation of acyclic olefins and the ring-opening polymerization reactions were two sides of the same coin. The connection between the two types of reactions was first uncovered in 1967 by Calderon, who also coined the generic term “olefin metathesis” to designate this class of chemical transformations (5). However, the true nature of the reaction was not recognized at that time. It was first believed that the polymerization took place via cleavage of a single-bond adjacent to the double bond rather than involving the double bond itself. Detailed historical accounts and references to early patents can be found in reviews issued by Banks in 1986 (6) and Eleuterio in 1991 (7).

2. Scope of the Reaction

Eventually, it became evident that metathesis had a wide variety of applications and that many olefinic substrates could undergo this reaction to afford an extensive range of new unsaturated products. Indeed, suitable substrates for metathesis include substituted alkenes, terminal and internal alkenes, cycloalkenes, dienes, polyenes, and even alkynes or alkanes. Through skeletal rearrangement, unsaturated products that can be acyclic compounds, small- or medium-size carbo- and heterocycles, macrocycles, or polymer chains are obtained. Depending on the types of substrate and transformation, several categories of metathesis have been defined. The most important ones are depicted in Fig. 1. Pathways involving cyclic olefins feature ring-closing metathesis (RCM), ring-opening metathesis (ROM), and ROMP. Reactions concerning only open-chain molecules comprise cross-metathesis (CM) and acyclic diene metathesis (ADMET), which is a step-growth polycondensation with elimination of ethylene.

Two or more of these basic operations can be combined in a one-pot procedure. In the so-called tandem, domino, or cascade metathesis processes, reactions occur in sequence. In other words, a subsequent reaction always takes place at the functionality formed in the previous step. The shortest general tandem metathesis between an endocylic olefin and an exocyclic C=C double bond is represented in Fig. 2. In the course of the reaction, the initial ring is opened by ROM and a new one is formed by RCM. In a slightly more elaborated sequence, an excess of acyclic olefin is added to the reaction mixture to enable a further CM. In both cases, the overall process is usually referred to as ring

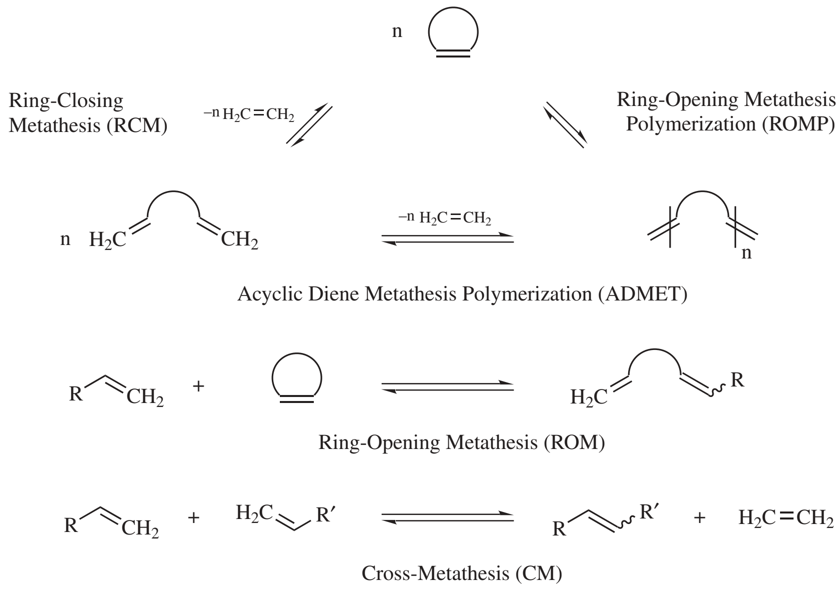


Fig. 1. Main types of olefin metathesis reactions.

rearrangement metathesis (RRM), since it affords products with a rearranged ring system. Alternatively, various metathesis reactions can proceed simultaneously and independently if suitable polyolefin substrates are employed. For example, several examples of double or even triple RCM reactions of tetraenes and hexaenes, respectively, have been described. Whether the reactions occur in sequence or in parallel, the accumulation of multiple metathesis events allows to build up complex structural scaffolds very efficiently and rapidly in a single operation.

Although olefin metathesis does not generate stereogenic centers per se, the reaction may be employed for the desymmetrization of prochiral polyolefins or for the kinetic resolution of racemates. So far, the asymmetric ring-closing metathesis (ARCM) and the asymmetric ring-opening cross-metathesis (AROCM) reactions have been the most investigated variations for inducing chirality in organic

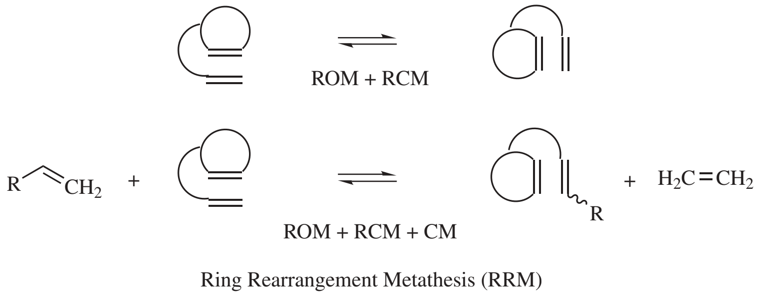
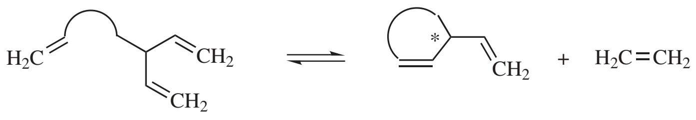
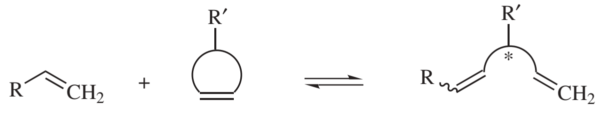


Fig. 2. Tandem olefin metathesis reactions.



Asymmetric Ring-Closing Metathesis (ARCM)



Asymmetric Ring-Opening Cross-Metathesis (AROCM)

Fig. 3. Asymmetric olefin metathesis reactions.

substrates (Fig. 3). Research in this field is still in its infancy and only a limited number of efficient chiral catalysts are presently available. Yet, significant advances were already made in the understanding of mechanisms that govern enantioselectivity (8) and new, improved, asymmetric catalytic systems are likely to emerge in the near future.

With regard to monomers, the ability of a cycloalkene to undergo ROMP is primarily related to the difference in free energy between the ring and the corresponding open-chain structure. Thermodynamic calculations indicate that among cycloalkenes comprising four to eight ring carbon atoms, the six-membered cycle is the only one with a positive ΔG value associated to its ring opening. Hence, it does not undergo ROMP unless there is ring strain in the molecule due to bridging, as in the bicyclo[2.2.1]hept-2-ene structure (norbornene, [498-66-8]). Steric factors, eg, substituents close to the double bond or other geometric constraints that could adversely affect formation of the metallacyclobutane intermediate (see the section THE EARLY CATALYSTS AND THE MECHANISM OF OLEFIN METATHESIS), are also important in determining the reactivity of a cyclic monomer.

Whereas ring-opening processes are enthalpically driven due to the relief of ring strain, RCM is entropically driven because the reaction cuts one substrate into two compounds. In both cases, high selectivities toward products can usually be achieved. On the other hand, the metathesis of acyclic olefins is essentially a thermoneutral process that eventually results in a statistical distribution of reactants and products. Therefore, it is necessary to shift the equilibrium in one direction in order to make the process suitable for preparative applications. Metathesis of an α-olefin yields ethylene and a symmetrical internal olefin. In such a case, the reaction can usually be driven to completion by removal of volatile ethylene. In the metathesis of a symmetrical olefin, the product molecule is the geometrical isomer of the reactant and thus metathetical (E/Z) isomerization, which accompanies productive metathesis of internal olefins, results from the exchange of alkylidene fragments.

The metathesis of alkadienes and polyenes may follow intra- or intermolecular pathways. The intramolecular metathesis of an α, ω-diene yields ethylene and an unsaturated carbocycle (or heterocycle) via RCM, whereas the intermolecular reaction results in the formation of ethylene and an oligomer or a polymer (the ADMET route of Fig. 1). Whether the intra- or intermolecular pathway dominates depends on the relative stabilities of the linear and cyclic products, strained cycloolefins being prone to undergo ROMP. In a manner analogous to step-growth polycondensation of polyesters, polyenes are formed by step-growth metathesis of the double bonds in a diene if the reaction is run under sufficient vacuum to remove the ethylene as it is formed, thereby shifting the equilibrium toward high molecular weight species. Yet, because the ADMET process is equilibrium driven, addition of excess ethylene to a macromolecular chain will shift the reaction in the reverse direction to give depolymerization. This procedure constitutes a possible method for recycling rubber and other unsaturated polymers.

3. Alkene Metathesis

In just a few decades, initiators for olefin metathesis have evolved from poorly characterized heterogeneous mixtures to well-defined, highly tunable, single-component metal complexes. Major advances in catalyst design have sparked off a tremendous growth of the field and an impressive range of applications have recently become available to the organic chemist, especially in polymer science and for fine synthesis. A large variety of transition-metal compounds have been investigated as catalysts for olefin metathesis. The most important ones are based on tungsten, molybdenum, rhenium, and ruthenium. Other catalytic systems based on titanium, tantalum, osmium, and iridium have also been used, although they usually display lesser activities. A brief history of olefin metathesis is outlined in Table 1 that summarizes some of the most significant milestones described in the following sections.

3.1. The Early Catalysts and the Mechanism of Olefin Metathesis.

Up to the late 1970s, all olefin metathesis reactions were accomplished with poorly defined, multicomponent homogeneous or heterogeneous catalytic systems. Heterogeneous catalysts generally consisted of a transition-metal oxide or an organometallic precursor deposited on a high surface area support, eg, rhenium(VII) oxide on alumina or molybdenum(VI) oxide on silica. Homogeneous catalysts were prepared in a variety of ways from a wide range of starting materials. They usually required the combination of a transition-metal compound, together with a main group element-based alkylating agent (the cocatalyst), and sometimes a third component (the promoter), eg, a tungsten(VI) salt activated by either a tetraalkyltin or an alkylaluminum chloride in the presence of water traces (22). Because the amount of active species formed under these conditions was very small ($<1\%$), the true nature of the metal coordination sphere and its oxidation state remained elusive.

These early metathesis initiators exhibited the typical features of Ziegler-type catalysts, ie, a high activity at the expense of a poor compatibility with polar functional groups, due to their strong Lewis acidic and alkylating properties. These characteristics initially restricted the scope of olefin metathesis to the production of unfunctionalized polymers. Besides, due to the high activity of most catalysts, the metal-carbene at the end of the growing polymer chain was able to react with carbon–carbon double bonds in the chain itself, either intramolecularly

Table 1. **Important Milestones in Olefin Metathesis**

Late 1950s	Industrial chemists discover accidentally olefin disproportionation during the systematic study of Ziegler-Natta polymerizations.[a]
1964	Fischer and Maasböl isolate and characterize the first stable metal carbene complex.[b]
1967	Calderon coins the term "olefin metathesis" to designate the exchange of carbon atoms between C=C double bonds.[c]
1971	Hérisson and Chauvin postulate the intermediacy of metal–alkylidene and metallacyclobutane species in olefin metathesis.[d]
1976	Katz demonstrates that Fischer-type carbene complexes of tungsten initiate olefin metathesis.[e]
1980	Schrock designs a metathetically active tantalum–alkylidene complex that provides experimental support to the Chauvin mechanism.[f]
1992	Grubbs introduces a series of well-defined ruthenium–alkylidene olefin metathesis catalysts.[g]
1999	Work by Herrmann (17), Grubbs (18,19), and Nolan (20) leads to a second generation of well-defined ruthenium-based olefin metathesis catalysts.
2001	Hoveyda and Schrock achieve high enantioselectivities in asymmetric ring-closing metathesis with a chiral molybdenum catalyst.[h]

[a] Refs. 9, 10.
[b] Ref. 11.
[c] Ref. 12.
[d] Ref. 13.
[e] Ref. 14.
[f] Ref. 15.
[g] Ref. 16.
[h] Ref. 21.

to give cyclic oligomers or intermolecularly to give linear oligomers. This phenomenon is known as "backbiting".

From a practical point of view, reproducibility was a major concern. The activity of a given system depended on its chemical, thermal, and mechanical history, and also on the rate and order of mixing the monomer, the catalyst, and the cocatalyst. The reactions were difficult to initiate and to control, because only minute amounts of active species were formed in the catalytic mixtures, which often decomposed over the course of the reaction. Nevertheless, thanks to their low cost and simple preparation, heterogeneous systems still hold an important place in industrial applications (see the section INDUSTRIAL APPLICATIONS OF ALKENE METATHESIS).

To address the problems associated with ill-defined, multicomponent catalytic systems, extensive basic research in organometallic chemistry was performed to get a better insight into the mechanisms at work (23). This quest led to the discovery of metal–alkylidene complexes (also referred to as metal-carbene complexes, in this article the two terms are not differentiated). The observation that such species constituted well-behaved, single-component catalysts for olefin metathesis provided the final clue in support of the mechanism first proposed by

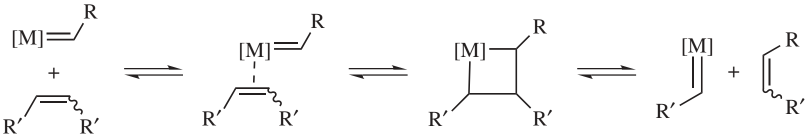


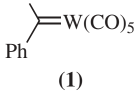
Fig. 4. Metallacyclobutane mechanism for olefin metathesis.

