

The Development of $L_2X_2Ru=CHR$ Olefin Metathesis Catalysts: An Organometallic Success Story

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ABSTRACT

In recent years, the olefin metathesis reaction has attracted widespread attention as a versatile carbon–carbon bond-forming method. Many new applications have become possible because of major advances in catalyst design. State-of-the-art ruthenium catalysts are not only highly active but also compatible with most functional groups and easy to use. This Account traces the ideas and discoveries that were instrumental in the development of these catalysts, with particular emphasis on $(PCy_3)_2Cl_2Ru=CHPh$ and its derivatives. The discussion includes an analysis of trends in catalyst activity, a description of catalysts coordinated with *N*-heterocyclic carbene ligands, and an overview of ongoing work to improve the activity, stability, and selectivity of this family of $L_2X_2Ru=CHR$ complexes.

The very foundation of organic synthesis consists of reactions that can reliably and efficiently form carbon–carbon bonds. One of these reactions, olefin metathesis, is currently undergoing an exciting renaissance as a synthetic method. Although double-bond scrambling reactions were initially reported in the mid-1950s,¹ it was not until several years later that Calderon and co-workers recognized that both ring-opening polymerization and the disproportionation of acyclic olefins were the same reaction. They coined the term “olefin metathesis” in 1967,² which we currently understand to mean the metal-catalyzed redistribution of carbon–carbon double bonds. As shown in Figure 1, this transformation has a variety of applications. The illustrated examples include ring-opening metathesis polymerization (ROMP), ring-closing metathesis (RCM), acyclic diene metathesis polymerization (ADMET), ring-opening metathesis (ROM), and cross-metathesis (CM or XMET). Through these reactions,

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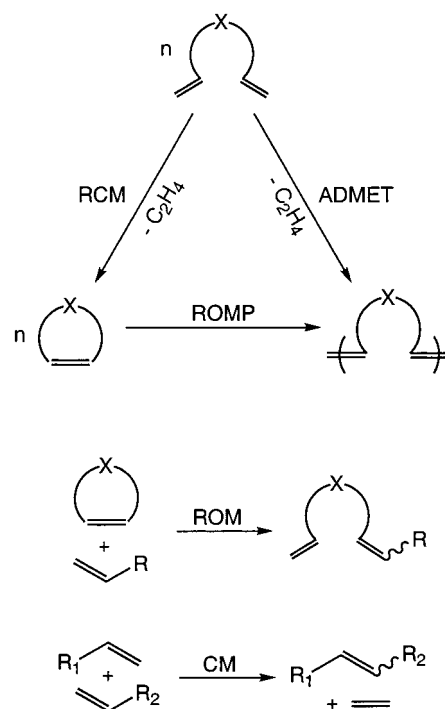


FIGURE 1. A variety of olefin metathesis reactions.

olefin metathesis provides a route to unsaturated molecules that are often challenging or impossible to prepare by any other means. Some of the most impressive achievements include the use of ROMP to make functionalized polymers, the syntheses of small to large heterocyclic systems by RCM, and the CM of olefins with pendant functional groups.

A number of reviews have been published in this area, all of which focus on the ever increasing uses of olefin metathesis in organic synthesis and polymer chemistry.^{3,4} Until a few years ago, however, the scope of the reaction was quite limited because of insufficient catalyst performance. It is only through major advances in catalyst design that tremendously expanded applications have recently become possible. To a large extent, these efforts to improve catalyst performance have been motivated and inspired by the desire to apply olefin metathesis to new synthetic challenges. For these reasons, the focus of this Account is the interplay between catalyst development and applications that has characterized progress in the field.

The organization of the Account follows the chronology in Figure 2. Our aim throughout is to highlight the strengths and weaknesses of various catalyst systems, and especially emphasize the improvements that were made at each stage of development. In this way, we intend to trace the evolution of ruthenium-based olefin metathesis catalysts from simple salts of limited utility to single-component, homogeneous catalysts that combine excellent activity with broad functional group tolerance.

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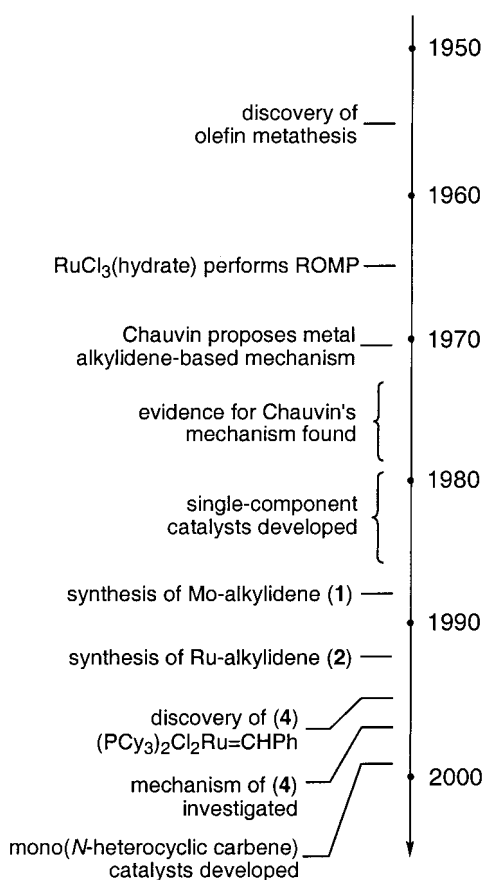


FIGURE 2. Time line of milestones in the development of olefin metathesis catalysts.

Background

From the mid-1950s to the early 1980s, all olefin metathesis was accomplished with poorly defined, multicomponent homogeneous and heterogeneous catalyst systems. These systems consisted of transition metal salts combined with main group alkylating agents or deposited on solid supports. Some of the classic combinations include WCl_6/Bu_4Sn , $WOCl_4/EtAlCl_2$, MoO_3/SiO_2 , and Re_2O_7/Al_2O_3 , among many others. Due to their low cost and simple preparation, these systems have an important place in commercial applications of olefin metathesis like the Shell Higher Olefin Process and the neohexene process.^{4b}

The utility of these catalysts, however, was limited by the harsh conditions and strong Lewis acids that they required and that made them incompatible with most functional groups. In addition, the reactions were difficult to initiate and control because very little of the active species formed in the catalyst mixtures. These problems motivated extensive work to better understand olefin metathesis, including detailed mechanistic studies. Many schemes were proposed over the years, but ultimately, the scheme developed by Chauvin was found to be most consistent with the experimental evidence, and it remains the generally accepted mechanism today.^{5,6} As illustrated in Figure 3, Chauvin proposed that olefin metathesis involves the interconversion of an olefin and a metal-alkylidene. This process is believed to occur via a metal-

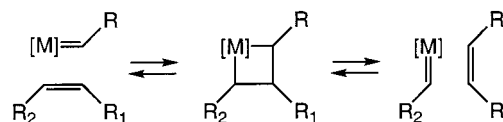


FIGURE 3. Mechanism of olefin metathesis.

lacyclobutane intermediate by alternating [2 + 2] cycloadditions and cycloreversions.

This mechanism influenced work on catalyst development in that it provided both a design rationale and a way to begin to understand catalyst activity. Subsequent efforts to synthesize alkylidene and metallacyclobutane complexes led to the discovery of the first single-component homogeneous catalysts for olefin metathesis during the late 1970s and early 1980s. These new catalysts included $(CO)_5W=CPh_2$,⁷ bis(cyclopentadienyl) titanacyclobutanes,⁸ tris(aryloxy) tantalacyclobutanes,⁹ and various dihaloalkoxide-alkylidene complexes of tungsten.¹⁰ As well-defined complexes, these catalysts exhibited better initiation and higher activity under milder conditions than ever before, and they enabled researchers to study structure–activity relationships and mechanism in detail.

The molybdenum and tungsten alkylidenes of the general formula $(NAr)(OR')_2M=CHR$ were the first of these catalysts to become widely used, particularly the molybdenum complex (1), where $Ar = 2,6-Pr^i_2-C_6H_3$, $R = CMe_2-Ph$, and $R' = C(CH_3)(CF_3)_2$.^{11,12} The most impressive feature of 1 is its high activity, which allows it to react with both terminal and internal olefins and to ROMP low-strain monomers, as well as to ring-close sterically demanding and electron-poor substrates.^{11–13} However, this catalyst and others based on the early transition metals are limited by the high oxophilicity of the metal centers, which renders them extremely sensitive to oxygen and moisture. As an example, the synthesis and handling of 1 requires an inert atmosphere and rigorously purified, dried, and degassed solvents and reagents. Aside from these inconveniences, early metal catalysts are more fundamentally limited by moderate to poor functional group tolerance, which reduces the number of potential substrates. Complex 1, for instance, is incompatible with aldehydes and alcohols.¹⁴ Of course, this problem of functional group tolerance may be evaded with protecting group strategies, but these are often tedious.

This brief history of olefin metathesis provides a context for subsequent work. The development of single-component catalysts was a major advance, but a great deal of room for improvement remained. Continuing research was motivated by the prospect of solving the problems related to oxophilicity and functional group tolerance, thereby unlocking even more of the potential of this reaction.

Functional Group Tolerance: Why Ruthenium?

In any catalyst system, functional groups in the substrate or solvent (including oxygen and water) can interfere with catalytic activity in several ways. They may bind competitively to the active metal center and deactivate the catalyst, or they may react directly with the metal center and

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

↑
Increasing
Reactivity

FIGURE 4. Functional group tolerance of early and late transition metal olefin metathesis catalysts.

destroy the active species. Thus, the key to improved functional group tolerance in olefin metathesis is the development of a catalyst that reacts preferentially with olefins in the presence of heteroatomic functionalities.

The advent of single-component catalysts allowed the relationships between structure and reactivity to be more clearly defined. These catalysts were observed to react more selectively with olefins as the metal centers were varied from left to right and bottom to top on the periodic table.¹⁵ This trend is illustrated for titanium, tungsten, molybdenum, and ruthenium in Figure 4.

Farthest to the left, titanium and tungsten catalysts are most strongly disposed to olefinate ketones and esters; in fact, this transformation is useful in organic synthesis.¹⁶ In comparison, molybdenum catalysts are more reactive toward olefins, although they also react with aldehydes and other polar or protic groups. Farthest to the right, ruthenium reacts preferentially with carbon-carbon double bonds over most other species, which makes these catalysts unusually stable toward alcohols, amides, aldehydes, and carboxylic acids. Because of this trend, it is possible to increase the functional group tolerance of an olefin metathesis catalyst by focusing on a later transition metal, such as ruthenium.

From $RuCl_3(\text{hydrate})$ to Well-Defined Ruthenium Alkylidene Complexes

In retrospect, ruthenium was an excellent candidate, but it was not seriously considered for more than two decades of research. At the time, this situation was caused by the discouragingly low metathesis activity of ruthenium salts, as well as a limited understanding of how to achieve functional group tolerance. Several reports from the 1960s had, in fact, described the ROMP of norbornene derivatives with $RuCl_3(\text{hydrate})$ in refluxing ethanol and under aqueous emulsion conditions.¹⁷ The polymer yields were small, but the observation that ROMP could take place in these protic solvents at all was an important precedent.

Starting in the late 1980s, the potential of ruthenium catalysts for ROMP applications was reexamined. In fact, $RuCl_3(\text{hydrate})$ did indeed catalyze ROMP, but the polymerizations were preceded by long initiation periods (20 h or more) when performed in organic solvents.^{18,19} In an attempt to decrease the initiation times, the reactions were repeated under more strictly anhydrous conditions, but this change caused initiation to take even longer. Quite unexpectedly, however, ROMP initiated after only 30 min in aqueous solution. Thus, water was found to be not only

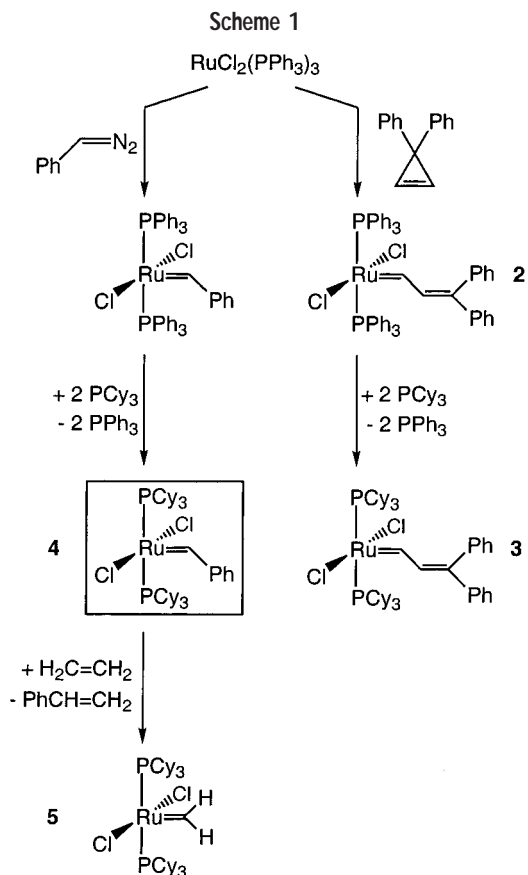
compatible with this catalyst system but actually beneficial to the initiation process.

Upon screening of other simple ruthenium complexes, $Ru(H_2O)_6(\text{tos})_2$ ($\text{tos} = p\text{-toluenesulfonate}$) was found to have even shorter initiation times, on the order of a few minutes.²⁰ This catalyst was able to ROMP functionalized norbornene, 7-oxanorbornene, and norbornadiene monomers, including hydroxyl-, carboxyl-, alkoxy-, and carboximide-substituted derivatives. The polymers from these reactions were obtained consistently in greater yields, and with higher molecular weights and lower polydispersities, than those prepared with most other catalysts known at that time. Furthermore, the $RuCl_3(\text{hydrate})$ and $Ru(H_2O)_6(\text{tos})_2$ catalyst solutions, which contained ruthenium-olefin adducts observable by 1H NMR, could be recycled a number of times.²¹

The initiation process remained unclear, but a number of observations suggested that the active species was a ruthenium alkylidene. For instance, acyclic olefins added during ROMP became incorporated at the ends of the polymer chains.²² A detailed analysis of the polymer microstructure and the trends in olefin activity were consistent with a chain-transfer mechanism, which had been seen previously with other alkylidene catalysts. Although none of the ruthenium alkylidene complexes known at that time could perform olefin metathesis, the success of early metal alkylidene catalysts was very suggestive. Thus, early attempts to generate ruthenium alkylidene species included the addition of ethyl diazoacetate, a carbene source, to ruthenium precursors. This reaction with $Ru(H_2O)_6(\text{tos})_2$ produced a species with activity higher than that of $Ru(H_2O)_6(\text{tos})_2$ alone.²³ In fact, this solution could even initiate the ROMP of monomers less strained than norbornene, such as cyclooctene, whereas the activity of $RuCl_3(\text{hydrate})$ or $Ru(H_2O)_6(\text{tos})_2$ is limited to more highly strained substrates.

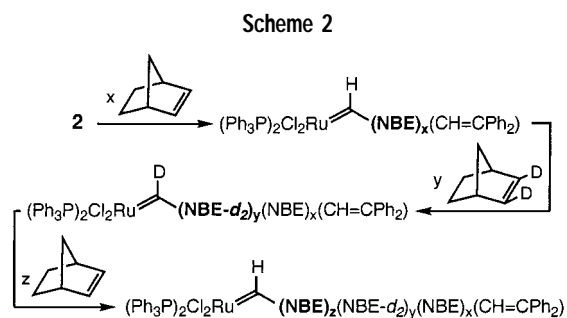
A breakthrough occurred when the methodology for the synthesis of tungsten alkylidenes, in which 3,3-disubstituted cyclopropenes are used as carbene precursors, was applied to the synthesis of a ruthenium catalyst.²⁴ The addition of diphenylcyclopropene to $RuCl_2(PPh_3)_3$ led to the isolation of **2** [as a mixture of *cis*- and *trans*-bis-(phosphine) isomers], the first well-defined, metathesis-active ruthenium alkylidene complex (Scheme 1).²⁵

Catalyst **2** polymerizes norbornene effectively in the presence or absence of water or ethanol. More significantly, a propagating alkylidene species is observed by 1H NMR during the ROMP of norbornene. As indicated in



Scheme 2, the propagating alkylidene signal vanishes when 2,3-dideuterio-norbornene is added, but reappears when protio-norbornene is added once again. This sequence of norbornene additions results in a block copolymer with alternating protio and deuterio segments. Additional experiments show that chain termination and transfer are slow relative to propagation, which also suggests a living polymerization.²⁶

Although the initiation behavior and functional group tolerance of **2** were exciting, its activity was limited to the ROMP of highly strained monomers. To extend this activity to the ROMP of low-strain monomers and the metathesis of acyclic olefins, the ligand environment was modified in a systematic way. Based on the trend followed by early transition metal catalysts, for which metathesis activity increases with more electron-withdrawing ligands,¹² a variety of cationic complexes and derivatives containing less basic phosphines were prepared and tested. After months of exploring this strategy without success, the most basic phosphine in the stockroom, which happened



to be PCy₃ (Cy = cyclohexyl), was used instead and led to²⁷ a fortuitous discovery—the larger and more basic the phosphine, the higher the metathesis activity.

As illustrated in Scheme 1, the PCy₃ analogue (**3**) and other derivatives can be obtained by phosphine exchange.²⁸ The catalytic activity of these complexes increases with the basicity of the phosphines in the order PPh₃ << PPrⁱ₃ < PCy₃. The PCy₃ derivative **3** catalyzes the ROMP of lower strain monomers, such as cyclopentene, and it became the first ruthenium alkylidene complex active toward acyclic olefins.

Although **3** is not as active as early metal catalysts such as **1**, it is much more versatile due to its functional group tolerance. For example, even in the presence of the common protecting groups trifluoroacetyl and *tert*-butoxycarbonyl, **3** is able to cyclize α,ω -dienes to five-, six-, and seven-membered carbo- and heterocycles in good yields.²⁹ This robust catalyst is air-stable as a solid and retains its activity even when exposed to water, alcohols, or acids. These characteristics make catalyst **3** ideal for a wide range of synthetic organic applications.

The difficulty of synthesizing diphenylcyclopropene initially limited the availability of these complexes, but the alternate reaction of RuCl₂(PPh₃)₃ with alkyl- and aryl-diazoalkane compounds led to good yields of substituted alkylidenes (Scheme 1).³⁰ With a variety of complexes in hand, the fundamental reactions of ruthenium alkylidenes were examined. The benzylidene catalyst **4**, for example, undergoes metathesis with ethylene within minutes at room temperature to quantitatively form the methylidene derivative **5**. This complex was the first metathesis-active methylidene species ever isolated. In contrast, the diphenylvinyl derivative **3** reacts slowly with ethylene, even under forcing conditions, and only partially converts to the methylidene (20% after a few hours). This difference in initiation properties is also reflected in the molecular weight distributions of ROMP products, which is broader for **3** than for **4**.^{30a} The most active catalyst of this series, complex **4**, combines the bulky and strongly electron-donating PCy₃ ligands with the readily initiated benzylidene moiety.