Hérisson and Chauvin in 1971, and which is now commonly accepted (13). Four basic steps are proposed in this mechanism: (*1*) coordination of the olefin to the metal center of a carbene (or alkylidene) complex, (*2*) a [2 + 2] cycloaddition forming a metallacyclobutane intermediate, (*3*) a cycloreversion step, and (*4*) decoordination of the olefin. All these steps are reversible as shown in Fig. 4.

Depending on the nature of the catalyst and the olefin, the relative stabilities of the metal-carbene and the metallacyclobutane vary. Thus, in some cases the metallacycle is a stable intermediate, while in other ones it is too unstable to be detected. For example, the metallacyclobutane has only been rarely observed with ruthenium-based catalysts (24). In these systems, it is more likely a transition state than a discrete intermediate.

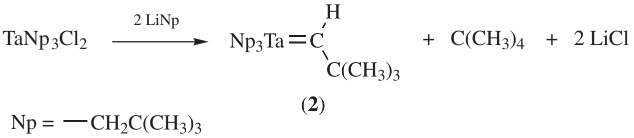
Further insights into the reaction mechanism with ruthenium(II) catalyst precursors were obtained by Grubbs and co-workers. They confirmed the overall mechanistic pathway summarized above for some of the most active catalyst precursors available to date, ie, complexes of the type $L_2Cl_2Ru{=}CHR$ where ruthenium(II) chloride is formally ligated to bulky and basic ligands L (phosphines or *N*-heterocyclic carbenes, NHC), and to an alkylidene fragment (see the section UNICOMPONENT METATHESIS INITIATORS BASED ON LATE TRANSITION METALS) (25–27). So far, many details of the exact sequence of interactions between the catalyst and the olefin remain unclear and it cannot be ruled out that some variations occur in the basic mechanism proposed by Hérisson and Chauvin, depending on the metal and the experimental conditions. For example, the observation that persistent radical anions are present in some metathesis polymerizations using ruthenium-based initiators led to the proposal of a somewhat different reaction pathway involving radicals (28,29).

3.2. Unicomponent Metathesis Initiators Based on Early Transition Metals. Katz was one of the first chemists to recognize the significance of the Hérisson and Chauvin mechanism and to demonstrate that stable metal-carbene complexes were able to initiate olefin metathesis reactions. Using the most reactive metal–carbene species known at that time, pentacarbonyl(diphenylmethylene)tungsten (**1**) [50276-12-5], he successfully polymerized strained and low strain cycloolefins with remarkably high stereoselectivities (30).



(1)

Another important milestone on the path to modern metathesis initiators was reached in the Schrock laboratory at M.I.T. with the synthesis of well-defined, high oxidation state imido alkylidene complexes of tantalum first, soon followed by tungsten and molybdenum. The successful development of such species owes a lot to the use of the neopentyl ligand ($CH_2C(CH_3)_3$, Np) in which no mode of decomposition involving β hydrogen atoms is possible. Indeed, a neopentyl group is sterically protected and tends to block intermolecular decomposition processes. At the same time, it promotes an intramolecular reaction through the activation of an α hydrogen atom, thereby yielding an alkylidene moiety that is most stable toward bimolecular decomposition. The trineopentylneopentylidene tantalum complex (**2**) [54294-45-0] was the first stable compound possessing a terminal alkylidene ligand isolated along these lines (eq. 2).



$$\mathrm{TaNp_3Cl_2} \xrightarrow{2\,\mathrm{LiNp}} \mathrm{Np_3Ta{=}C}\begin{matrix}\mathrm{H}\\ \mathrm{C(CH_3)_3}\end{matrix} + \mathrm{C(CH_3)_4} + 2\,\mathrm{LiCl} \qquad (2)$$

(**2**)

$$\mathrm{Np} = -\mathrm{CH_2C(CH_3)_3}$$

The fundamental work of Schrock helped gain a better understanding of the parameters that affect the activity of the catalysts based on early transition metals (31,32). The strategy elaborated to obtain highly efficient, well-defined, four-coordinate high oxidation state alkylidene complexes implied the selection of bulky alkoxide ligands, which lower the lowest unoccupied molecular orbital (LUMO) of the metal and favor reactions with olefins while blocking bimolecular decompositions. The design of tetrahedral Mo(VI) and W(VI) complexes that contain a neopentylidene and two alkoxide ligands also required that a sterically bulky dianionic ligand be the fourth substituent. In this respect, the 2,6-dimethyl- or 2,6-diisopropylphenyl imido ligands were found to maximize steric bulk while limiting the possibility of side reactions. All together, the sterically bulky nature of all four ligands in $(RO)_2M(NR')(CH\text{-}t\text{-}Bu)$ complexes prevented coupling of the neopentylidene ligands and allowed many such species to be isolated and characterized. The presence of the carbene ligand M=CHR is readily detected by proton nuclear magnetic resonance (^{1}H nmr) spectroscopy, since the alkylidene proton resonates at particularly low field (typical δ values: 10–15 ppm).

One of the main advantages of high oxidation state metal alkylidene complexes over the earlier ill-defined metathesis initiators (see previous section) is that they do not require a cocatalyst for activation and that their activity and selectivity can be controlled by an appropriate choice of the ancillary ligands. The rate of olefin metathesis is especially high for molybdenum complexes. The relatively high stability of tungstenacyclobutane intermediates is possibly the reason why metathesis with a tungsten catalyst is often slower than with its molybdenum counterpart, even though the reaction of a W=C bond with a C=C bond is believed to proceed faster than the reaction of the analogous Mo=C unit with the same C=C bond. As an example, the synthesis of imido alkylidene complexes **4a–d** from sodium molybdate is described in Fig. 5. The key step yields the dimethoxyethane adduct **3** [126949-63-1] as a versatile intermediate that reacts readily with alkoxides, even when they are poor nucleophiles.

Prominent among these initiators are Schrock's four-coordinate alkoxy imido complexes of molybdenum, **4a** and **4b**, with a bulky aryl substituent on

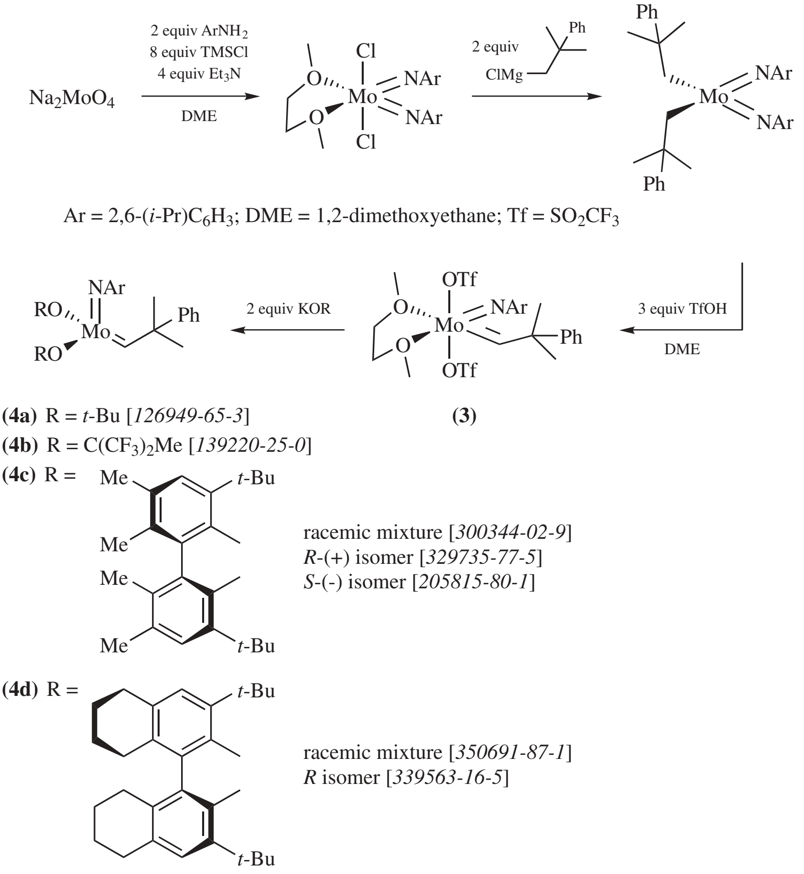
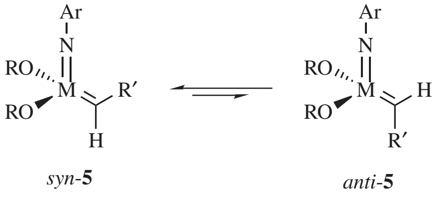


Fig. 5. Synthetic route for the preparation of molybdenum imido alkylidene complexes.

the imido group and bulky, electron-withdrawing alkoxide ligands OR that, as already pointed out, provide steric shield and contribute to increase the electrophilicity of the metal center. Such complexes constitute very active and well-behaved metathesis precatalysts (31,33). Complex **4a** is a relatively mild initiator most suited for the living ROMP of functionalized norbornenes and norbornadienes that do not contain activated protons. Complex **4b** displays a broader range of applicability and has been successfully employed for a variety of metathesis reactions, including ROMP, RCM, and CM. Both **4a** and **b** are commercially available. These and related complexes are, however, very sensitive toward oxygen and moisture and must be handled under rigorously inert atmosphere in dry solvents using Schlenk techniques or a glove box.

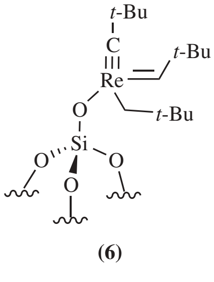
Since the imido ligand is bound to the metal through a pseudo-triple bond in complexes of type **4**, the electron pair on the nitrogen atom is donated into an empty *d* orbital on the metal center. Therefore, the M–N–Ar angle is $\sim 180^\circ$ and the *d* orbital employed for π bonding of the imido ligand to the metal must lie perpendicular to the M–N–Ar plane. Hence, two spatial arrangements are possible for the alkylidene moiety (*syn*- and *anti*-**5**, eq. 3). It turns out that the two isomers have dramatically different reactivities and that the rate at which they interconvert by rotation around the metal–carbon bond can vary significantly as a function of the OR and imido ligands. The minor anti isomer in **5** (M = Mo) has been shown to be orders of magnitude more reactive than the syn one (34).



(3)

In addition to this stereoisomerism, chiral alkoxides may serve as ligands for high oxidation state imido alkylidene complexes of molybdenum and tungsten. For example, Mo-based compounds associated with enantiomerically pure biphenolate or binaphtolate derivatives **4c** and **d**, respectively (see Fig. 5) have been used in a variety of metathesis reactions to induce asymmetry. Both enantiomers (and the racemate) of compound **4c** are commercially available. High enantiomeric excesses (ee) could be achieved for kinetic resolutions, asymmetric ring-closing metathesis (ARCM), or in the enantioselective synthesis of medium-size cyclic ethers and amines via tandem AROM/CM. Recent advances to make chiral Mo-based catalysts more user-friendly and practical to use include their *in situ* preparation from readily available precursors and their immobilization on polymeric as well as inorganic supports to ease separation and recycling (32,35).

In contrast with the early ill-defined metal oxides deposited on silica or alumina (see the section The Early Catalysts and the Mechanism of Olefin Metathesis), "single-site" heterogeneous catalysts displaying well-defined, active sites uniform in composition and distribution were later synthesized via surface organometallic chemistry (SOMC) and fully characterized (36). In these systems based on molybdenum, tungsten, or rhenium, the surface operates as a classical ligand in terms of coordination chemistry and serves as a substitute for the bulky alkoxy groups that proved essential in the homogeneous catalysts. The remaining discrete ligands are tailored to tune the activity, the selectivity, and the catalyst lifetime. Complex **6** is an example of a well-defined rhenium(VII) carbene–carbyne heterogeneous catalyst covalently linked to silica. This complex was found to display catalytic performances comparable to the best classical heterogeneous catalysts in the disproportionation of propene or in the cross-metathesis of propene and isobutene (37).

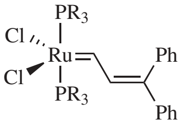


(6)

3.3. Unicomponent Metathesis Initiators Based on Late Transition Metals.

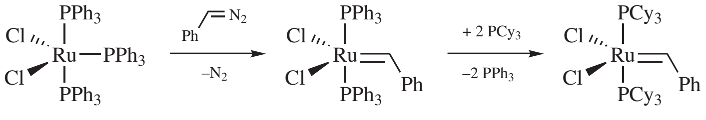
Among the many carbene complexes based on late transition metals from groups 8–10 that were tested as potential metathesis catalysts, ruthenium derivatives stand out for their versatility and efficiency. Carbene precursors associated with iron, cobalt, and rhodium react stoichiometrically with olefins to generate cyclopropanes. With ruthenium and osmium, a low coordination number of the metal usually results in catalytic metathesis activity, whereas high coordination number complexes lead to stoichiometric cyclopropanation. Iridium tends to act only as a metathesis initiator in ill-defined systems. However, both osmium and iridium complexes are generally less active than their ruthenium counterparts. They are also much more expensive, therefore they have not been widely studied.

Complex **7a** was the first well-defined olefin metathesis catalyst based on ruthenium synthesized in the Grubbs' laboratory at Caltech. Poorly active, it only polymerized highly strained cycloolefins, eg, norbornene and bicyclo[3.2.0]-hept-6-ene. In sharp contrast with the Mo-based systems developed by Schrock (see previous section) where the more electron withdrawing the ancillary ligands, the higher the catalytic activity, ruthenium(II) complexes need to be associated with powerful electron-donating ligands in order to display high catalytic activities. Thus, initiator **7b** containing the strongly basic tricylohexylphosphine ligand (PCy_3) proved to be a much more efficient metathesis promoter than its parent **7a**. Tailoring phosphine bulkiness is also crucial for achieving high catalytic efficiencies. Indeed, tricyclohexylphosphine, or to a somewhat lesser extent triisopropylphosphine, yielded active catalytic systems, whereas no or little activity was observed with the more sterically demanding tritertiobutylphosphine and tricyclooctylphosphine ligands, a likely consequence of the excessive steric crowding imparted by the phosphine moiety.



(7a) R = Ph [140853-27-6]
(7b) R = Cy [151491-95-1]

With the $L_2X_2Ru{=}CHR$ structure identified as a promising target for designing well-defined, highly efficient metathesis initiators, considerable synthetic efforts were thrown into the preparation of new species more readily accessible and more active than **7**. Two major routes were successfully devised to produce kilogram-scale quantities of stable ruthenium alkylidene complexes. The first one uses phenyldiazomethane as a carbene transfer reagent to introduce a benzylidene fragment onto the $RuCl_2(PPh_3)_3$ starting material (Fig. 6). The reaction proceeds quickly and safely at −78°C even on a large scale. Subsequent phosphine exchange with PCy_3 affords $RuCl_2({=}CHPh)(PCy_3)_2$ (**9**) [172222-30-9] in high yield and purity (38). This complex is obtained as a purple microcrystalline powder. It is commercially available and often referred to as the *(first generation) Grubbs catalyst*. Because of its relative ease of synthesis, high catalytic activity, and broad functional group tolerance, it constitutes



(8) **(9)**

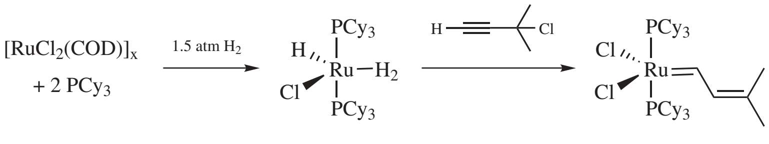
Fig. 6. Synthetic route for the preparation of ruthenium alkylidene complexes with phenyldiazomethane.

the most frequently used well-defined, Ru-based olefin metathesis catalyst in research laboratories (39).

The rearrangement of propargyl halides provides a second route to ruthenium alkylidene complexes. This procedure utilizes readily available alkynes as vinylcarbene precursors and introduces the PCy_3 ligand directly in the first step of a convenient one-pot procedure. There is no need to isolate the intermediate hydrido complex **10** and the phosphine exchange step is bypassed. This results in saving time and avoids the extensive washings required in alternate preparations (40). The reaction is currently performed on the multi-kilogram scale with 3-chloro-3-methyl-1-butyne to produce the dimethylvinylalkylidene catalyst **11** [194659-03-5] (Fig. 7). Although slightly less active than the corresponding benzylidene species, **9**, complex **11** is also less expensive and often sufficient for initiating ROMP reactions. Thus, it has been used predominantly in commercial applications for the synthesis of polymeric materials (see the section POLYDICYCLOPENTADIENE).

Extensive mechanistic studies on the first generation of ruthenium catalysts suggested that diphosphino complexes, eg, **8**, **9**, or **11**, form a highly active monophosphine intermediate **13** (formally a 14-electron complex) during the catalytic cycle (Fig. 8). According to this mechanism, the overall catalytic activity of a generic species **12** is dictated by the relative rates of three processes: (*1*) phosphine dissociation (initiation, k_1), (*2*) phosphine recoordination (k_{-1}), and (*3*) olefin binding (k_2). The recoordination of free PR_3 is competitive with substrate binding and the balance between the two processes determines the propagation rate, provided that the subsequent formation of the metallacyclobutane intermediate is fast (cf. Fig. 4). High catalytic activities are therefore anticipated when initiation occurs readily (ie, k_1 is large) and when the coordinatively unsaturated intermediate **13** reacts preferentially with an olefinic substrate instead of free phosphine (ie, k_2/k_{-1} is large).

This rational analysis led to the synthesis of mixed complexes of type **12** where one phosphine is replaced by a *N*-heterocyclic carbene ligand (NHC).



COD = 1,5-cyclooctadiene

(10) **(11)**

Fig. 7. Synthetic route for the preparation of ruthenium alkylidene complex **11** by insertion−elimination with propargyl chloride.

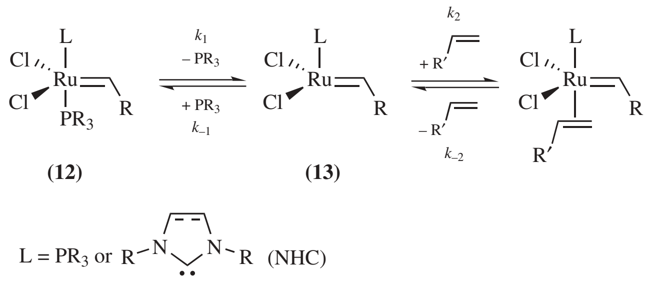


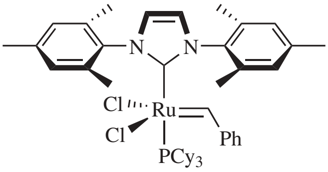
Fig. 8. Proposed mechanistic pathway for the activation of ruthenium alkylidene complexes.

Such mixed-ligand olefin metathesis catalysts were first investigated by the group of Herrmann in Munich (17). Additional reports by Grubbs (18,19) and Nolan (20) followed soon thereafter. Compared to phosphines, NHCs are better σ-donors and form stronger bonds to metal centers. Indeed, the Ru−NHC bond strengths were calculated to be 20–40 kcal/mol stronger than Ru−PR$_3$ bond strengths. Although the substitution of one PCy$_3$ ligand in **9** with a NHC decreases the phosphine dissociation rate (k_1) of about two orders of magnitude, the selectivity for binding olefinic substrates over free phosphine (k_2/k_{-1}) increases simultaneously by four orders of magnitude. In other words, once the phosphine comes off, coordination of olefin is highly favored compared to rebinding of PCy$_3$. As a consequence, the NHC complexes can perform multiple olefin metathesis events before they recoordinate phosphine and return to their resting state (26). It follows that mixed phosphine/NHC complexes are dramatically superior to the bis(phosphine) or bis(NHC) species when considering overall metathesis activities. Further kinetic studies have also shown that the rate of phosphine dissociation increases with decreasing phosphine donor strength. Complexes containing a NHC and a triarylphosphine (**12**, L = NHC; PR$_3$ = PPh$_3$) exhibit significantly improved initiation relative to the same complexes with a more basic tricycloalkylphosphine (**12**, L = NHC; PR$_3$ = PCy$_3$). Conversely, phosphine reassociation shows no direct correlation with intrinsic electronic factors (41). In a number of cases, these second generation ruthenium catalysts could rival with the molybdenum initiators in terms of activity, while maintaining a superior stability and a broader functional group compatibility.

The key to the synthesis of mixed ligand complexes is to use NHCs bearing two mesityl groups on their nitrogen atoms (mesityl (Mes) is 2,4,6-trimethylphenyl), because they give stable complexes in which only one phosphine is substituted. Most other aryl-substituted NHCs lacking substituents on all ortho positions or alkyl-substituted NHCs either decompose or give double substitution. Metathesis initiators are typically 16-electron complexes displaying a distorted square-pyramidal geometry with the alkylidene ligand in the apical position and a trans diphosphine or trans phosphine-NHC arrangement. The ortho methyl groups on the mesityl substituent favor a perpendicular arrangement of the mesityl and imidazole rings by limiting *N*-mesityl rotation. In contrast, five-coordinate ruthenium carbene complexes that contain strong

π-acceptor ligands, eg, CO, favor a trigonal-bipyramidal geometry and are not active in metathesis (42).

Regarding the nature of the *N*-heterocyclic ring, the imidazole system has been the most extensively investigated so far. Thanks to its aromaticity and the presence of electron-pair donating atoms next to the divalent carbon, it stabilizes the nucleophilic carbene center (43). Thus, the first stable singlet carbenes isolated by Arduengo in the 1990s were unsaturated imidazol-2-ylidene species, later complemented by their saturated imidazolidin-2-ylidene analogues (44). Accordingly, two NHCs bearing mesityl groups on a five-membered ring are available, an unsaturated one (abbreviated IMes) and its saturated dihydro derivative (abbreviated SIMes or H_2IMes). Highly active and stable ruthenium alkylidene complexes are obtained with both ligands, although the SIMes catalyst is somewhat superior in certain cases, but the trend is not general. The two species are depicted in structures **14** and **15**, respectively. The alkylidene proton and carbon atoms in this family of compounds show up, respectively, at ~ 18–20 and 295–305 ppm relative to tetramethylsilane (TMS) in nmr spectra. Complex **15** [246047-72-3] is commercially available and is nicknamed the *Super Grubbs* or *second generation Grubbs catalyst*. Related complex **16** [503044-55-1], where the five-membered imidazolidin-2-ylidene ligand was replaced by a six-membered pyrimidin-2-ylidene ring demonstrated a lower activity in olefin metathesis reactions, a likely consequence of increased steric hindrance (45). Similarly, ruthenium complex **17** [845641-17-0] containing a four-membered *N*-heterocyclic carbene ligand also yielded a slower catalyst than **14** or **15**(46).



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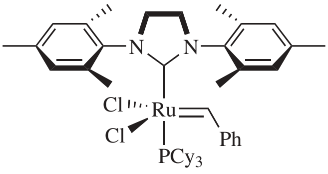

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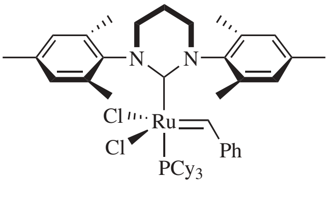
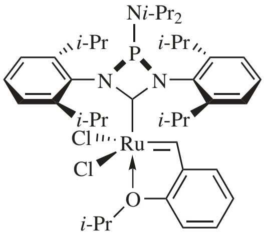
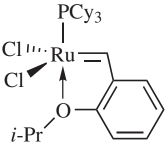


(16)

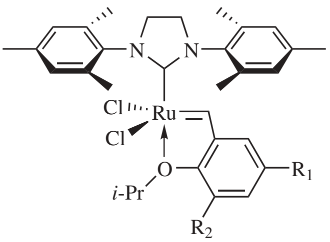


(17)

The scope of ruthenium-catalyzed olefin metathesis was further expanded by the introduction of derivatives of **9** and **15** containing monodentate and/or chelating N-, O-, P- and Cl-donor ligands. Among them, the styrenyl ether complex **18** and its non-phosphine analogues **19a–c** stand out for their high stability toward air and moisture. Hence, they are conveniently purified and recycled by column chromatography without any special precautions. The chelation of the ether influences the initiation and propagation rates defined in Fig. 8 for the corresponding nonchelated initiators. Complex **18** [203714-71-0] initiates ~ 30 times slower but propagates nearly four times faster than **9**. Complex **19a** [301224-40-8], an air stable bright green solid is a fast initiating catalyst that proved particularly efficient in cross-metathesis of electron-deficient olefins, offering reactivity levels and selectivities surpassing those displayed by the phosphine-bearing complex **15** (47). Both compounds **18** and **19a** are commercially available, although expensive. They are known, respectively, as the *first and second generation Hoveya-Grubbs catalysts*.



(18)



(19a) $R_1 = R_2 = H$ [301224-40-8]
(19b) $R_1 = NO_2$, $R_2 = H$ [502964-52-5]
(19c) $R_1 = H$, $R_2 = Ph$ [478944-19-3]

Over the past few years, intense catalytic engineering efforts were directed toward fine tuning the electronic and steric properties of the styrenyl ether moiety in phosphine-free complexes, **19**. Two main successful approaches were followed to destabilize the Ru–O bond and ease the decoordination of the ether ligand in order to generate the catalytically active 14-electron species more efficiently. Thus, Grela has reduced the electron density on the Ru-chelating isopropoxy group by introducing a strong electron-withdrawing nitro substituent on the styrene ring. The resulting complex **19b** showed a dramatic increase of reactivity compared to **19a** and was active in the RCM of trisubstituted olefins even at 0°C (48). Similar enhancements were also reported by Blechert, whose strategy involved the steric destabilization of the Ru–O bond by introducing a bulky phenyl or naphthyl substituent adjacent to the isopropoxy group on the styrenyl ring. For example, complex **19c** outperformed catalyst precursors **15** and **19a** in all cases, whether it was for RCM, CM, ROCM, or ROMP applications (49,50).