The Applications of Ruthenium-Based Catalysts

These first members of an entire family of $L_2X_2Ru=CHR$ complexes opened new vistas in olefin metathesis. Because these catalysts possess a favorable combination of activity and functional group compatibility, they attracted a great deal of attention soon after the initial reports. In 1990, for example, only 35 publications regarding olefin metathesis were published.³¹ Slightly less than a decade later, in 1999, the number of publications rose to 250 during this year alone. Of this literature, 75% of the authors described using ruthenium-based catalysts for olefin metathesis, and a full 62% specifically used complex **3** or **4**. Because many reviews have focused on applications,³ we present here only a brief survey of reports that have been connected with catalyst development in this

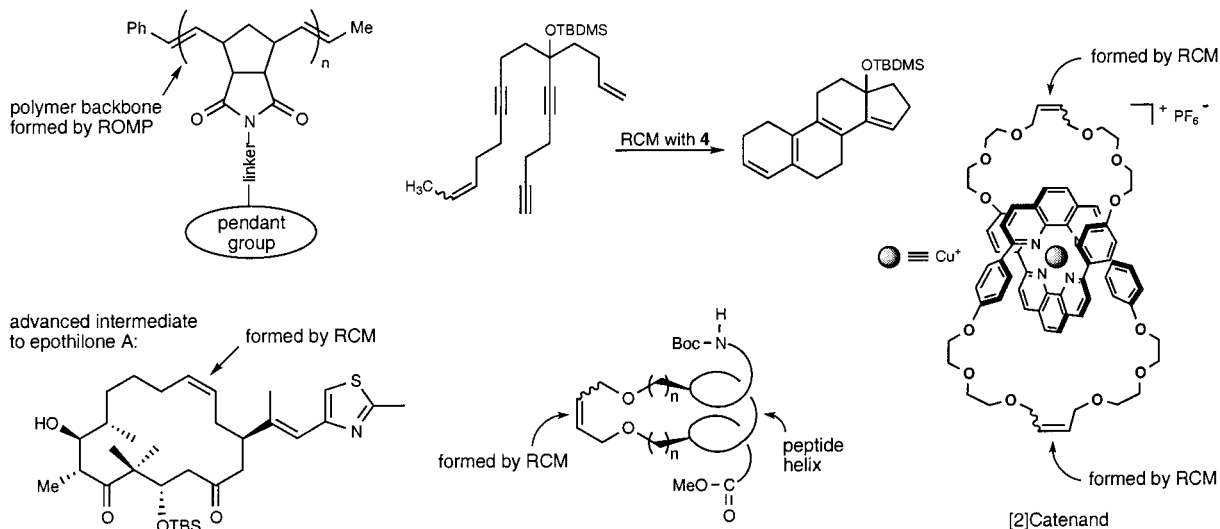


FIGURE 5. Applications using $(PCy_3)_2Cl_2Ru=CHPh$ (**4**).

laboratory. A selection of these applications is illustrated in Figure 5.

Historically, the most common application of olefin metathesis has been the preparation of new materials through ROMP. ROMP is a convenient route to polymers because it maintains backbone unsaturation and allows the direct incorporation of functionality from the monomer. The functional group tolerance of ruthenium catalysts has extended ROMP to a more diverse set of monomers. In a recent example, **4** was used to synthesize side-chain liquid crystalline polymers from mesogen-containing monomers.³² Others have applied ROMP to highly functionalized and hydrophilic substrates, such as norbornene derivatives with pendant sugars, amino acids, and vancomycin subunits (Figure 5).³³ The living nature of ROMP catalyzed by **3** and **4** leads to nearly monodisperse polymers and allows the lengths of polymer chains to be controlled by chain termination or adjustment of the monomer/catalyst ratio. Because the propagating species remains attached at the end of the polymer chain even after complete consumption of the monomer, it is also possible to synthesize block copolymers by this route.^{32b} Oligomers and polymers may also be synthesized with ADMET chemistry.^{3d} For example, main-chain ferroelectric liquid crystal oligomers have been made by the ADMET of α,ω -diene mesogens with catalyst **3**.³⁴

The scope of olefin metathesis has been further extended in aqueous media through modifications of catalyst **4**. Although **4** is active in the presence of protic species, it is limited by being insoluble in water, and emulsion conditions are not suitable for all applications.³⁵ Substitution of the PCy_3 ligands with water-soluble phosphines, such as $Cy_2P(CH_2)_2NMe_3^+Cl^-$ and $Cy_2P[4-(N,N\text{-dimethylpiperidinium})]^+Cl^-$, makes these complexes water soluble. As an example of their activity, these catalysts promote the living ROMP of water-soluble monomers in the presence of Brønsted acids (e.g., HCl).³⁶ The acid serves to protonate a phosphine ligand and also remove hydroxide ions that lead to catalyst decomposition. These water-soluble catalysts also allowed the RCM reaction in

water and methanol for the first time.³⁷ It is necessary to use phenyl-substituted substrates for these reactions instead of α,ω -dienes because the propagating methylenide species is unstable.

Without question, the area of olefin metathesis that has expanded most dramatically in recent years is RCM. Catalysts **3** and **4** have made it possible to cyclize substrates containing diverse functionality.³ New methodologies, such as ring-opening/ring-closing sequences³⁸ and the RCM of dienyne (Figure 5),³⁹ have allowed the construction of fused ring systems⁴⁰ and bridged bicycloalkenes.⁴¹ RCM is proving useful in total synthesis, where it has been applied to targets ranging from relatively small molecules such as frontaline⁴² to complex ones such as epothilone A (Figure 5).⁴³ It is also possible to use this methodology to cyclize polypeptides and introduce carbon-carbon cross links into peptides (Figure 5).⁴⁴

One of the major applications of RCM has been the synthesis of medium to large ring systems. This methodology was first utilized in the synthesis of macrolides by Villemin and Tsuji.⁴⁵ Most importantly, these early workers demonstrated that it was essential to work at substrate concentrations of $\leq 6 \times 10^{-3}$ M to obtain cyclic products rather than oligomers. Subsequent work in this area with catalysts **1** and **4** has included the synthesis of manzamin A and other macrolides.⁴⁶

Several RCM applications take advantage of templates to direct ring formation. An example of this strategy is the ring closing of polyether-containing olefins, which can be assisted by preorganization around alkali metal ions.⁴⁷ Similarly, phenanthroline-containing olefins assembled with Cu^+ templates undergo RCM to form [2]catenates in excellent yields (Figure 5).⁴⁸

There has also been renewed interest in CM applications. For instance, the CM of unhindered terminal olefins with symmetrically disubstituted internal olefins provides the desired cross products in good to excellent yields.⁴⁹ This methodology was successfully extended to several terminal olefins with allylic disubstitution, such as acrolein acetals and vinyl boronates.^{49b,50}

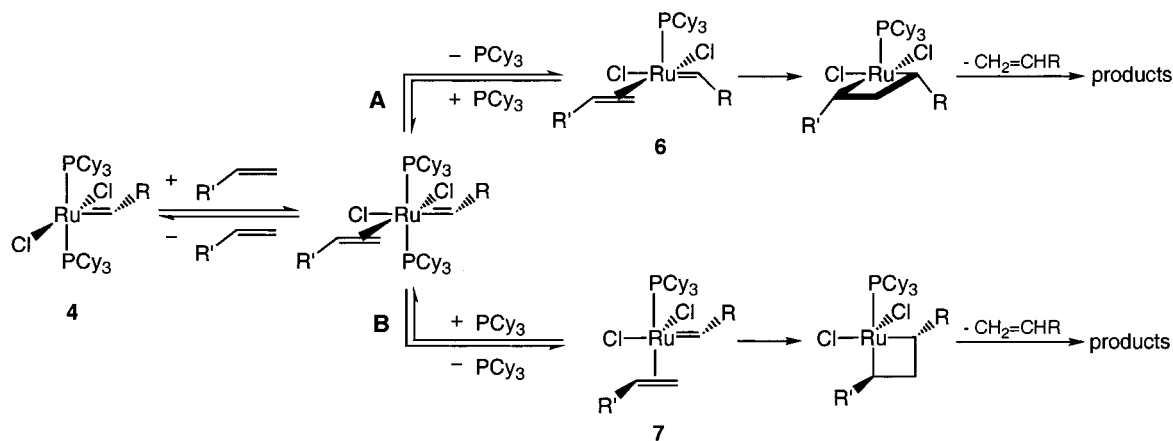


FIGURE 6. Proposed mechanism for $(PCy_3)_2Cl_2Ru=CHPh$ (4).

donating ability of the phosphine ligands. The steric bulk of the ligands may also contribute to phosphine dissociation by destabilizing the crowded bis(phosphine) olefin complex. In hindsight, then, the choice of PCy_3 was a fortunate circumstance, because those phosphines that are more basic or bulkier than PCy_3 result in unstable complexes.

In contrast to the trend for phosphines, the halide ligands correlate with decreasing activity as they become larger and more strongly electron donating, in the order $Cl > Br \gg I$. Since the incoming olefin may initially bind trans to a halide, a more electron-donating halide should weaken the ruthenium–olefin bond and disfavor olefin coordination. These small changes in the steric and electronic character of the X- and L-type ligands combine to influence olefin binding, phosphine dissociation, and the stability of intermediates, which results in large variations of catalyst activity.

The overall activity also depends on catalyst initiation and thus on the nature of the alkylidene moiety. In general, alkyl-substituted alkylidenes display more efficient initiation than the methylidene complex (5).⁶² The initiation of ester-substituted alkylidenes $[Ru]=CHCO_2R$ occurs even more rapidly than for alkyl derivatives, but these complexes also tend to be less stable.⁶³ The benzylidene (4) seems to be an intermediate case; the phenyl group is somewhat electron withdrawing, but its size may assist phosphine dissociation.

The catalyst lifetime is another important factor in its overall activity. The kinetics of the thermal decomposition pathways of various catalysts reveal that substituted alkylidene complexes decompose by a different mechanism than the methylidene complex, which is the only propagating species observed during RCM. For substituted alkylidenes, observations are consistent with a bimolecular decomposition mechanism involving phosphine dissociation followed by coupling of mono(phosphine) species.⁶⁴ In contrast, the methylidene complex decomposes through a unimolecular pathway that is independent of concentration. In this way, the relative stabilities of the initiating and propagating species directly influence catalyst activity. These observations also explain why relatively high catalyst loadings are required for RCM reactions.

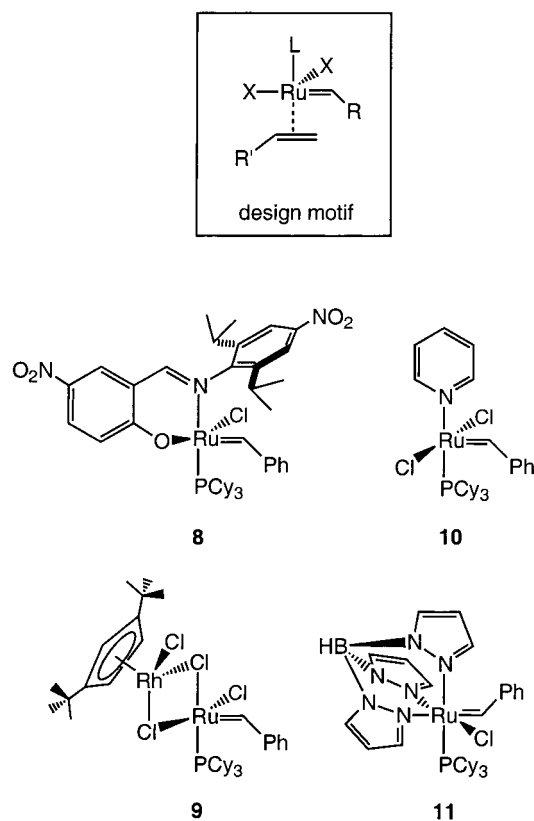


FIGURE 7. Applications of the catalyst design motif to $L_2X_2Ru=CHR$ complexes.

Recent Developments in Catalyst Design

These mechanistic studies allowed us to identify a number of factors that contribute to the activity of these catalysts. The key insight was that $(PCy_3)_2Cl_2Ru=CHPh$ forms a highly active mono(phosphine) intermediate during the catalytic cycle. As a design motif, this intermediate became a starting point for the development of improved catalysts. The examples in Figure 7 show a variety of ligand arrays that incorporate this design motif. Although all of these complexes are active to some degree, they tend to have either enhanced stability and low activity, or the reverse, high activity and poor stability. The bidentate salicylaldimine complex (8) is an example of the first case; it is significantly more stable than the parent complex 4 at

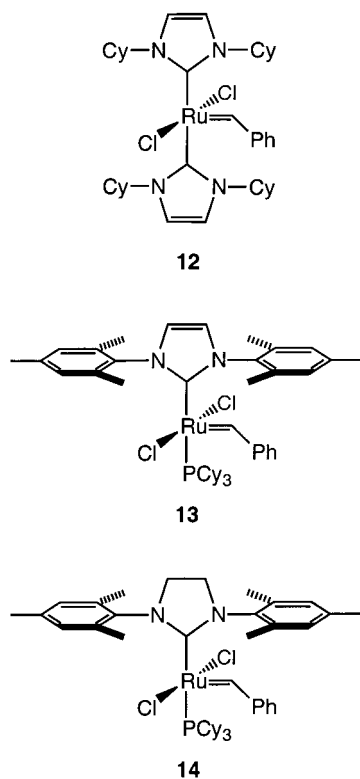


FIGURE 8. Ruthenium catalysts containing *N*-heterocyclic carbene ligands.

elevated temperatures, but its activity is much lower.⁶⁵ In contrast, the heterobimetallic (**9**) and pyridine-coordinated (**10**) complexes have very high activity for only a short time before the catalysts decompose.⁶⁶ The tris(pyrazolyl)-borate catalyst (**11**) has similar problems; acid must be added for initiation, but even then its activity is poor.⁶⁷

The properties of these complexes illustrate several mechanistic points. First, for olefin metathesis to begin, at least one of the ancillary ligands must be labile enough for catalyst activation. Complexes **8** and **11** do not readily meet this condition, and their activity is limited. Second, because decomposition of **4** is known to be second order and inversely proportional to phosphine concentration, it is generally important to maintain a low concentration of the mono(phosphine) species. Complexes **9** and **10** do not fulfill this requirement because they contain ancillary ligands that either are too labile or cannot sufficiently stabilize the reaction intermediates. These examples demonstrate that any approach to increase the concentration of the mono(phosphine) intermediate is futile if it also accelerates catalyst decomposition. For this reason, additives such as CuCl and HCl that increase phosphine dissociation enhance catalyst activity but simultaneously promote catalyst decomposition.

Mindful of these lessons, we became interested in the potential of *N*-heterocyclic carbene ligands to meet the necessary criteria.⁶⁸ We were prompted to examine these ligands by the report of complex **12** by Herrmann and co-workers (Figure 8).⁶⁹ This bis(substituted) complex showed little improvement in activity compared to **4**, but we believed that we could apply the design motif in Figure 7 to this system by making *monosubstituted* derivatives. It

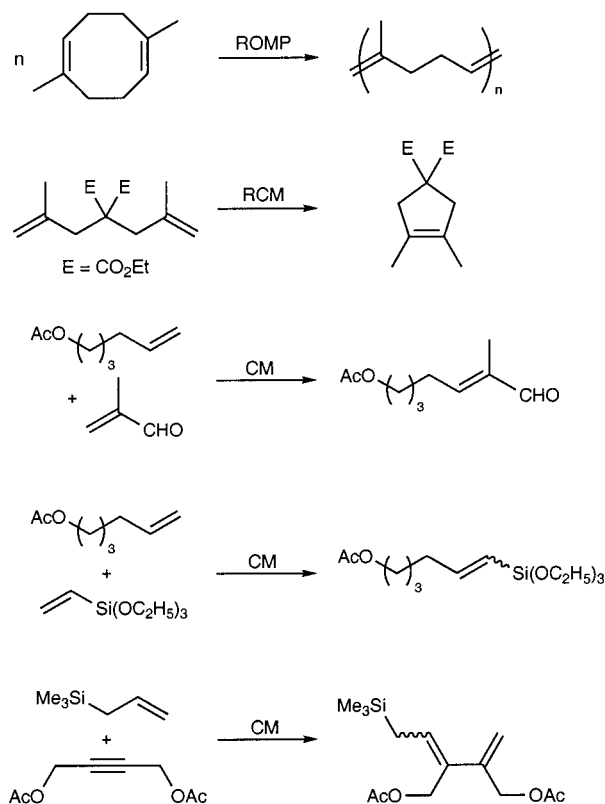


FIGURE 9. Applications using catalyst **14**.

is well known that, compared to phosphines, *N*-heterocyclic carbene ligands are stronger σ donors and much less labile.^{68,70} As a result, the *N*-heterocyclic carbenes in **12** are not able to readily dissociate. A mixed-ligand complex, however, could overcome this problem in two ways. Initially, the more strongly electron-donating carbene ligand might enhance the dissociation of the more labile trans phosphine from the metal center. Then, by virtue of its steric bulk and electron-donating properties, the same ligand should more effectively stabilize the electron-deficient intermediates and promote olefin metathesis.

After exploring a variety of ligand derivatives, we found that a mesityl-substituted *N*-heterocyclic carbene worked well. Our initial disclosure of catalyst **13** (Figure 8)⁷¹ was closely followed by related reports.⁷² Soon thereafter, we discovered that catalyst **14**, which contains an *N*-heterocyclic carbene with a saturated backbone, is even more active.⁷³ These new catalysts display performance that was previously possible only with the most active early metal systems. The superior activity of **14** includes high rates of ROMP for low-strain substrates and even the ROMP of sterically hindered substrates containing trisubstituted olefins such as 1,5-dimethyl-1,5-cyclooctadiene (Figure 9).⁷⁴ Both **13** and **14** are able to perform the RCM of sterically demanding dienes to form tri- and tetrasubstituted olefins.^{71,73} In addition, catalyst **14** produced the first example of CM to yield a trisubstituted olefin,⁷⁵ as well as CM and RCM reactions where one partner is directly functionalized with a deactivating group, such as acrylate or siloxane (Figure 9).⁷⁶ This catalyst has also been used to extend the scope of alkene-alkyne cross metathesis to

cases where the alkyne is disubstituted and contains coordinating functionality (Figure 9).⁷⁷ Remarkably, **14** remains effective at loadings as low as 0.05 mol % for RCM reactions and 0.0001 mol % (monomer:catalyst = 1 000 000) for ROMP.⁷³ On the basis of these promising new applications, we expect that these catalysts will become widely used.⁷⁸

This “next generation” of catalysts is most significant because it combines the best characteristics of early and late metal centers into a single species. Until now, it had seemed that functional group tolerance was gained at the expense of activity. Catalysts **13** and **14**, however, rival the activity of early metal catalysts such as **1** and retain the functional group tolerance of $(PCy_3)_2Cl_2Ru=CHPh$ (**4**). These developments illustrate the extent to which it is possible to tune a metal center by modifying the ligand environment.

Although the exact mechanism of these powerful new catalysts remains unclear, we have made a number of interesting observations. For example, **13** and **14** initiate much more slowly than the parent complex **4**,⁷⁹ and recent results indicate that this may be due to slower phosphine dissociation.⁸⁰ Other studies suggest that the bulky mesityl groups in these catalysts may contribute to high activity, in part because of interactions with the alkylidene moiety.⁸⁰ The mesityl substituents may also provide the metal center with considerable steric protection and contribute to the high thermal stability of these catalysts. Additional studies are underway to identify the origin of the differences between catalysts **13** and **14**, in which only the backbone of the *N*-heterocyclic carbene ligand is changed. Preliminary ab initio quantum mechanical calculations⁸¹ and experimental evidence⁸² indicate that both the σ -basicity and π -acidity of the ligands play a role in catalyst activity. Ongoing work in this laboratory is directed toward answering these questions.

Current Directions and Outlook

Olefin metathesis has become a standard synthetic method because of the wide variety of applications that are now feasible and the ease with which $L_2X_2Ru=CHR$ catalysts can be used. Furthermore, the activity and functional group tolerance of ruthenium catalysts is now sufficiently high for olefin metathesis to begin to compete with more traditional carbon–carbon bond-forming methods, such as the Diels–Alder and Wittig reactions. There is considerable interest in further catalyst development, however, because these catalysts remain incapable of performing some of the most demanding transformations, including CM to form tetrasubstituted olefins and the ROMP of barrelenes. In addition, ruthenium catalysts are limited by incompatibility with basic functional groups, most notably nitriles and amines. We anticipate that these problems will be overcome in future developments as olefin metathesis chemistry continues to be an active area of research.