A great deal of attention has also been paid to the immobilization of well-defined ruthenium alkylidene complexes onto solid supports (51). The reasons that motivated research in this area are threefold. First, contamination of products with metal traces is a critical issue with ruthenium initiators, particularly when pharmaceutical applications are envisaged, but also in polymer chemistry, because of the persistent color usually associated with catalyst residues. While Mo-based initiators and their decomposition products are easily extracted by adding a base, the removal of ruthenium-containing by-products is often a lot more tedious. Second, recourse to sophisticated, single-component metathesis promoters significantly adds to the cost of a process, therefore the possibility of

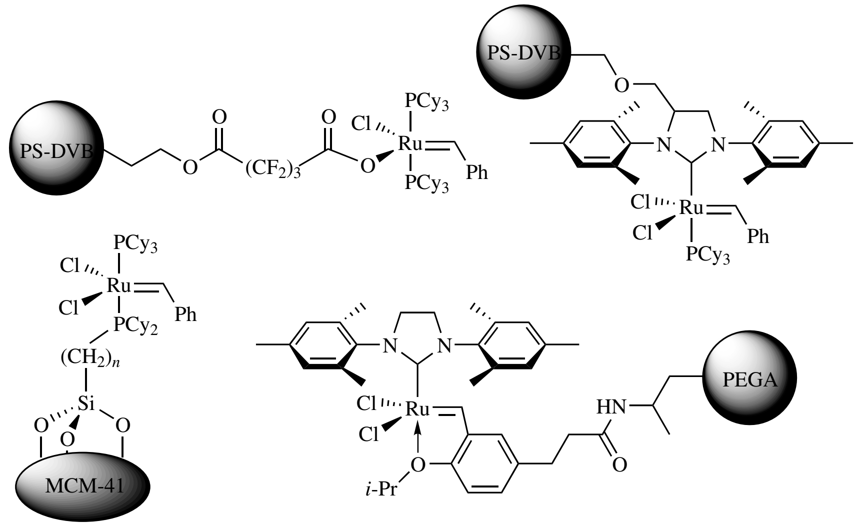
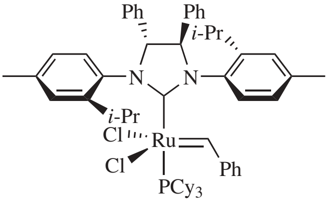


Fig. 9. Examples of solid-supported ruthenium catalysts for olefin metathesis.

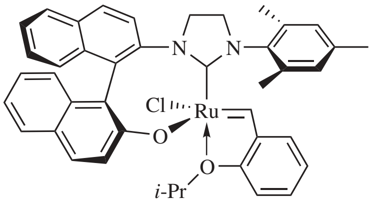
reusing or recycling the catalyst precursors is a highly sought feature. Third, supported catalysts give access to high throughput techniques and can be used in continuous flow reactors.

Several approaches have been proposed to graft ruthenium active species onto organic or inorganic supports. They differ in the choice of the attachment point and the nature of the solid matrix. Thus, immobilization was achieved via phosphine, NHC, alkylidene, or halogen ligand exchange. Polymeric supports employed so far include polystyrene cross-linked with divinylbenzene (PS-DVB), polyethyleneglycol (PEG), or the highly hydrophilic ω-aminopoly(ethyleneglycol) amide (PEGA-NH_2). Various forms of porous and nonporous silica were also used to prepare heterogeneous systems, among them sol–gel glass monoliths and mesoporous MCM-41. A few representative assemblages of solid-supported ruthenium catalysts are depicted in Fig. 9 (51).

Up to now, there have been very few examples of asymmetric olefin metathesis catalyzed by ruthenium complexes (52). The first investigations in this field were reported in 2001 by Grubbs and co-workers. Atropoisomeric NHC ligands were prepared from optically active diamines and used as substitutes for SIMes in mixed phosphine–NHC benzylidene complexes, thereby providing an asymmetric version of the second generation Grubbs catalyst. High ee (up to 90%) were obtained in the desymmetrization of achiral trienes through ARCM. Complex **20** [372951-09-2] was the most efficient chiral inductor in the series under scrutiny, although the identity of the optimal catalyst varied strongly with the substrate nature (19). Hoveyda later disclosed a modification of its own catalyst where a peripheral phenolic oxygen coordinates to ruthenium and locks the aromatic group into a twisted chiral conformation. Thus, complex **21** [438001-40-2] is stereogenic at the metal center and effectively promotes AROCM reactions (up to 98% ee) of substrates that would polymerize with chiral molybdenum catalysts (53,54).



(20)



(21)

3.4. Molybdenum- versus Ruthenium-Based Metathesis Catalysts.

The advent of well-defined, single-component catalysts allowed the study of the relationship between their structure and reactivity in great details. Although there is some common ground between molybdenum or tungsten catalysts on one hand, and ruthenium initiators on the other hand (the active species have a 14-electron metal center associated with an alkylidene fragment in both cases), there are also significant differences between each other. As the metal center is shifted from left to right and from bottom to top in the Periodic Table, its selectivity for olefins over more polar functionalities increases. This general trend is illustrated for titanium-, tungsten-, molybdenum-, and ruthenium-based metathesis catalysts in Table 2 (39). It can be rationalized on the basis of the hard and soft acids and bases (HSAB) theory developed by Pearson (55). Since late transition-metals possess more *d* electrons than early ones, they are softer acids and they interact preferentially with soft bases like olefins than with harder oxygen-containing functional groups.

This difference of behavior has significant consequences in terms of reactivity and practical applications. In contrast to their ruthenium-based counterparts, molybdenum alkylidene species are highly sensitive to air and moisture and must be handled under inert atmosphere in rigorously anhydrous solvents. Furthermore, the early transition-metal complexes are incompatible with aldehydes, ketones, carboxylic acids, most alcohols and primary amines. Yet, they remain effective in the presence of nitriles and sterically crowded alcohols. They are also unaffected by thioethers and phosphines, two functional groups that readily inactivate most ruthenium initiators of the first generation. Although ruthenium catalysts of the second generation display higher activities and a better

Table 2. **Functional Group Tolerance of Early and Late Transition-Metal Olefin Metathesis Catalysts**

Titanium	Tungsten	Molybdenum	Ruthenium	
acids	acids	acids	**olefins**	
alcohols, water	alcohols, water	alcohols, water	acids	
aldehydes	aldehydes	aldehydes	alcohols, water	↑ **Increasing**
ketones	ketones	**olefins**	aldehydes	**Reactivity**
esters, amides	**olefins**	ketones	ketones	
olefins	esters, amides	esters, amides	esters, amides	

compatibility with organic functionalities than their predecessors, molybdenum complexes still exhibit a unique level of reactivity and constitute the most effective chiral catalysts presently available for asymmetric transformations. Thus, both families of catalysts offer complementary reactivity and selectivity patterns.

4. Industrial Applications of Alkene Metathesis

Olefin metathesis has opened up new routes to important petrochemicals, oleochemicals, polymers, and specialty chemicals. The transformation often gives access with remarkable atom economy to structures that are not available by any other means, or only via multistep painstaking procedures. Currently, there is still a marked dichotomy between major industrial processes, which rely on inexpensive, ill-defined, multicomponent catalytic systems, and research laboratory applications, where the use of well-defined metal-alkylidene complexes is often favored to guarantee high activities under reproducible conditions, albeit at the price of a much higher cost. Relentless competition to develop catalysts that are even more efficient and tolerant, easily accessible, and possibly recyclable should, however, result in a rapid change of paradigm (56).

4.1. Production of Olefins. *The Phillips Triolefin Process and the Olefin Conversion Technology.* By the late 1960s, Phillips Petroleum developed the first commercial process based on olefin metathesis. The main objective at that time was to convert cheap propene into more valuable ethene and 2-butene (cf. eq. 1). The reaction conditions depended on the catalytic system employed. With cobalt molybdate on alumina, temperatures of 120–210°C at 25–30 bar were sufficient to achieve propene conversion of $\sim 40\%$ (corresponding to equilibrium), whereas higher temperatures (300–375°C) were required with tungsten(VI) oxide on silica. The Phillips triolefin process was operated from 1966 to 1972 by Shawinigan Chemicals near Montreal in Canada. The plant had a capacity of 50,000 tons of feedstock per year and the propene was obtained from a local naphtha cracker (57,58).

Because olefin metathesis is a reversible reaction, propene can also be produced from ethylene and 2-butene depending on the market price of the feedstocks. Indeed, the rising demand for polymerization-grade propene in the 1980s led to a reverse of the Phillips triolefin process known as olefin conversion technology (OCT), which is now offered for license by ABB Lummus Global in Houston, Texas.

In the OCT process (Fig. 10), butene and ethylene feeds are mixed together and sent through a guard bed to remove trace impurities. The mixture is heated before entering a fixed-bed reactor where metathesis occurs over a WO_3/SiO_2 heterogeneous catalyst at temperatures > 260°C and 30–35 bar. The reaction can be carried out with (*E*)- or (*Z*)-2-butene as well as 1-butene provided that a second catalyst (MgO) is added to promote isomerization of the terminal alkene into its more stable internal isomer. The conversion of butene is $> 60\%$ per pass with a selectivity for propene $> 90\%$. The reactor effluent is fractionated and the C_2 and C_4 cuts are recycled.

This process and some variations on this theme were implemented by several companies using different sources of butene. Since 1985, Lyondell operates

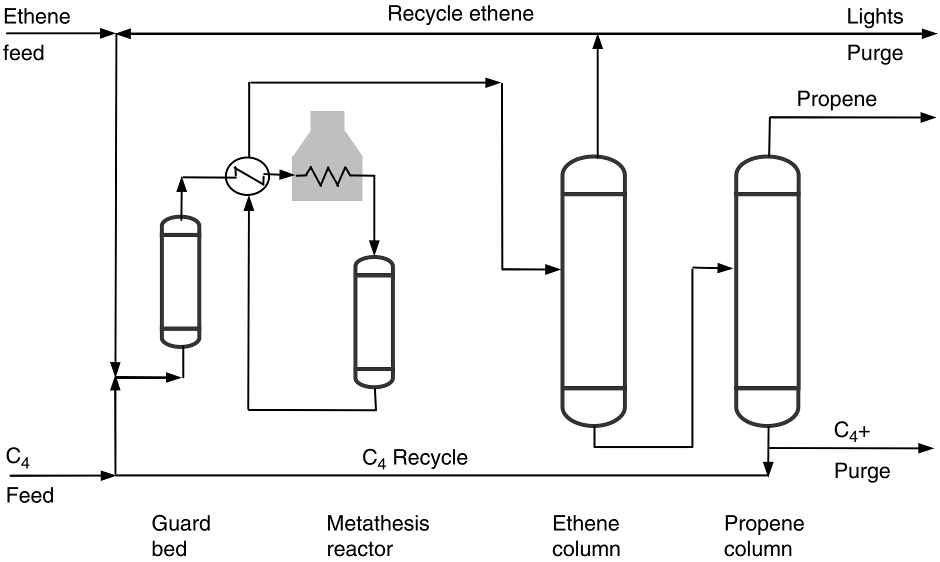


Fig. 10. The OCT process (reverse Phillips triolefin process). Reprinted from Ref. 79 with permission from Elsevier.

a plant to produce propene with a capacity of 136,000 tons/year in Channelview, Texas, using a technology developed by its sister company ARCO. In the original process, ethylene was first dimerized into 2-butenes with a homogeneous nickel catalyst. Presently, butenes isolated from raffinate-2 are more likely to be used. They are reacted with additional ethylene in a metathesis step to yield propene. In a 2001 joint venture, BASF and Atofina brought on stream a steam cracker plant in Port Arthur, Texas, which incorporates an OCT unit to convert ethylene and butenes into propene. The OCT technology is also currently implemented in Japan and China to meet increasing propene demand in Asia (59).

A modification of the triolefin process developed jointly by Axens, a subsidiary of Institut Français du Pétrole (IFP) in France, and the Chinese Petroleum Corporation in Taiwan utilizes rhenium(VII) oxide on alumina to convert ethylene and 2-butene into propene. The catalyst is more active than its predecessors and operates already at room temperature. It is loaded in a moving bed reactor at 35°C and 60 bar to afford a 63% conversion (equilibrium) per pass. However, this process called Meta-4 is not yet applied industrially. Another OCT-derived process called Automed metathesizes butene to produce 3-hexene, which is subsequently isomerized into 1-hexene, a high value comonomer used inter alia in the polymerization of ethylene. The reaction has been tested at the pilot plant scale by Sinopec at its Tianjin site in China (59).

Olefin disproportionation reactions can also be carried out at room temperature in homogeneous phase with complexes of molybdenum or tungsten activated by alkyl aluminum halides. Such systems do not seem to have been used industrially despite their high activity. Common to all metathesis processes with catalysts based on early transition metals is the need to purify carefully the feed of any polar impurities and dienes, since these materials poison the catalysts. Active species based on less oxophilic metals do not suffer (or to a much lesser extent) from these drawbacks.

The Shell Higher Olefins Process. The Shell higher olefin process (SHOP) is one of the most ingenious in the chemical industry. Its initial objective was the preparation of linear α-olefins and fatty alcohols with the most suitable chain lengths for surfactants, that is, C_{11}–C_{15}. The SHOP sequence comprises a combination of four reactions interlaced with fractionation and recycling (60). The first step is the oligomerization of ethylene in the presence of a homogeneous nickel-phosphine catalyst. A spread of chain lengths is obtained with a Schulz-Flory type distribution (roughly a "bell-shaped" C_4–C_{40} distribution). The process is engineered so that the peak of the distribution is centered around C_{10}–C_{14}. These desired α-olefins make for ~ 30% of the reaction mixture, which means that ~ 70% of unwanted chain lengths is produced. The different fractions are separated by distillation in a second step and the C_{10}–C_{14} olefins are hydroformylated to C_{11}–C_{15} aldehydes, which are further hydrogenated *in situ* to the corresponding alcohols. The overall functional group interconversion constitutes the third step. Next, the C_4–C_{10} and C_{16}–C_{40} α-olefins are isomerized into internal olefins using heterogeneous catalysts, eg, magnesium oxide granules. At the end of this fourth step, the double bonds are distributed randomly throughout the alkenes. The fifth step involves cross-metathesis of the short- and long-chain internal olefins on an alumina-supported molybdenum catalyst. The reaction is carried out at 100–125°C and 10 bar. It affords a broad statistical distribution of chain lengths, some of which being in the C_{10}–C_{14} range. This desired fraction represents 10–15% of the total distribution. It is removed by distillation in the sixth step and the internal olefins are recycled and subjected again to metathesis, the operation being repeated to extinction.