The next major challenge for olefin metathesis is the stereoselectivity of the reaction. Kinetic resolution and

asymmetric RCM have been accomplished with chiral molybdenum-based catalysts,⁸³ and we are currently exploring the potential of chiral ruthenium-based systems.⁷³ The problem of olefin stereoselectivity in CM and macrocyclic RCM reactions is a more complex one, however. The stereochemical outcome is presumably governed by the conformations and relative stabilities of the substrate, intermediates, and products, but these factors are currently impossible to model. Thus far, we have been able to influence *E* or *Z* selectivity through steric⁴⁹ and electronic⁷⁶ substrate features in specific cases, but we currently lack a general solution to this problem.

Concurrent to the work described in this Account, additional members of this catalyst family have been developed in the laboratories of H. Werner, P. Dixneuf, K. Caulton, A. Noels, K. Kirchner, A. Fürstner, A. Hoveyda, and P. Hofmann, among others. A number of researchers are also working on the related topics of alkyne and imine metathesis.^{84,85}

Conclusions

During the past 40 years, there has been considerable progress in understanding the design and mechanism of olefin metathesis catalysts. Ruthenium-based catalysts, in particular, have undergone a dramatic evolution from simple salts to highly tuned alkylidene complexes. As we have attempted to show, a number of ideas and discoveries were instrumental in this process. High activity and stability, as well as broad functional group tolerance, have been achieved through the careful study of structure–activity relationships, and it is in this sense that the development of these catalysts has been an organometallic success story. As work toward catalysts with specifically tailored properties continues, we look forward to exciting future developments.

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References

- (1) (a) Eleuterio, H. S. Olefin metathesis: chance favors those minds that are best prepared. *J. Mol. Catal.* **1991**, *65*, 55–61. (b) Eleuterio, H. The discovery of olefin metathesis. *CHEMTECH* **1991**, 92–95. (c) Banks, R. L. Discovery and development of olefin disproportionation. *CHEMTECH* **1986**, 112–117. (d) Anderson, A. W.; Merckling, N. G. Polymeric bicyclo[2.2.1]hept-2-ene. U.S. Patent 2,721,189, 1955; *Chem. Abstr.* **1956**, *50*, 3008i.
- (2) (a) Calderon, N. The Olefin Metathesis Reaction. *Acc. Chem. Res.* **1972**, *5*, 127–132. (b) Calderon, N.; Chen, H. Y.; Scott, K. W. Olefin Metathesis—A Novel Reaction for Skeletal Transformations of Unsaturated Hydrocarbons. *Tetrahedron Lett.* **1967**, *34*, 3327–3329.
- (3) Reviews during the past few years include the following: (a) Jørgensen, M.; Hadwiger, P.; Madsen, R.; Stütz, A. E.; Wrodnigg, T. M. Olefin Metathesis in Carbohydrate Chemistry. *Curr. Org. Chem.* **2000**, *4*, 565–588. (b) Maier, M. E. Synthesis of Medium-Sized Rings by the Ring-Closing Metathesis Reaction. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073–2077. (c) Roy, R.; Das, S. K. Recent applications of olefin metathesis and related reactions in carbohydrate chemistry. *Chem. Commun.* **2000**, 519–529. (d) Buchmeiser, M. R. Homogeneous Metathesis Polymerization by Well-Defined Group VI and Group VIII Transition-Metal Alkylidenes: Fundamentals and Applications in the Preparation of Advanced Materials. *Chem. Rev.* **2000**, *100*, 1565–1604. (e) Kingsbury, C. L.; Mehrman, S. J.; Takacs, J. M. A Comprehensive Review of the Applications of Transition Metal-Catalyzed Reactions to Solid-

- Phase Synthesis. *Curr. Org. Chem.* **1999**, *3*, 497–555. (f) Phillips, A. J.; Abell, A. D. Ring-Closing Metathesis of Nitrogen-Containing Compounds: Applications to Heterocycles, Alkaloids, and Peptidomimetics. *Aldrichimica Acta* **1999**, *32*, 75–89. (g) Wright, D. L. Application of Olefin Metathesis to Organic Synthesis. *Curr. Org. Chem.* **1999**, *3*, 211–240. (h) Randall, M. L.; Snapper, M. L. Selective olefin metatheses—new tools for the organic chemist: A review. *J. Mol. Catal. A* **1998**, *133*, 29–40. (i) Ivin, K. J. Some recent applications of olefin metathesis in organic synthesis: A review. *J. Mol. Catal. A* **1998**, *133*, 1–16. (j) Noels, A. F.; Demonceau, A. From olefin cyclopropanation to olefin metathesis through catalyst engineering: recent applications of olefin metathesis to fine organic synthesis and to polymer chemistry. *J. Phys. Org. Chem.* **1998**, *11*, 602–609. (k) Armstrong, S. K. Ring closing diene metathesis in organic synthesis. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371–388. (l) Grubbs, R. H.; Chang, S. Recent Advances in Olefin Metathesis and Its Application in Organic Synthesis. *Tetrahedron* **1998**, *54*, 4413–4450. (m) Pariya, C.; Jayaprakash, K. N.; Sarkar, A. Alkene metathesis: new developments in catalyst design and application. *Coord. Chem. Rev.* **1998**, *168*, 1–48. (n) Naota, T.; Takaya, H.; Murahashi, S.-I. Ruthenium-Catalyzed Reactions for Organic Synthesis. *Chem. Rev.* **1998**, *98*, 2599–2660.
- (4) For other guides to the literature of olefin metathesis, we direct the reader to the following monographs: (a) Dörwald, F. Z. *Metal Carbenes in Organic Synthesis*; Wiley-VCH: Weinheim, 1999. (b) Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Metathesis Polymerization*; Academic Press: London, 1997.
- (5) Hérisson, J.-L.; Chauvin, Y. Catalysis of olefin transformations by tungsten complexes. II. Telomerization of cyclic olefins in the presence of acyclic olefins. *Makromol. Chem.* **1971**, *141*, 161–167.
- (6) For a detailed account of the data that supports this mechanism, see the following papers and references therein: (a) Leconte, M.; Basset, J. M.; Quignard, F.; Larroche, C. Mechanistic Aspects of the Olefin Metathesis Reaction. In *Reactions of Coordinated Ligands*; Braterman, P. S., Ed.; Plenum: New York, 1986; Vol. 1, pp 371–420. (b) Grubbs, R. H. Alkene and Alkyne Metathesis Reactions. In *Comprehensive Organometallic Chemistry*; Wilkinson, G.; Stone, F. G. A.; Abel, E. W., Eds.; Pergamon: Oxford, 1982; Vol. 8, Chapter 54, pp 499–551. (c) Katz, T. J.; McGinnis, J. Metathesis of Cyclic and Acyclic Olefins. *J. Am. Chem. Soc.* **1977**, *99*, 1903–1912. (d) Grubbs, R. H.; Carr, D. D.; Hoppin, C.; Burk, P. L. Consideration of the Mechanism of the Metal Catalyzed Olefin Metathesis Reaction. *J. Am. Chem. Soc.* **1976**, *98*, 3478–3483. (e) Katz, T. J.; Rothchild, R. Mechanism of the Olefin Metathesis of 2,2'-Divinylbiphenyl. *J. Am. Chem. Soc.* **1976**, *98*, 2519–2526. (f) Katz, T. J.; McGinnis, J. The Mechanism of the Olefin Metathesis Reaction. *J. Am. Chem. Soc.* **1975**, *97*, 1592–1594. (g) Grubbs, R. H.; Burk, P. L.; Carr, D. D. Consideration of the Mechanism of the Olefin Metathesis Reaction. *J. Am. Chem. Soc.* **1975**, *97*, 3265–3267. (h) Reference 4b, Chapter 3.
- (7) (a) Katz, T. J.; Sivavec, T. M. Metal-Catalyzed Rearrangement of Alkene–Alkynes and the Stereochemistry of Metallacyclobutene Ring Opening. *J. Am. Chem. Soc.* **1985**, *107*, 737–738. (b) Katz, T. J.; Lee, S. J.; Acton, N. Stereospecific Polymerization of Cycloalkenes Induced by a Metal-Carbene. *Tetrahedron Lett.* **1976**, *47*, 4247–4250.
- (8) Grubbs, R. H.; Tumas, W. Polymer Synthesis and Organotransition Metal Chemistry. *Science* **1989**, *243*, 907–915.
- (9) Wallace, K. C.; Liu, A. H.; Dewan, J. C.; Schrock, R. R. Preparation and Reactions of Tantalum Alkylidene Complexes Containing Bulky Phenoxide or Thiolate Ligands. Controlling Ring-Opening Metathesis Polymerization Activity and Mechanism through Choice of Anionic Ligand. *J. Am. Chem. Soc.* **1988**, *110*, 4964–4977.
- (10) (a) Kress, J.; Osborn, J. A.; Greene, R. M. E.; Ivin, K. J.; Rooney, J. J. First Direct Observation of the Simultaneous Presence and of the Interconversion of Chain-Propagating Metal–Carbene and Metallacyclobutane Complexes in a Catalytic Olefin Metathesis Reaction: The Ring-Opening Polymerization of Norbornene. *J. Am. Chem. Soc.* **1987**, *109*, 899–901. (b) Kress, J.; Agüero, A.; Osborn, J. A. Recent Advances in the Chemistry of Tungsten–Carbene Complexes. *J. Mol. Catal.* **1986**, *36*, 1–12. (c) Quignard, F.; Leconte, M.; Basset, J.-M. Synthesis and Catalytic Properties of $W(OAr)_2Cl_2(CHCMe_3)(OR)_2$ and $W(OAr)_2Cl(CHCMe_3)(CH_2CMe_3)(OR)_2$ (Ar = 2,6-disubstituted phenyl; R = Et or Pr'), New Unicomponent Catalysts for Metathesis of Acyclic and Cyclic Olefins, with or without Functional Groups. *J. Chem. Soc., Chem. Commun.* **1985**, 1816–1817.
- (11) (a) Bazan, G. C.; Oskam, J. H.; Cho, H.-N.; Park, L. Y.; Schrock, R. R. Living Ring-Opening Metathesis Polymerization of 2,3-Difunctionalized 7-Oxanorbornenes and 7-Oxanorbornadienes by $Mo(CHCMe_2R)(N-2,6-C_6H_3-i-Pr_2)(O-t-Bu)_2$ and $Mo(CHCMe_2R)(N-2,6-C_6H_3-i-Pr_2)(OCMe_2CF_3)_2$. *J. Am. Chem. Soc.* **1991**, *113*, 6899–6907. (b) Bazan, G. C.; Khosravi, E.; Schrock, R. R.; Feast, W. J.; Gibson, V. C.; O'Regan, M. B.; Thomas, J. K.; Davis, W. M. Living Ring-Opening Metathesis Polymerization of 2,3-Difunctionalized Norbornadienes by $Mo(CH-t-Bu)(N-2,6-C_6H_3-i-Pr_2)(O-t-Bu)_2$. *J. Am. Chem. Soc.* **1990**, *112*, 8378–8387. (c) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. Synthesis of Molybdenum Imido Alkylidene Complexes and Some Reactions Involving Acyclic Olefins. *J. Am. Chem. Soc.* **1990**, *112*, 3875–3886. (d) Schrock, R. R.; Feldman, J.; Cannizzo, L. F.; Grubbs, R. H. Ring-Opening Polymerization of Norbornene by a Living Tungsten Alkylidene Complex. *Macromolecules* **1987**, *20*, 1169–1172.
- (12) For reviews of this area, see: (a) Schrock, R. R. Olefin Metathesis by Molybdenum Imido Alkylidene Catalysts. *Tetrahedron* **1999**, *55*, 8141–8153. (b) Schrock, R. R. Living Ring-Opening Metathesis Polymerization Catalyzed by Well-Characterized Transition-Metal Alkylidene Complexes. *Acc. Chem. Res.* **1990**, *23*, 158–165.
- (13) (a) Kirkland, T. A.; Grubbs, R. H. Effects of Olefin Substitution on the Ring-Closing Metathesis of Dienes. *J. Org. Chem.* **1997**, *62*, 7310–7318. (b) Grubbs, R. H.; Miller, S. J.; Fu, G. C. Ring-Closing Metathesis and Related Processes in Organic Synthesis. *Acc. Chem. Res.* **1995**, *28*, 446–452.
- (14) For a survey of the functional group compatibilities of various catalysts, see ref 3k.
- (15) Grubbs, R. H. The Development of Functional Group Tolerant ROMP Catalysts. *J. Macromol. Sci.—Pure Appl. Chem.* **1994**, *A31*, 1829–1833.
- (16) (a) Brown-Wensley, K. A.; Buchwald, S. L.; Cannizzo, L.; Clawson, L.; Ho, S.; Meinhardt, D.; Stille, J. R.; Straus, D.; Grubbs, R. H. Cp_2TiCH_2 Complexes in Synthetic Applications. *Pure Appl. Chem.* **1983**, *55*, 1733–1744. (b) Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. Titanium-Mediated Methylene-Transfer Reactions. Direct Conversion of Esters into Vinyl Ethers. *J. Am. Chem. Soc.* **1980**, *102*, 3270–3272.
- (17) (a) Michelotti, F. W.; Keaveney, W. P. Coordinated polymerization of the bicyclo[2.2.1]hept-2-ene ring system (norbornene) in polar media. *J. Polym. Sci.* **1965**, *A3*, 895–905. (b) Rinehart, R. E.; Smith, H. P. The Emulsion Polymerization of the Norbornene Ring System Catalyzed by Nobel Metal Compounds. *Polym. Lett.* **1965**, *3*, 1049–1052.
- (18) Novak, B. M.; Grubbs, R. H. The Ring Opening Metathesis Polymerization of 7-Oxabicyclo[2.2.1]hept-5-ene Derivatives: A New Acyclic Polymeric Ionophore. *J. Am. Chem. Soc.* **1988**, *110*, 960–961.
- (19) Several other groups subsequently published related results: (a) Zenkl, E.; Stelzer, F. The aqueous ring-opening metathesis polymerization of 7-oxa-norbornene-2,3-dicarboxylic acid dimethyl ester and norbornene with Ru catalysts. *J. Mol. Catal.* **1992**, *76*, 1–14. (b) Lu, S.-Y.; Quayle, P.; Heatley, F.; Booth, C.; Yeates, S. G.; Padget, J. C. Aqueous Ring-Opening Metathesis Polymerization of *exo,exo*-2,3-Bis(methoxymethyl)-7-oxanorbornene Catalyzed by Ruthenium Trichloride. *Macromolecules* **1992**, *25*, 2692–2697. (c) Feast, W. J.; Harrison, D. B. Aqueous metathesis polymerizations of heteropolycyclic alkenes using transition metal chloride catalysts. *J. Mol. Catal.* **1991**, *65*, 63–72.
- (20) (a) Hillmyer, M. A.; Lepetit, C.; McGrath, D. V.; Novak, B. M.; Grubbs, R. H. Aqueous Ring-Opening Metathesis Polymerization of Carboximide-Functionalized 7-Oxanorbornenes. *Macromolecules* **1992**, *25*, 3345–3350. (b) Novak, B. M.; Grubbs, R. H. Catalytic Organometallic Chemistry in Water: The Aqueous Ring-Opening Metathesis Polymerization of 7-Oxanorbornene Derivatives. *J. Am. Chem. Soc.* **1988**, *110*, 7542–7543.
- (21) McGrath, D. V.; Grubbs, R. H.; Ziller, J. W. Aqueous Ruthenium(II) Complexes of Functionalized Olefins: The X-ray Structure of $Ru(H_2O)_2(\eta^1(O):\eta^2(C,C)-OCOCH_2CH=CHCH_3)_2$. *J. Am. Chem. Soc.* **1991**, *113*, 3611–3613.
- (22) France, M. B.; Grubbs, R. H.; McGrath, D. V.; Paciello, R. A. Chain Transfer during the Aqueous Ring-Opening Metathesis Polymerization of 7-Oxanorbornene Derivatives. *Macromolecules* **1993**, *26*, 4742–4747.
- (23) France, M. B.; Paciello, R. A.; Grubbs, R. H. Initiation of Ring-Opening Metathesis Polymerization in Protic Media. Extension of $[Ru(H_2O)_6]^{2+}$ Catalyzed Polymerizations to Less-Strained Cyclic Monomers. *Macromolecules* **1993**, *26*, 4739–4741.
- (24) Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. Synthesis of Tungsten Vinyl Alkylidene Complexes via the Reactions of $WCl_2(NAr)(PX_3)_3$ (X = R, OMe) Precursors with 3,3-Disubstituted Cyclopropenes. *J. Am. Chem. Soc.* **1993**, *115*, 8130–8145.
- (25) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. Ring-Opening Metathesis Polymerization (ROMP) of Norbornene by a Group VIII Carbene Complex in Protic Media. *J. Am. Chem. Soc.* **1992**, *114*, 3974–3975.