The SHOP technology is highly versatile. Although it is primarily intended for the production of C_{11}–C_{15} detergent alcohols, any other chain length may be separated by fractionation, should a market exist for it. For example, C_6 or C_8 olefins may be used in copolymerization with ethylene and the C_{10} fraction converted into products such as synthetic lubricants, plasticizer alcohols, etc. Shell Chemicals operates SHOP units at Stanlow (UK) and Geismar, Louisiana, with a total production of linear alpha and internal olefins close to 1,200,000 tons/year. These higher olefins are sold under the trade name Neodene.

Synthesis of Neohexene. The manufacture of neohexene (3,3-dimethyl-1-butene) [558-37-2] is accomplished by cross-metathesis of technical grade diisobutene with ethylene (ethenolysis). The isomer that goes through metathesis is 2,4,4-trimethyl-2-pentene, the internal double bond of which reacts readily with ethylene (eq. 4). A catalyst is added to isomerize other diisobutenes with terminal double bonds into the desired internal olefin. In the industrial process (Fig. 11), the dimers of isobutene are first fractionated to remove an oxidation inhibitor that would otherwise poison the dual catalytic system. The purified diisobutene feed enters the top of the reactor containing the catalysts along with an ethylene stream compressed to the required pressure. The separation of reactants and products is achieved by stripping and fractionation. With a heterogeneous catalyst mixture of WO_3/SiO_2 and MgO, the selectivity to neohexene is ~ 85% at 370°C and 30 bar for an average 60–70% diisobutene conversion. The isobutene

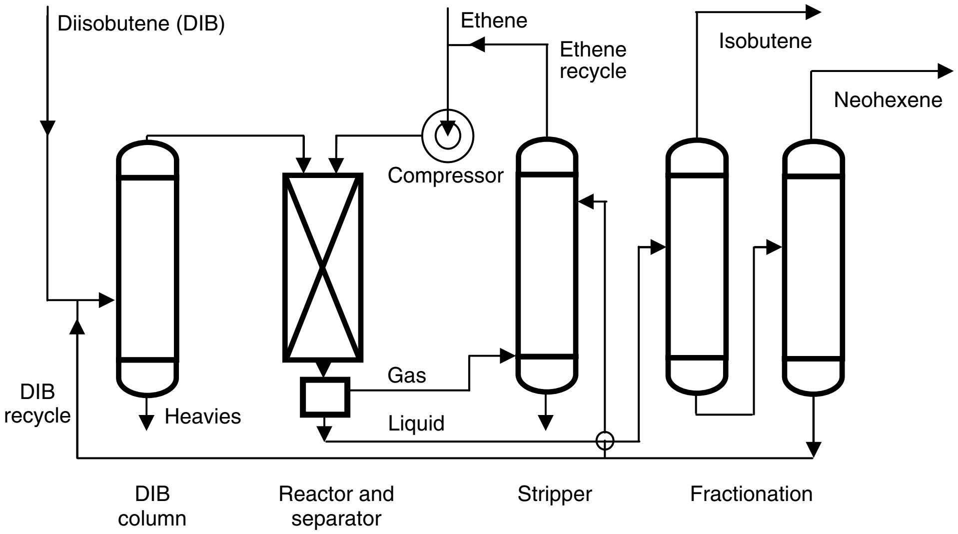
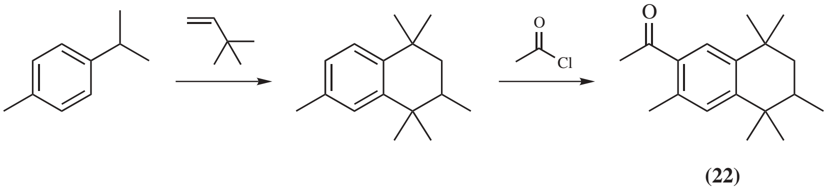


Fig. 11. The neohexene process. Reprinted from Ref. 79 with permission from Elsevier.

coproduct is recycled by dimerization in a separate reactor. A neohexene unit built in 1980 with an initial capacity of 1600 tons/year (but expanded several times) is operating at Chevron Phillips Houston petrochemical complex in Pasadena, Texas (59).

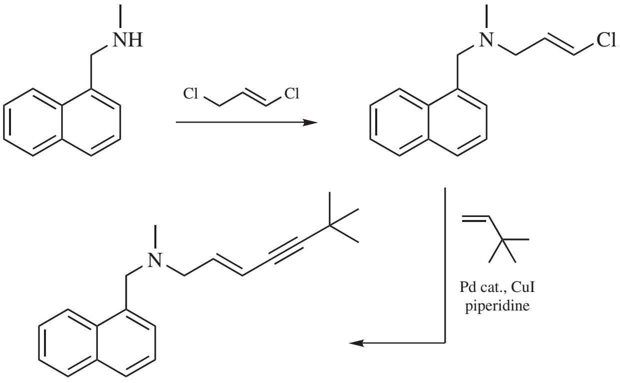
$$(H_3C)_3C{-}CH{=}C(CH_3)_2 + H_2C{=}CH_2 \xrightleftharpoons{\text{catalyst}} (H_3C)_3C{-}CH{=}CH_2 + H_2C{=}C(CH_3)_2 \tag{4}$$

Neohexene is an important intermediate in the synthesis of bicyclic musk perfumes (61). For example, its reaction with *p*-cymene (4-isopropyltoluene) followed by acetylation affords 7-acetyl-1,1,3,4,4,6-hexamethyltetrahydronaphthalene, **22** [21145-77-7], an inexpensive synthetic fragrance that shows excellent odor and fixation properties (Fig. 12). Because compound **22** is also highly stable toward light and alkali, it is widely used in cosmetic and detergent formulations under the trade names Tonalide, Tetralide, Fixolide, or Extralide. Concern is raising, however, that due to their low biodegradability, synthetic musk fragrances are not innocuous and tend to accumulate in different compartments of the aquatic environment, in indoor–ambient air, house dust, and in addition, in human samples (62).



(22)

Fig. 12. Synthesis of a bicyclic musk perfume from *p*-cymene and neohexene.



(23)

Fig. 13. Synthesis of the antimycotic agent terbinafine with neohexene.

Neohexene is also used to make synthetic antimycotic agents, eg, terbinafine (*trans*-*N*-methyl-*N*-(1-naphthylmethyl)-6,6-dimethyl-2-hepten-4-ynyl-1-amine), **23** [91161-71-6]. This allyl amine derivative acts as a specific inhibitor of squalene epoxidase, a key enzyme in fungal ergosterol biosynthesis (63,64). It can be prepared by coupling the terminal alkyne with a vinyl chloride derived from *N*-methyl-1-naphthalenemethanamine using a palladium catalyst in the presence of copper(I) iodide and an amine (Sonogashira coupling) (Fig. 13) (65).

Synthesis of α,ω-Diolefins. Another application of alkene metathesis is the manufacture of α,ω-diolefins by ethenolysis of cycloolefins (58). Terminal dienes are of industrial interest as cross-linking agents in olefin polymerization. They are also used as starting materials in fine synthesis where they allow the preparation of α,ω-difunctional intermediates leading to fragrances, agrochemicals, and pharmaceuticals. Among them, 1,5-hexadiene [592-42-7] and to a lesser extent 1,9-decadiene [1647-16-1] are produced in multiton quantities. These compounds result from the ethenolysis of 1,5-cyclooctadiene and cyclooctene, respectively (Fig. 14). 1,5-Cyclooctadiene comes from the dimerization of butadiene and yields cyclooctene by selective hydrogenation. 1,5-Hexadiene can also be prepared by the metathesis of 1,5,9-cyclododecatriene with 3 equiv of ethylene. Similarly, 1,13-tetradecadiene [21964-49-8] can be obtained via ethenolysis of cyclododecene.

In the late 1980s, Shell and Phillips developed routes to α,ω-diolefins for the specialty market. The first commercial plant, operating under the name FEAST (Further Exploitation of Advanced Shell Technology) was opened in 1987 in Berre l'Etang (France) and has a capacity of 3000 tons/year. The reactions take place in the liquid phase under extremely mild conditions (0–20°C, 1–2 bar) using a promoted Re_2O_7/Al_2O_3 catalyst.

Synthesis of Fine Chemicals. The use of olefin metathesis for the synthesis of biologically active compounds and fine chemicals has grown rapidly over the past few years. Both CM and RCM are particularly suited for the construction of small open-chain molecules and macrocycles, respectively (66). These reactions served, inter alia, as key steps in the synthesis of various agrochemicals and pharmaceuticals, eg, macrocyclic peptides, cyclic sulfonamides, novel

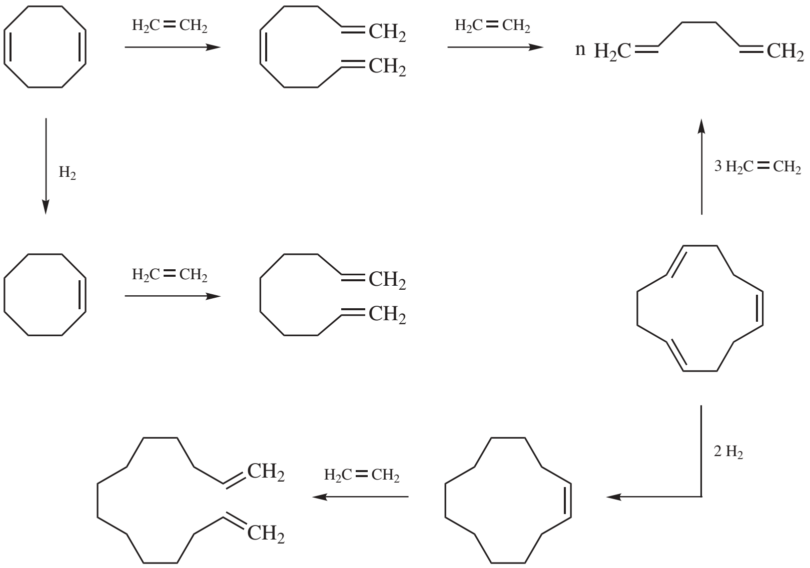


Fig. 14. Synthesis of α, ω-diolefins via olefin metathesis.

macrolides, or insect pheromones (67). When targeting this last category of molecules, ruthenium-alkylidene complexes proved especially efficient catalysts. For example, the cross-metathesis of 11-eicosenyl acetate and 3-hexene (4 equiv) catalyzed by the second generation Grubbs catalyst $RuCl_2(=CHPh)(PCy_3)(SIMes)$ (**15**) afforded 11-tetradecenyl acetate in 84% yield (Fig. 15). This product acts as a sex pheromone for the omnivorous leafroller, a common pest of apples, grapes, peaches, pears, and nectarines. Recourse to traps filled with this synthetic equivalent of the sex attractant emitted by the females confuses the males and disrupt the mating cycle. Thus, the use of pheromones is an effective and environmentally-friendly method for controlling insect populations. The (*E*/*Z*) distribution of internal double bonds in 11-tetradecenyl acetate obtained by ruthenium-catalyzed metathesis matches the one observed in the natural pheromone [(*E*/*Z*) = 82/18] and the two starting materials, 11-eicosenyl acetate and 3-hexene, are easily prepared from commodity chemicals (jojoba oil and 1-butene, respectively) (68).

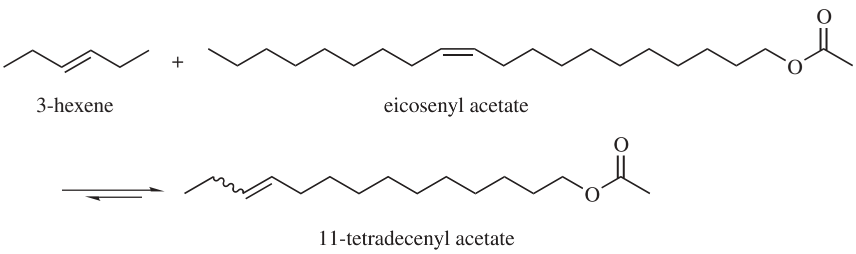


Fig. 15. Synthesis of the omnivorous leafroller pheromone 11-tetradecenyl acetate by cross-metathesis.