- (26) Wu, Z.; Benedicto, A. D.; Grubbs, R. H. Living Ring-Opening Metathesis Polymerization of Bicyclo[3.2.0]heptene Catalyzed by a Ruthenium Alkylidene Complex. *Macromolecules* **1993**, *26*, 4975–4977.
- (27) Nguyen, S. T. The Designs, Syntheses, and Applications of Well-Defined, Single Component Group VIII Olefin Metathesis Catalysts. Ph.D. Thesis, California Institute of Technology, 1995; Chapter 8.
- (28) Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. Syntheses and Activities of New Single-Component, Ruthenium-Based Olefin Metathesis Catalysts. *J. Am. Chem. Soc.* **1993**, *115*, 9858–9859.
- (29) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. Catalytic Ring-Closing Metathesis of Functionalized Dienes by a Ruthenium Carbene Complex. *J. Am. Chem. Soc.* **1993**, *115*, 9856–9857.
- (30) (a) Schwab, P.; Grubbs, R. H.; Ziller, J. W. Synthesis and Applications of $RuCl_2(=CHR)(PR_3)_2$: The Influence of the Alkylidene Moiety on Metathesis Activity. *J. Am. Chem. Soc.* **1996**, *118*, 100–110. (b) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. A Series of Well-Defined Metathesis Catalysts—Synthesis of $[RuCl_2(=CHR)(PR_3)_2]$ and Its Reactions. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039–2041.
- (31) Data obtained with keyword searches in the Institute for Scientific Information *Web of Science* database.
- (32) (a) Weck, M.; Mohr, B.; Maughon, B. R.; Grubbs, R. H. Synthesis of Discotic Columnar Side-Chain Liquid Crystalline Polymers by Ring-Opening Metathesis Polymerization (ROMP). *Macromolecules* **1997**, *30*, 6430–6437. (b) Maughon, B. R.; Weck, M.; Mohr, B.; Grubbs, R. H. Influence of Backbone Rigidity on the Thermotropic Behavior of Side-Chain Liquid Crystalline Polymers Synthesized by Ring-Opening Metathesis Polymerization. *Macromolecules* **1997**, *30*, 257–265.
- (33) (a) Arimoto, H.; Nishimura, K.; Kinumi, T.; Hayakawa, I.; Uemura, D. Multi-valent polymer of vancomycin: enhanced antibacterial activity against VRE. *Chem. Commun.* **1999**, 1361–1362. (b) Kanai, M.; Mortell, K. H.; Kiessling, L. L. Varying the Size of Multivalent Ligands: The Dependence of Concanavalin A Binding on Neoglycopolymers Length. *J. Am. Chem. Soc.* **1997**, *119*, 9931–9932. (c) Mortell, K. H.; Weatherman, R. V.; Kiessling, L. L. Recognition Specificity of Neoglycopolymers Prepared by Ring-Opening Metathesis Polymerization. *J. Am. Chem. Soc.* **1996**, *118*, 2297–2298.
- (34) Walba, D. M.; Keller, P.; Shao, R.; Clark, N. A.; Hillmyer, M.; Grubbs, R. H. Main-Chain Ferroelectric Liquid Crystal Oligomers by Acyclic Diene Metathesis Polymerization. *J. Am. Chem. Soc.* **1996**, *118*, 2740–2741.
- (35) Lynn, D. M.; Kanaoka, S.; Grubbs, R. H. Living Ring-Opening Metathesis Polymerization in Aqueous Media Catalyzed by Well-Defined Ruthenium Carbene Complexes. *J. Am. Chem. Soc.* **1996**, *118*, 784–790.
- (36) (a) Lynn, D. M.; Mohr, B.; Grubbs, R. H.; Henling, L. M.; Day, M. W. Water-Soluble Ruthenium Alkylidenes: Synthesis, Characterization, and Application to Olefin Metathesis in Protic Solvents. *J. Am. Chem. Soc.* **2000**, *122*, 6601–6609. (b) Lynn, D. M.; Mohr, B.; Grubbs, R. H. Living Ring-Opening Metathesis Polymerization in Water. *J. Am. Chem. Soc.* **1998**, *120*, 1627–1628. (c) Mohr, B.; Lynn, D. M.; Grubbs, R. H. Synthesis of Water-Soluble, Aliphatic Phosphines and Their Application to Well-Defined Ruthenium Olefin Metathesis Catalysts. *Organometallics* **1996**, *15*, 4317–4325.
- (37) Kirkland, T. A.; Lynn, D. M.; Grubbs, R. H. Ring-Closing Metathesis in Methanol and Water. *J. Org. Chem.* **1998**, *63*, 9904–9909.
- (38) Zuercher, W. J.; Hashimoto, M.; Grubbs, R. H. Tandem Ring Opening-Ring Closing Metathesis of Cyclic Olefins. *J. Am. Chem. Soc.* **1996**, *118*, 6634–6640.
- (39) Zuercher, W. J.; Scholl, M.; Grubbs, R. H. Ruthenium-Catalyzed Polycyclization Reactions. *J. Org. Chem.* **1998**, *63*, 4291–4298.
- (40) Kim, S.-H.; Zuercher, W. J.; Bowden, N. B.; Grubbs, R. H. Catalytic Ring Closing Metathesis of Dienes: Construction of Fused Bicyclic $[n.m.0]$ Rings. *J. Org. Chem.* **1996**, *61*, 1073–1081.
- (41) Morehead, A.; Grubbs, R. H. Formation of bridged bicycloalkenes via ring closing metathesis. *Chem. Commun.* **1998**, 275–276.
- (42) Scholl, M.; Grubbs, R. H. Total synthesis of (–)- and (+)-frontalin via ring-closing metathesis. *Tetrahedron Lett.* **1999**, *40*, 1425–1428.
- (43) (a) Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. The Art and Science of Total Synthesis at the Dawn of the Twenty-First Century. *Angew. Chem., Int. Ed.* **2000**, *39*, 45–122. (b) Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.; Roschangar, F.; Sarabia, F.; Ninkovic, S.; Yang, Z.; Trujillo, J. I. The Olefin Metathesis Approach to Epithilone A and Its Analogues. *J. Am. Chem. Soc.* **1997**, *119*, 7960–7973. (c) Meng, D.; Su, D.-S.; Balog, A.; Bertinato, P.; Sorensen, E. J.; Danishefsky, S. J.; Zheng, Y.-H.; Chou, T.-C.; He, L.; Horwitz, S. B. Remote Effects in Macrolide Formation through Ring-Forming Olefin Metathesis: An Application to the Synthesis of Fully Active Epithilone Congeners. *J. Am. Chem. Soc.* **1997**, *119*, 2733–2734.
- (44) (a) Blackwell, H. E.; Grubbs, R. H. Highly Efficient Synthesis of Covalently Cross-Linked Peptide Helices by Ring-Closing Metathesis. *Angew. Chem., Int. Ed.* **1998**, *37*, 3281–3284. (b) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. Application of Ring-Closing Metathesis to the Synthesis of Rigidified Amino Acids and Peptides. *J. Am. Chem. Soc.* **1996**, *118*, 9606–9614. (c) Miller, S. J.; Grubbs, R. H. Synthesis of Conformationally Restricted Amino Acids and Peptides Employing Olefin Metathesis. *J. Am. Chem. Soc.* **1995**, *117*, 5855–5856.
- (45) (a) Villemin, D. Synthese De Macrolides Par Metathese. *Tetrahedron Lett.* **1980**, *21*, 1715–1718. (b) Tsuji, J.; Hashiguchi, S. Applications of Olefin Metathesis to Organic Synthesis. Synthesis of Civetone and Macrolides. *Tetrahedron Lett.* **1980**, *21*, 2955–2958.
- (46) (a) Martin, S. F.; Humphrey, J. M.; Ali, A.; Hillier, M. C. Enantioselective Total Syntheses of Ircinal A and Related Manzamine Alkaloids. *J. Am. Chem. Soc.* **1999**, *121*, 866–867. (b) Fürstner, A.; Langemann, K. Conformationally Unbiased Macrocyclization Reactions by Ring Closing Metathesis. *J. Org. Chem.* **1996**, *61*, 3942–3943. (c) Martin, S. F.; Liao, Y.; Wong, Y.; Rein, T. A Novel Approach to the Asymmetric Synthesis of Manzamine A. Construction of the Tetracyclic ABCE Ring System. *Tetrahedron Lett.* **1994**, *35*, 691–694. (d) Borer, B. C.; Deerenberg, S.; Bieraguel, H.; Pandit, U. K. The First Synthesis of the ABCD Ring System of Manzamine A. Construction of the Macrocyclic Ring D. *Tetrahedron Lett.* **1994**, *35*, 3191–3194.
- (47) Marsella, M. J.; Maynard, H. D.; Grubbs, R. H. Template-Directed Ring-Closing Metathesis: Synthesis and Polymerization of Unsaturated Crown Ether Analogs. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1101–1103.
- (48) (a) Weck, M.; Mohr, B.; Sauvage, J.-P.; Grubbs, R. H. Synthesis of Catenane Structures via Ring-Closing Metathesis. *J. Org. Chem.* **1999**, *64*, 5463–5471. (b) Mohr, B.; Weck, M.; Sauvage, J.-P.; Grubbs, R. H. High-Yield Synthesis of [2]Catenanes by Intramolecular Ring-Closing Metathesis. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1308–1310.
- (49) (a) Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. New Approaches to Olefin Cross-Metathesis. *J. Am. Chem. Soc.* **2000**, *122*, 58–71. (b) O'Leary, D. J.; Blackwell, H. E.; Washenfelder, R. A.; Grubbs, R. H. A New Method for Cross-Metathesis of Terminal Olefins. *Tetrahedron Lett.* **1998**, *39*, 7427–7430.
- (50) O'Leary, D. J.; Blackwell, H. E.; Washenfelder, R. A.; Miura, K.; Grubbs, R. H. Terminal Olefin Cross-Metathesis with Acrolein Acetals. *Tetrahedron Lett.* **1999**, *40*, 1091–1094.
- (51) Maynard, H. D.; Grubbs, R. H. Purification Technique for the Removal of Ruthenium from Olefin Metathesis Reaction Products. *Tetrahedron Lett.* **1999**, *40*, 4137–4140.
- (52) Wilhelm, T. E.; Belderrain, T. R.; Brown, S. N.; Grubbs, R. H. Reactivity of $Ru(H)(H_2)Cl(PCy_3)_2$ with Propargyl and Vinyl Chlorides: New Methodology To Give Metathesis-Active Ruthenium Carbenes. *Organometallics* **1997**, *16*, 3867–3869.
- (53) Alternatively, the reaction of $XCHCl_2$ ($X = Ph, CO_2Me, H$) with $Ru(0)$ precursors, such as $[Ru(\eta^4\text{-cyclooctadiene})(\eta^6\text{-cyclooctatriene})]$ or $[Ru(H_2)_2(\text{cyclohexene})(PCy_3)_2]$, may be used: Belderrain, T. R.; Grubbs, R. H. Reaction between Ruthenium(0) Complexes and Dihalide Compounds. A New Method for the Synthesis of Ruthenium Olefin Metathesis Catalysts. *Organometallics* **1997**, *16*, 4001–4003. A one-pot synthesis starting from $RuCl_3(\text{hydrate})$ has also been reported: Wolf, J.; Stüer, W.; Grünwald, C.; Werner, H.; Schwab, P.; Schulz, M. Ruthenium Trichloride, Tricyclohexylphosphane, 1-Alkynes, Magnesium, Hydrogen, and Water—Ingredients of an Efficient One-Pot Synthesis of Ruthenium Catalysts for Olefin Metathesis. *Angew. Chem., Int. Ed.* **1998**, *37*, 1124–1126.
- (54) In the United States, suppliers include Fluka, Strem Chemicals, and Boulder Scientific.
- (55) Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. Well-Defined Ruthenium Olefin Metathesis Catalysts: Mechanism and Activity. *J. Am. Chem. Soc.* **1997**, *119*, 3887–3897.
- (56) Maughon, B. R.; Grubbs, R. H. Ruthenium Alkylidene Initiated Living Ring-Opening Metathesis Polymerization (ROMP) of 3-Substituted Cyclobutenes. *Macromolecules* **1997**, *30*, 3459–3469.
- (57) Wu, Z.; Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. Reactions of Ruthenium Carbenes of the Type $(PPh_3)_2(X)_2Ru=CH-CH=CPh_2$ ($X = Cl$ and CF_3COO) with Strained Acyclic Olefins and Functionalized Olefins. *J. Am. Chem. Soc.* **1995**, *117*, 5503–5511.
- (58) Tallarico, J. A.; Bonitatebus, P. J.; Snapper, M. L. Ring-Opening Metathesis. A Ruthenium Catalyst Caught in the Act. *J. Am. Chem. Soc.* **1997**, *119*, 7157–7158.

- (59) (a) Adlhart, C.; Hinderling, C.; Baumann, H.; Chen, P. Mechanistic Studies of Olefin Metathesis by Ruthenium Carbene Complexes Using Electrospray Ionization Tandem Mass Spectrometry. *J. Am. Chem. Soc.* **2000**, *122*, 8204–8214. (b) Hinderling, C.; Adlhart, C.; Chen, P. Olefin Metathesis of a Ruthenium Carbene Complex by Electrospray Ionization in the Gas Phase. *Angew. Chem., Int. Ed.* **1998**, *37*, 2685–2689.
- (60) Aagaard, O. M.; Meier, R. J.; Buda, F. Ruthenium-Catalyzed Olefin Metathesis: A Quantum Molecular Dynamics Study. *J. Am. Chem. Soc.* **1998**, *120*, 7174–7182.
- (61) Cucullu, M. E.; Li, C.; Nolan, S. P.; Nguyen, S. T.; Grubbs, R. H. Thermochemical Investigation of Phosphine Ligand Substitution Reactions Involving $trans-(PR_3)_2Cl_2Ru=CH-CH=CPh_2$ Complexes. *Organometallics* **1998**, *17*, 5565–5568.
- (62) Ulman, M.; Grubbs, R. H. Relative Reaction Rates of Olefin Substrates with Ruthenium(II) Carbene Metathesis Initiators. *Organometallics* **1998**, *17*, 2484–2489.
- (63) Ulman, M.; Belderrain, T. R.; Grubbs, R. H. A series of ruthenium(II) ester-carbene complexes as olefin metathesis initiators: metathesis of acrylates. *Tetrahedron Lett.* **2000**, *41*, 4689–4693.
- (64) Ulman, M.; Grubbs, R. H. Ruthenium Carbene-Based Olefin Metathesis Initiators: Catalyst Decomposition and Longevity. *J. Org. Chem.* **1999**, *64*, 7202–7207.
- (65) Chang, S.; Jones, L.; Wang, C.; Henling, L. M.; Grubbs, R. H. Synthesis and Characterization of New Ruthenium-Based Olefin Metathesis Catalysts Coordinated with Bidentate Schiff-Base Ligands. *Organometallics* **1998**, *17*, 3460–3465.
- (66) (a) Dias, E. L.; Grubbs, R. H. Synthesis and Investigation of Homo- and Heterobimetallic Ruthenium Olefin Metathesis Catalysts Exhibiting Increased Activities. *Organometallics* **1998**, *17*, 2758–2767. (b) Dias, E. L. Ruthenium-Based Olefin Metathesis Catalysts: Synthesis, Mechanism, and Activity. Ph.D. Thesis, California Institute of Technology, 1998; Chapter 3.
- (67) Sanford, M. S.; Henling, L. M.; Grubbs, R. H. Synthesis and Reactivity of Neutral and Cationic Ruthenium(II) Tris(pyrazolyl)borate Alkylidenes. *Organometallics* **1998**, *17*, 5384–5389.
- (68) For a comprehensive survey of N-heterocyclic carbenes, see: (a) Bourissou, D.; Guerret, O.; Gabbaï, F. P.; Bertrand, G. Stable Carbenes. *Chem. Rev.* **2000**, *100*, 39–91. (b) Arduengo, A. J. Looking for Stable Carbenes: The Difficulty in Starting Anew. *Acc. Chem. Res.* **1999**, *32*, 913–921. (c) Herrmann, W. A.; Köcher, C. N-Heterocyclic Carbenes. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2163–2187.
- (69) (a) Weskamp, T.; Schattenmann, W. C.; Spiegler, M.; Herrmann, W. A. A Novel Class of Ruthenium Catalysts for Olefin Metathesis. *Angew. Chem., Int. Ed.* **1998**, *37*, 2490–2493. (b) Herrmann, W. A.; et al. Corrigenda. *Angew. Chem., Int. Ed.* **1999**, *38*, 262.
- (70) Huang, J.; Schanz, H.-J.; Stevens, E. D.; Nolan, S. P. Stereoelectronic Effects Characterizing Nucleophilic Carbene Ligands Bound to the Cp^*RuCl ($Cp^* = \eta^5-C_5Me_5$) Moiety: A Structural and Thermochemical Investigation. *Organometallics* **1999**, *18*, 5375–5380.
- (71) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. Increased Ring Closing Metathesis Activity of Ruthenium-Based Olefin Metathesis Catalysts Coordinated with Imidazolin-2-ylidene Ligands. *Tetrahedron Lett.* **1999**, *40*, 2247–2250.
- (72) (a) Weskamp, T.; Kohl, F. J.; Herrmann, W. A. N-heterocyclic carbenes: novel ruthenium-alkylidene complexes. *J. Organomet. Chem.* **1999**, *582*, 362–365. (b) Weskamp, T.; Kohl, F. J.; Hieringer, W.; Gleich, D.; Herrmann, W. A. Highly Active Ruthenium Catalysts for Olefin Metathesis: The Synergy of N-Heterocyclic Carbenes and Coordinatively Labile Ligands. *Angew. Chem., Int. Ed.* **1999**, *38*, 2416–2419. (c) Ackermann, L.; Fürstner, A.; Weskamp, T.; Kohl, F. J.; Herrmann, W. A. Ruthenium Carbene Complexes with Imidazolin-2-ylidene Ligands Allow the Formation of Tetrasubstituted Cycloalkenes by RCM. *Tetrahedron Lett.* **1999**, *40*, 4787–4790. (d) Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. Olefin Metathesis-Active Ruthenium Complexes Bearing a Nucleophilic Carbene Ligand. *J. Am. Chem. Soc.* **1999**, *121*, 2674–2678.
- (73) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. Synthesis and Activity of a New Generation of Ruthenium-Based Olefin Metathesis Catalysts Coordinated with 1,3-Dimesityl-4,5-dihydroimidazol-2-ylidene Ligands. *Org. Lett.* **1999**, *1*, 953–956.
- (74) Bielawski, C. W.; Grubbs, R. H. Highly Efficient Ring-Opening Metathesis Polymerization (ROMP) Using New Ruthenium Catalysts Containing N-Heterocyclic Carbene Ligands. *Angew. Chem., Int. Ed.* **2000**, *39*, 2903–2906.
- (75) Chatterjee, A. K.; Grubbs, R. H. Synthesis of Trisubstituted Alkenes via Olefin Cross-Metathesis. *Org. Lett.* **1999**, *1*, 1751–1753.
- (76) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. Synthesis of Functionalized Olefins by Cross and Ring-Closing Metatheses. *J. Am. Chem. Soc.* **2000**, *122*, 3783–3784.
- (77) (a) Stragies, R.; Voigtmann, U.; Blechert, S. Improved ene-ene-cross metathesis utilizing a dihydroimidazole carbene ruthenium complex. *Tetrahedron Lett.* **2000**, *41*, 5465–5468. (b) Smulik, J. A.; Diver, S. T. Expanded Scope in Ethylene-Alkyne Cross-Metathesis: Coordinating Heteroatom Functionality at the Propargylic Position. *Org. Lett.* **2000**, *2*, 2271–2274.
- (78) Catalyst **14** will soon be available from Strem Chemicals: Second generation Grubbs's catalyst. *The Strem Chemiker* **2000**, *1*, 30.
- (79) Ulman, M. Selectivity, Activity and Stability of Ruthenium-Carbene Based Olefin Metathesis Initiators. Ph.D. Thesis, California Institute of Technology, 2000; Chapter 5.
- (80) Sanford, M. S.; Grubbs, R. H., manuscript in preparation.
- (81) Ding, S.; Feldmann, M. T.; Grubbs, R. H.; Goddard, W. A. Ab Initio Studies of the Ruthenium-Carbene-Phosphine Olefin Metathesis Catalysts: Rapid Screening for Design of Improved Catalysts, submitted.
- (82) Trnka, T. M.; Grubbs, R. H., manuscript in preparation.
- (83) (a) Fujimura, O.; Grubbs, R. H. Asymmetric Ring-Closing Metathesis Catalyzed by Chiral Molybdenum Alkylidene Complexes. *J. Org. Chem.* **1998**, *63*, 824–832. (b) Fujimura, O.; Grubbs, R. H. Asymmetric Ring-Closing Metathesis: Kinetic Resolution Catalyzed by a Chiral Molybdenum Alkylidene Complex. *J. Am. Chem. Soc.* **1996**, *118*, 2499–2500. (c) Zhu, S. S.; Cefalo, D. R.; La, D. S.; Jamieson, J. Y.; Davis, W. M.; Hoveyda, A. H.; Schrock, R. R. Chiral Mo-Binol Complexes: Activity, Synthesis, and Structure. Efficient Enantioselective Six-Membered Ring Synthesis through Catalytic Metathesis. *J. Am. Chem. Soc.* **1999**, *121*, 8251–8259. (d) Alexander, J. B.; La, D. S.; Cefalo, D. R.; Hoveyda, A. H.; Schrock, R. R. Catalytic Enantioselective Ring-Closing Metathesis by a Chiral Biphen-Mo Complex. *J. Am. Chem. Soc.* **1998**, *120*, 4041–4042.
- (84) Alkyne metathesis: (a) Bunz, U. H. F.; Kloppenburg, L. Alkyne Metathesis as a New Synthetic Tool: Ring-Closing, Ring-Opening, and Acyclic. *Angew. Chem., Int. Ed.* **1999**, *38*, 478–481. (b) Fürstner, A.; Mathes, C.; Lehmann, C. W. $Mo[N(t-Bu)(Ar)]_3$ Complexes As Catalyst Precursors: In Situ Activation and Application to Metathesis Reactions of Alkynes and Dienes. *J. Am. Chem. Soc.* **1999**, *121*, 9453–9454.
- (85) Imine metathesis: (a) Zuckerman, R. L.; Krska, S. W.; Bergman, R. G. Zirconium-Mediated Metathesis of Imines: A Study of the Scope, Longevity, and Mechanism of a Complicated Catalytic System. *J. Am. Chem. Soc.* **2000**, *122*, 751–761. (b) Cantrell, G. K.; Geib, S. J.; Meyer, T. Y. Ring-Opening of a Cyclic Imine: The First Step of Imine ROMP. *Organometallics* **1999**, *21*, 4250–4252. (c) Cantrell, G. K.; Meyer, T. Y. Catalytic C=N Bond Formation by Metal-Imide-Mediated Imine Metathesis. *J. Am. Chem. Soc.* **1998**, *120*, 8035–8042. (d) McInnes, J. M.; Blake, A. J.; Mountford, P. Reactions of titanium imido complexes with α -diamines: complexation versus $Ti=N/C=N$ bond metathesis. *J. Chem. Soc., Dalton Trans.* **1998**, 3623–3328.

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