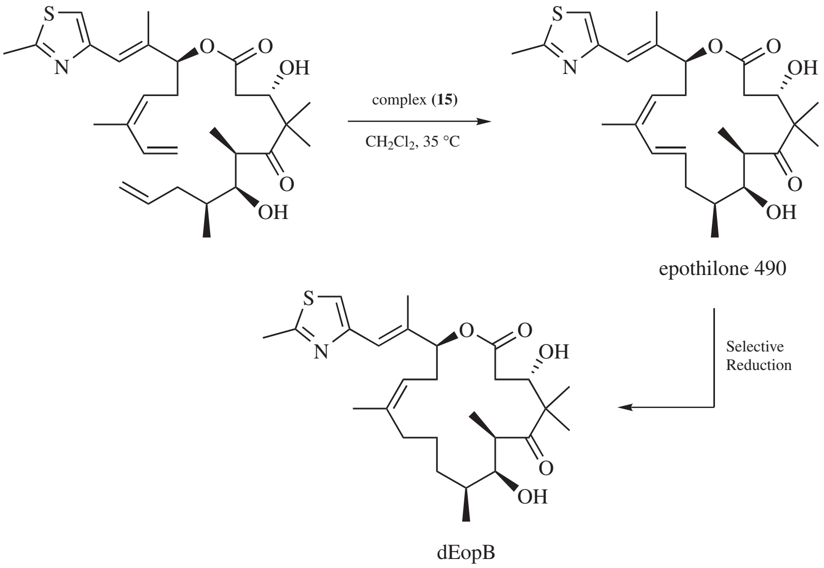


Fig. 16. Synthesis of 12,13-desoxyepothilone (dEopB) by ring-closing metathesis.

The synthesis of epothilones has also benefited from the superior catalytic activity and high functional group tolerance of the second generation Grubbs catalyst, **15**. For example, Danishefsky has selected this complex to close the macrocyle of epothilone 490 (Fig. 16). Selective reduction of this key intermediate with diimide then affords 12,13-desoxyepothilone B (dEpoB) in 55% overall yield for the two steps (69). Epothilones have stirred much excitement in the scientific community and have stimulated the creativity of synthetic organic chemists because of their promising anticancer properties. These cytotoxic macrolides exhibit the same mode of action than paclitaxel, which is sold as Taxol by Bristol-Myers Squibb. They all bind to microtubules and inhibit their depolymerization (molecular disassembly) into tubulin. In contrast to paclitaxel, epothilones seem, however, to retain potency against multiple drug resistant tumors.

Applications in Oleochemistry. Although fossil fuels still constitute the main feedstock for energy production and organic synthesis, the search for alternative renewable natural resources is a major challenge for the twenty-first century. Several vegetable oils have become important world commodities and a number of applications already exist for oleochemicals in various areas, eg, cosmetics, soaps, detergents, polymer additives, and coatings. Because fatty acid esters derived from sunflower, soybean, rapeseed, or linseed oil are unsaturated, they can undergo metathesis. Consequently, the conversion of raw materials derived from seed oils into valuable products via olefin metathesis has been a research focus for decades. Results have been mitigated so far. Significant progresses were made, nevertheless, when the Grubbs catalysts and related ruthenium-alkylidene complexes became available (70). For example, a 2004 study from the Dow Chemical Company showed that the ethenolysis of methyl oleate catalyzed by Grubbs benzylidene complex $RuCl_2(=CHPh)(PCy_3)_2$ (**9**) resulted in the highly selective formation of 1-decene and methyl 9-decenoate

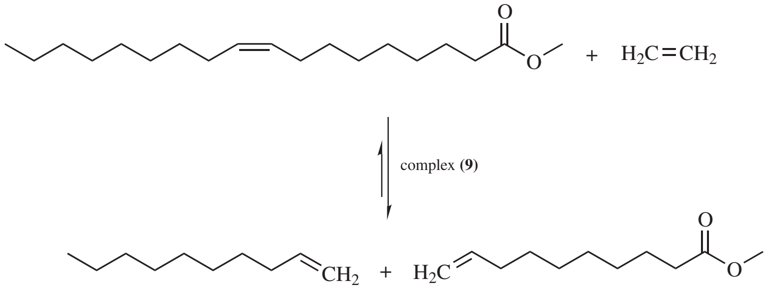
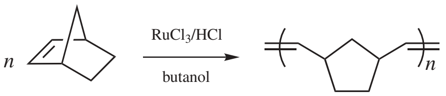


Fig. 17. Ethenolysis of methyl oleate.

(Fig. 17). Methyl 9-decenoate is a key intermediate in the synthesis of many chemical products. After hydrolysis and hydrogenation, it yields decanoic acid and decanol, two substances used in the synthesis of lubricants and plasticizers. It can also be used to produce fragrances, pheromones, prostaglandins, or even nylon-10 polyamide after conversion into 10-aminodecanoic acid. Its metathesis coproduct 1-decene is also an important intermediate in organic synthesis and has a variety of applications on its own in polymers, surfactants and lubricants manufacture. At 25°C and 4-bar ethylene, catalyst turnovers (TO) close to 3000 were recorded for the production of methyl 9-decenoate and 1-decene from methyl oleate in the presence of catalyst **9**. Although substantial, these values remained well below the 50,000 TO threshold required for a commercially viable process with homogeneous ruthenium catalysts in batch reactor operation (71).

4.2. Production of Polymers. Olefin metathesis technology has broad applicability for polymer synthesis, either via ADMET or ROMP (72). Several industrial processes involving homogeneous ROMP reactions have been developed and brought into practice. Most of them use ill-defined multicomponent catalytic systems based on molybdenum, tungsten, or ruthenium salts, along with various cocatalysts. From an economical point of view, ROMP is an attractive process for making polyalkenamers, when cheap monomers are available or when the resulting polymers display special properties compensating for their high price. Metathesis-derived polycycloalkenes tend to be elastomeric materials, and because metathesis preserves the double bonds, they are also vulcanizable.

Polynorbornene and Its Hydrogenated Derivatives. The first commercial metathesis polymer was polynorbornene. It was introduced on the market in 1976 by CdF-Chimie in France and in 1978 in the United States and Japan, under the trade name Norsorex. Norbornene is bicyclo[2.2.1]hept-2-ene [498-66-8], a strained bicyclic olefin that readily undergoes ring opening, as the reaction contributes to relieve its internal tension. This monomer is prepared on a large scale by a Diels-Alder reaction between cyclopentadiene and ethylene. The ROMP process operates in air with a very simple catalytic system made of ruthenium trichloride and hydrogen chloride in butanol (eq. 5). It gives a 90% trans polymer with a very high molecular weight (> 3,000,000 g/mol). Polynorbornene can be used in oil spill recovery since it absorbs up to 5–10 times its weight of oil. When vulcanized, it gives an elastomer used for damping noise and vibrations. The polymer is presently produced in Carling (France) by Atofina and developed worldwide by the Japanese company Nippon Zeon (59).



(5)

Cyclic olefin polymers are also manufactured by ring-opening metathesis polymerization of norbornene derivatives followed by hydrogenation (Fig. 18). Because of the bulky (multi)cyclic units attached to the polymer backbone, these materials are amorphous and display a high glass-transition temperature (T_g), optical clarity, low shrinkage, low moisture absorption, and low birefringence (73). They also feature outstanding molding processability. These properties make them suitable for the production of plastic lenses and optical storage media. Although the demand for such optoelectronic devices is currently limited and cycloolefin polymers occupy a specialty niche, applications are gradually expanding and future developments are anticipated. There are several types of commercial cyclic olefin polymers offered mainly by two suppliers, Japan Synthetic Rubber (JSR) and Zeon Chemicals, under the trade names Arton for the former company and Zeonex or Zeonor for the second one. They differ by the nature of the cyclic monomer and the polymerization method used. Production on the JSR site is located in Chiba, Japan. Its annual output capacity was tripled in 2004 and now reaches 3000 tons/year. Zeon operations at the Mizushima plant in Japan were also expanded recently to peak at a capacity of 10,000 tons/year (74).

Polyoctenamer. Another important industrial application of ROMP is the polymerization of cyclooctene [931-88-4] to yield linear and cyclic polyoctenamers (eq. 6). The monomer feedstock is synthesized from 1,3-butadiene via 1,5-cyclooctadiene. The metathesis reaction takes place in the presence of a tungsten-based catalyst and is practically quantitative. The products obtained contain at least 25 wt% of macrocycles. The formation of these cyclic oligomers is due to intramolecular backbiting side reactions competing with the propagation

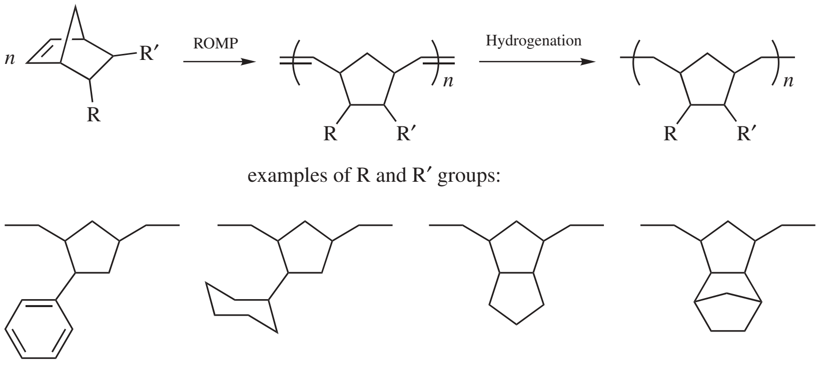
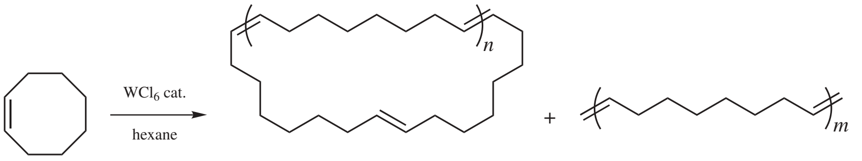


Fig. 18. Synthesis of hydrogenated polynorbornenes.

step in the chain mechanism. The bulk of the material is made of high molecular weight linear chains (~100,000 g/mol). The cis/trans ratio, which determines the degree of crystallinity of the polymers, may be altered to some extent by adapting the experimental conditions, but trans double bonds are predominant in all cases. Polyoctenamers have been commercialized since 1980 by Degussa-Hüls under the trade name Vestenamer. The annual capacity for their production was ~ 12,000 tons in 1989. Vestenamers are vulcanizable elastomers used as blending materials, mostly in the rubber industry (58).



(6)

Polydicyclopentadiene. Much interest has been paid to the ROMP of *endo*-dicyclopentadiene (DCPD) [77-73-6], an inexpensive by-product of the petrochemical industry, since it is the dimer of cyclopentadiene, the largest component of the C_5 stream obtained by steam cracking of naphtha (60). In the course of DCPD polymerization, the more strained norbornene ring undergoes metathesis, together with some of the double bonds in the less-strained cyclopentene ring, giving rise to cross-linking (Fig. 19). The resulting thermoset polymer is tough and rigid, with a high modulus and excellent impact strength. The process is most conveniently accomplished via reaction injection molding (RIM). The RIM technique allows to shape pieces and parts by direct polymerization of low molecular weight components in a mold through a mixing activated reaction. Hardening occurs almost instantaneously and large objects (up to 300 kg) can be cast in a single operation.

The commercial production of molded objects from DCPD-based feed using RIM technology was developed in the 1980s, mainly by Hercules Inc. under the trade name Metton and by B.F. Goodrich under the trade name Telene. These processes use classical ill-defined catalytic systems based on molybdenum, tungsten, or rhenium generated *in situ* by mixing two streams of monomer and precursors. In the Metton liquid molding resin, one stream contains DCPD, tungsten salts ($WCl_6 + WOCl_4$), nonylphenol (to solubilize the inorganic

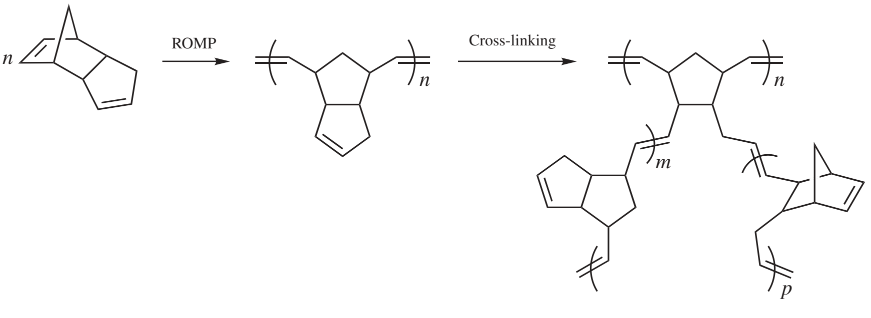


Fig. 19. Ring-opening metathesis polymerization of dicyclopentadiene.

compounds in the monomer), additives, and fillers. The second stream contains DCPD, a cocatalyst ($EtAlCl_2$), retarder, additives, and fillers. The two streams are combined in a mixing chamber and injected into the mold, where an exothermic polymerization takes place after a short induction period. In the Telene process, the catalyst precursor is tetrakis(tridodecylammonium)octamolybdate activated with a mixture of diethylaluminum chloride, propanol, and silicon tetrachloride. B.F. Goodrich has licensed its DCPD-RIM technology to Cymetech (Huntsville, Texas) and to Nippon Zeon, which applies it under the trade name Pentam. Poly-DCPD stemming from these three product lines (Metton, Telene, and Pentam) has been used mainly for outdoor applications, because of persistent odor problems due to residual monomer in molded parts. Thus, it can be found in automobile bumpers, snowmobile and truck hoods, tractor fenders, industrial containers, etc (59). During the late 1990s, the polymerization of dicyclopentadiene has experienced new developments owing to the emergence of stable ruthenium-alkylidene complexes that are both highly active and user-friendly. In particular, the Grubbs catalysts of the first and second generations have hold the attention of process scientists. In the field of ROMP, these well-behaved initiators were first employed commercially in the polymerization of dicyclopentadiene, because of the many potentials of poly-DCPD resins. Indeed, the unique properties offered by these materials, a ready processability combined with exceptional toughness and corrosion resistance, make them well-suited for a variety of applications, most notably in high performance and self-healing composites (75). Ruthenium-promoted RIM of poly-DCPD proceeds almost quantitatively, even for very bulky objects, thereby suppressing effectively the odor of the monomer. The catalysts are also less sensitive to air and moisture than those based on early transition metals. In the United States, Cymetech now offers poly-DCPD products derived from either ill-defined molybdenum-based systems (the Telene range acquired from B.F. Goodrich) or well-characterized ruthenium complexes (the Prometa line developed with Materia Inc., Pasadena, California). In Japan, Cymetech has teamed with Hitachi Chemical to promote the ruthenium technology under the Metathene designation (76).

Other ROM Polymers. Other selectively functionalized ROM polymers enabled by the new generation of ruthenium catalysts are currently under intense scrutiny, if not yet commercialized, for a variety of combinatorial chemistry and life science applications (77). Recourse to immobilized reagents, catalysts, and scavengers is a well-established methodology to achieve high throughput in the screening of biologically active agents or in the generation of chemical libraries. Most supported reagents developed so far are based on either polystyrene beads or inorganic solids. Despite tremendous advances in this field, loading capacities remain limited and access to the active sites is not always optimal. To overcome these restrictions, swelling polymers in which every monomer unit incorporates the desired functionality are actively sought. From a practical point of view, this objective is most conveniently achieved by carrying out ROMP reactions in the presence of ruthenium initiators. Thanks to their remarkable functional group tolerance and high activity, these catalysts are indeed well suited to polymerize monomers that were quantitatively functionalized prior to ring opening. For example, Barrett has prepared a number of polynorbornene-based reagents and scavengers using Grubbs ruthenium-alkylidene

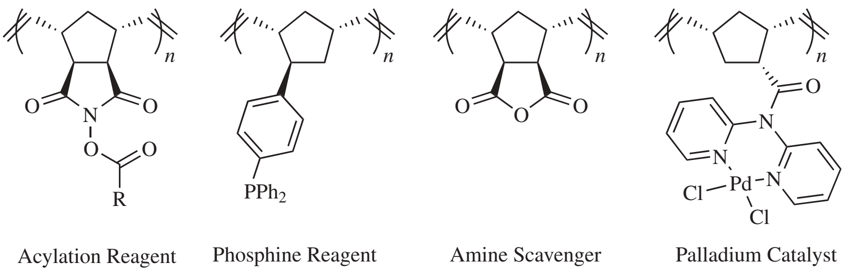


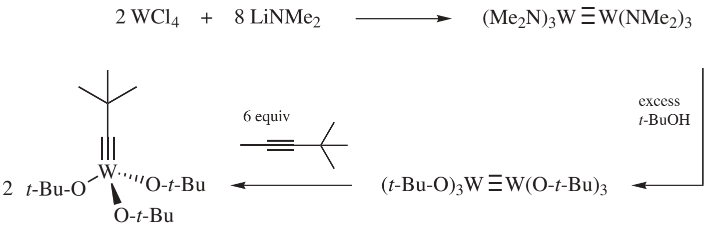
Fig. 20. Examples of ROM polymer-supported reagents, scavenger, and catalyst.

catalysts (Fig. 20). The monomers were easily assembled by Diels-Alder reaction between cyclopentadiene and a suitable dienophile or by palladium-catalyzed reactions involving norbornadiene. Buchmeiser used a similar approach to generate an array of dipyridyl-based palladium catalysts active in Heck, Suzuki, and Sonogashira couplings, as well as in amination reactions (78).

5. Alkyne Metathesis

The earliest report of alkyne metathesis dates back to 1968 and involved heterogeneous catalytic systems obtained from tungsten oxides on silica operating at 200−450°C. Homogeneous catalysts prepared from molybdenum hexacarbonyl or related metal sources and simple phenol additives followed a few years later (80). The nature of the active species and the reaction mechanism remained elusive at that time. Moreover, the catalysts were not particularly efficient and required high temperatures to perform. During the 1990s, the polymerization chemistry of substituted acetylenes experienced spectacular developments with the advent of Schrock's well-defined imido alkylidene complexes of molybdenum and tungsten $(RO)_2M(NAr)(CHR')$ (see the section UNICOMPONENT METHATHESIS INITIATORS BASED ON EARLY TRANSITION METALS). These complexes function as living polymerization catalysts for substituted acetylenes, eg, ortho-substituted phenylacetylenes, and α, ω-diynes. Since the initiation efficiency is quantitative, polymers with a specific molecular weight can be targeted.

The pursuit of well-defined metal-alkylidene catalysts for alkene metathesis also led to the discovery of high oxidation state carbyne (or alkylidyne) complexes, first of tantalum and later of tungsten, molybdenum, and rhenium. Some of these species were found to metathesize alkynes with remarkable ease, principally those based on molybdenum and tungsten (80). Reasons underlying the rational design of alkylidene catalyst precursors also apply to their alkylidyne counterparts. Thus, steric protection is needed in order to prevent bimolecular decomposition and the use of bulky alkoxide ligands proved crucial for obtaining long-lived metathesis initiators. A large variety of $(RO)_3M{\equiv}CR'$ complexes was synthesized along these lines, primarily tungsten derivatives. Among them, complex **24** [78234-36-3] stands out for its remarkable activity under mild conditions and is the most widely used Schrock alkylidyne catalyst for alkyne metathesis. It is conveniently prepared, even on a fairly large scale, from tungsten(IV) chloride

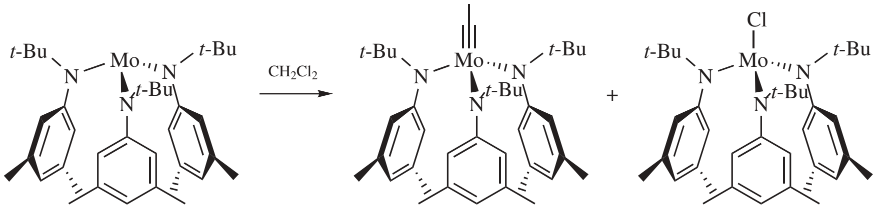


24

Fig. 21. Synthetic route for the preparation of tungsten alkylidyne complex **24**.

(Fig. 21). The key step involves the cleavage of a W≡W triple bond with neoheptyne, a process that is a metathetical event itself (81). Complex **24** is stable for extended periods of time when stored under inert atmosphere in a refrigerator.

Recently, significant progresses in catalytic engineering were made on two fronts. The first breakthrough was the discovery by Fürstner and co-workers of a new family of high oxidation state trisamido complexes of early transition metals that act as well-defined unimolecular catalyst precursors for alkyne metathesis. The most significant representative of this class of compounds is the sterically hindered molybdenum complex **25**. Although it does not react with alkynes per se, this precatalyst is readily activated upon treatment with various halogen sources, the most convenient one being dichloromethane. Two major molybdenum-containing products are formed under these conditions: the known methylidyne complex **26** [405159-77-5] and the monochloro adduct **27** [251306-52-2] (eq. 7). Although carbyne, **26**, reacts with alkynes, it does not sustain catalytic turnover. Complex **27**, on the other hand, is an efficient catalyst precursor, which exhibits a remarkable tolerance toward many polar functional groups, in sharp contrast with tungsten alkylidyne **24** (82,83). This superior compatibility is attributed to the shielding effect of the bulky ligand sphere, which attenuates the effective Lewis acidity of the metal center.



(25) **(26)** **(27)** (7)

A second development came from investigations aimed at improving the classical molybdenum carbonyl-phenol system. Studies showed that the use of cocatalysts bearing strong electron-withdrawing substituents, such as *p*-chloro-, *p*-trifluoromethyl-, or *o*-fluorophenol led to high yields and fast reaction rates under optimized conditions. This revised multicomponent process is very attractive from a practical point of view, because it requires only readily available and

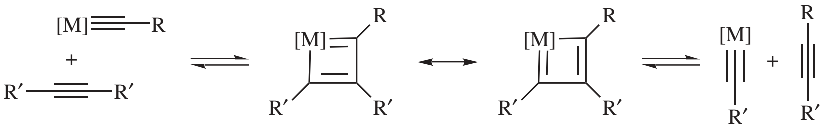


Fig. 22. Metallacyclobutadiene mechanism for alkyne metathesis.

shelf-stable catalyst precursors that can be used in reagent-grade solvents without any particular precaution. On the negative side, the active species formed *in situ* remain highly sensitive against many polar functional groups. Furthermore, the methodology requires rather high reaction temperatures (~130°C) and quite often preactivation with a sacrificial alkyne (84).

Regardless of whether well-defined carbyne complexes or *in situ* generated systems are examined, the exact nature of the true catalytic species remains unknown. It is, however, expected that high valent metal centers play a key role in alkyne metathesis. Hence, two possible mechanistic pathways are conceivable: the alkylidyne mechanism and the metallacyclopentadiene mechanism. In the alkylidyne mechanism, metallacyclobutadiene intermediates are initially formed from alkynes and carbyne complexes in much the same way that metallacyclobutanes are formed from olefins and metal alkylidene complexes (cf. Fig. 4). The reaction proceeds via a series of $[2+2]$ cycloaddition and cycloreversion steps that lead to the split of internal alkynes (Fig. 22). In several cases, metallacyclobutadienes were isolated and characterized. They successfully promoted catalytic turnover when submitted to metathetical conditions.

In the metallacycle mechanism, a metallacyclopentadiene species is first formed through oxidative coupling of two alkyne partners with a metal catalyst (Fig. 23). Reductive elimination then affords a cyclobutadiene complex, whose isomerization, followed by oxidative addition, gives a regioisomer of the first metallacyclobutadiene intermediate. Metathesis products are eventually released upon cycloreversion.

Despite the rather long history of alkyne metathesis and the availability of several efficient catalytic systems covering a wide range of substrates, the reaction has not received as much attention from the organic community than olefin

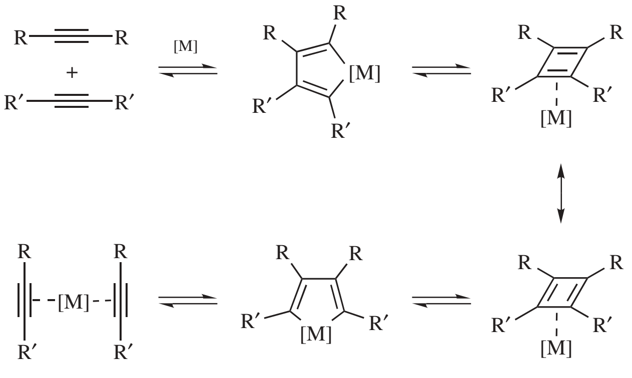


Fig. 23. Metallacyclopentadiene mechanism for alkyne metathesis.

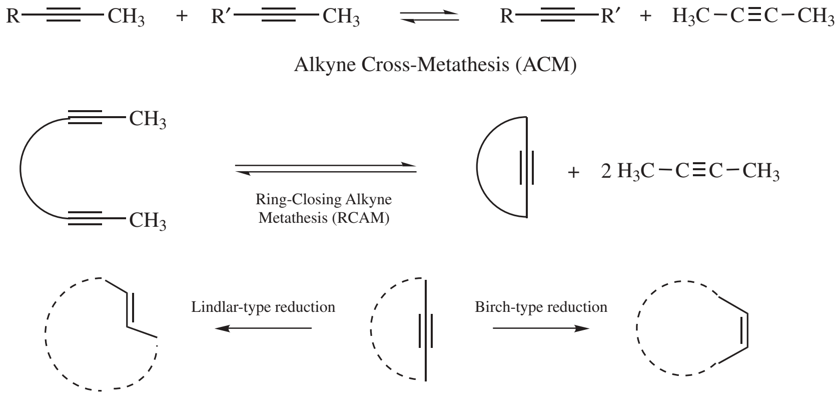


Fig. 24. Main types of alkyne metathesis reactions and postmetathesis reduction.

metathesis. So far, only two kinds of alkylidyne unit exchanges were mainly investigated for the synthesis of small unsaturated molecules, namely, alkyne cross-metathesis (ACM) and ring-closing alkyne metathesis (RCAM) (Fig. 24). These reactions are often accompanied by a postmetathesis reduction step to afford (cyclo)olefins with a controlled stereochemistry about the double bond. While alkene metathesis provides a more straightforward approach for exchanging substituents across double bonds, the geometrical isomer distribution that ensues is usually governed by steric and/or thermodynamic factors. Thus, mixtures of (*E*)- and (*Z*)-olefins (or only the most thermodynamically stable isomer) are obtained, and the stereochemical outcome of the reaction may be hard to predict. In sharp contrast with this situation, recourse to alkyne metathesis followed by a partial reduction of the triple bond using either Lindlar- or Birch-type procedures gives access to any given isomer at will (Fig. 24).

This concept has been exploited by Fürstner in elegant syntheses of natural products using ACM or RCAM reactions. For instance, the total synthesis of prostaglandin E_2-1,15-lactone (PGE_2 lactone) **30** was accomplished by ring-closing diyne precursor **28** in the presence of molybdenum complex, **25**, activated with dichloromethane in toluene at 80°C (85). The catalytic system employed did not affect the C=C double bond present in the starting material and preserved all labile structural elements, including the chiral center α to the carbonyl group. Lindlar hydrogenation of cycloalkyne **29** followed by acidic cleavage of the protecting *tertio*-butyldimethylsilyloxy group (OTBDMS) afforded the desired target molecule in 53% overall yield from **28** (Fig. 25).

In the supramolecular arena, acyclic diyne metathesis (ADIMET) was successfully employed to prepare alkyne-bridged macrocycles and polymers (84). A particularly interesting application of this technique leads to poly(*p*-phenyleneethynylene) (PPE) derivatives that show great potential for sensory and molecular wire devices (86). Schrock's tungsten-carbyne complex, **24**, initially served as catalyst for these reactions. Yet, it was soon realized that undefined species generated *in situ* from simple multicomponent systems led to similar results under less stringent experimental conditions. For example, mixtures of molybdenum hexacarbonyl and *p*-chlorophenol were active in

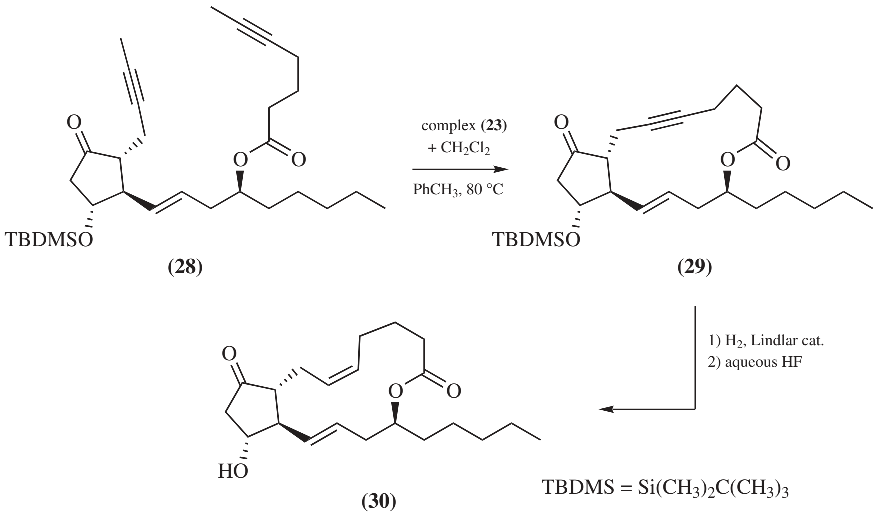
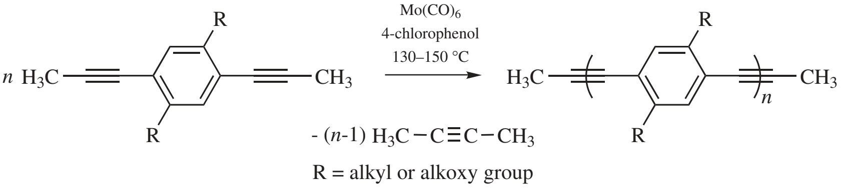


Fig. 25. Synthesis of prostaglandin E_2-1,15-lactone by ring-closing alkyne metathesis.

the polymerization of dipropynylated dialkyl- or dialkoxybenzenes to furnish dialkyl-PPEs of high molecular weight in quantitative yields (eq. 8) (87).



(8)

Alkynes can also be polymerized by chain growth in the presence of transition metal catalysts to give high molecular weight polymers (88). Suitable monomers include acetylene, mono- and disubstituted acetylenes and α, ω-diynes (Fig. 26). The main chain of the resulting materials is made of alternating carbon−carbon double bonds. This polyconjugated backbone confers unique

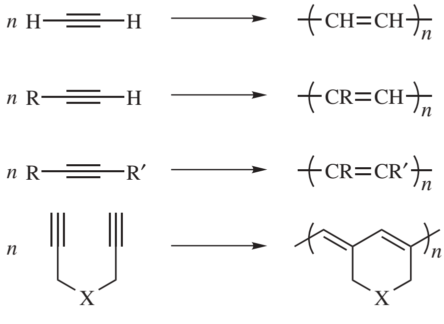


Fig. 26. Main types of alkyne polymerizations.

characteristics to the polymers. Outstanding features, such as conductivity, gas permeability, non-linear optical properties, magnetic properties, photo- and electroluminescent properties not accessible from the corresponding vinyl polymers become available. For example, polyacetylene [25067-58-7] is the best known conducting organic polymer. When appropriately doped, it even exhibits metallic conductivity. Introduction of side groups further improves its processability and endows it with novel properties and functions. Both Schrock- and Grubbs-type well-defined alkylidene complexes were investigated as catalyst precursors for acetylene polymerizations, together with a wide range of other transition metal species, spanning from group 4 to 10. Metal-carbene initiators (either preformed or generated *in situ*) are likely to react via metathetical pathways, but an insertion mechanism bearing no relation to metathesis is also possible when metal-alkyl species are present.

6. Ene–Yne Metathesis

Enyne metathesis is a powerful method for the synthesis of 1,3-dienes (89,90). It involves bond reorganization between an alkene and an alkyne to produce a butadiene (Fig. 27). The procedure was initially restricted to intramolecular rearrangements due to the difficulty in controlling the chemo- and stereoselectivities in intermolecular processes. Indeed, in the latter case, enyne metathesis is competing with both olefin and diyne homocoupling reactions. Furthermore, a mixture of isomeric cross-products is usually obtained, due to the distribution of (*E*) and (*Z*) double bonds within the butadiene skeleton. Conversely, side reactions are minimized in the intramolecular transformation as a result of entropic effects and the proximity of the reacting moieties. Significant enhancements in the selectivity of intermolecular cross-metathesis reactions between alkene and alkyne partners were, however, recently reported. Therefore, both the intra- and intermolecular variants are now commonly used in organic synthesis. Various terms have been used to designate the two possibilities, depending on the type of mechanism and substrates involved. In this text, the intramolecular reaction will be referred to as ring-closing enyne metathesis (RCEYM) and its intermolecular version as ene yne metathesis (EYM) to underline the parallel with the corresponding olefin metathesis transformations (cf. Fig. 1). Contrasting with the RCM or CM of two alkene moieties, however, no ethylene or any other by-product

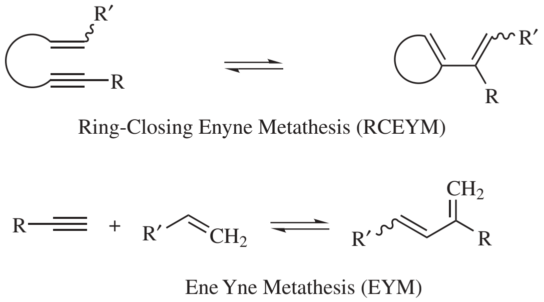


Fig. 27. Main types of enyne metathesis reactions.

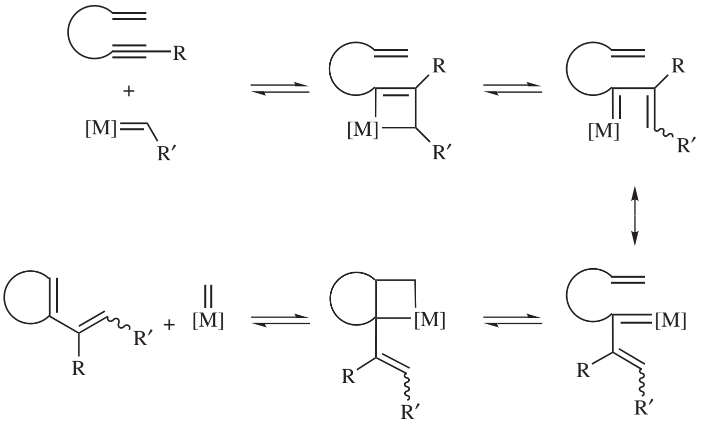


Fig. 28. Metallacyclobutene mechanism for enyne metathesis.

is released during enyne metathesis. Thus, C–C bond formation occurs with complete atom economy.

Two kinds of mechanisms were proposed for enyne metathesis. Because the reaction bears an obvious kinship to alkene metathesis, the intermediacy of metallacycles was postulated in reactions catalyzed by transition metal-carbene complexes of chromium, tungsten, molybdenum, and ruthenium (Fig. 28). With these initiators, the reaction formally proceeds via [2 + 2] cycloaddition between the triple bond of the alkyne partner and the carbene complex to give a metallacyclobutene intermediate. Ring opening of this complex via cycloreversion produces a new alkylidene fragment that can form a metallacyclobutane with the alkene partner and release the final product.

The second type of mechanism is called skeletal reorganization and is catalyzed by various late transition metal salts. Ruthenium, palladium, and platinum derivatives were mainly used, but systems based on iridium, rhodium, silver, gold, or even gallium were also investigated. Our understanding of the exact sequence of events operating under these conditions remains limited. For the enyne cycloisomerization catalyzed by palladium(II), Trost proposed the generic pathway depicted in Fig. 29. The reaction is triggered by bidentate coordination of

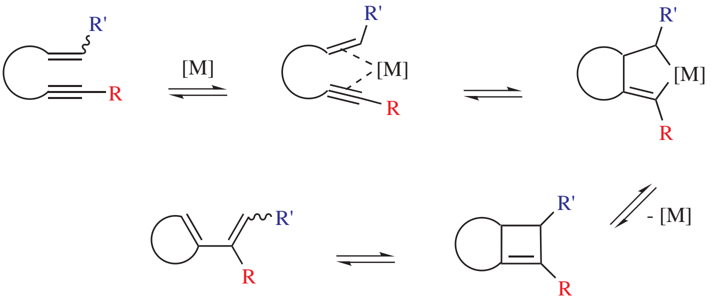
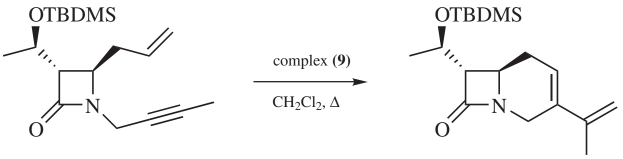


Fig. 29. Skeletal reorganization mechanism for enyne metathesis.

the enyne to the metal center followed by oxidative cyclization to produce a metallacyclopentene intermediate. Reductive elimination of the metal then affords a cyclobutene that could undergo electrocyclic ring opening in order to relieve the ring strain. This general mechanism can be altered to accommodate specificities of the actual catalytic system employed. For example, one can envision bond reorganization triggered by only one π system binding to the metal and alternative fates to the metallacyclopentene intermediate, such as β-hydride elimination.

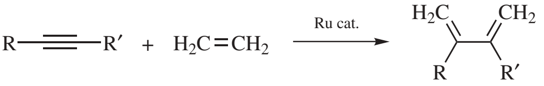
Most of the recent synthetic applications of enyne metathesis use ruthenium alkylidene catalysts because of their commercial availability, functional group tolerance, and constant development (91). In particular, first and second generation ruthenium carbene complexes developed by Grubbs (eg, complexes **9** and **15**, respectively) were used to promote RCEYM reactions with high efficiencies. For example, Barrett and co-workers synthesized bicyclic β-lactams by RCM of enyne and obtained carbacephem, **31**, in quantitative yield (eq. 9) (92).



TBDMS = $Si(CH_3)_2C(CH_3)_3$ **(31)**

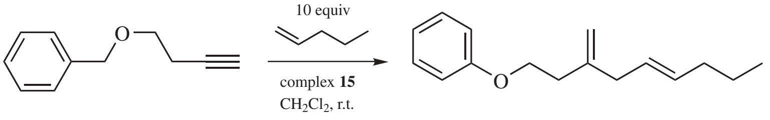
(9)

Recourse to ethylene as the alkene reagent in EYM reactions constitutes an elegant method for synthesizing 1,3-dienes from alkynes (eq. 10). For these reactions, the second generation Grubbs catalyst $RuCl_2(=CHPh)(PCy_3)(SIMes)$ (**15**) proved much superior than its first generation counterpart $RuCl_2(=CHPh)(PCy_3)_2$ (**9**), especially when internal or electron-deficient alkynes served as substrates. The products obtained are valuable synthetic intermediates that can be further functionalized through Diels-Alder cycloaddition to capitalize on the complexity-building potential of the butadiene motif.



(10)

Thanks to a clear-sighted interpretation of the mechanisms at work, Mori demonstrated that the introduction of ethylene under balloon pressure in RCEYM systems led to significantly improved yields and decreased reaction times, although the gas was *not* incorporated into the product. This beneficial effect was attributed to the formation of $[Ru]{=}CH_2$ active species in higher concentration and to the concomitant reduction of unproductive catalytic resting states when ruthenium-alkylidene catalyst precursors were exposed to ethylene. Enhanced (*E*)-selectivities were also observed in cross-metathesis reactions between certain alkenes and terminal alkynes carried out in the presence of ethylene. Under these conditions, the intervention of ruthenium-methylidene species is believed to hasten the equilibration that favors the most thermodynamically stable isomers. Competing ethylene-alkyne metathesis could be suppressed by using a large excess of the higher alkene. As a consequence, most of the enyne metathesis reactions currently performed utilize ethylene as a copromoter, even those involving an intramolecular coupling or intermolecular coupling with a higher alkene partner. Incorporation of ethylene to the reaction mixture, either as a static atmosphere or via perfusion, is often referred to as *Mori's* conditions. As an example, the ene yne cross-metathesis between benzyl butynyl ether and 1-pentene catalyzed by the second generation Grubbs catalyst, **15**, under ethylene atmosphere afforded solely cross-metathesis product **32** in 88% yield (eq. 11). No trace of the corresponding (*Z*) isomer could be detected in the reaction mixture (93).



(32)

(11)

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