Ring-Closing Metathesis and Related Processes in Organic Synthesis

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Introduction

Carbon–carbon bond forming reactions remain among the most important for the synthesis of organic structures. The transition metal alkylidene-catalyzed olefin metathesis reaction (eq 1) and the related transition metal alkylidene-mediated carbonyl olefination reaction (eq 2) are two such processes. Historically, olefin metathesis has been studied extensively both from the mechanistic standpoint and in the context of polymer synthesis.[1] In contrast, its application to the synthesis of complex organic molecules and natural products has been limited.[2] The related reaction, transition metal-mediated carbonyl olefination, is not as extensively studied mechanistically nor in synthetic applications. Among the reasons for this gap in methodology has been the incompatibility of traditional catalysts with the polar functional groups typically encountered in organic synthesis.


$$(1)$$

$$(2)$$
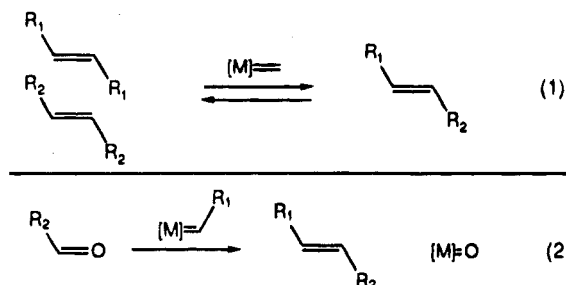
It is now accepted that the two metal alkylidene-based reactions are mechanistically related, involving the intermediacy of metallacyclic and oxametallacyclic intermediates, respectively.[3] In the case of olefin metathesis (eq 3), a [2 + 2] cycloaddition occurs between the metal alkylidene and the olefin substrate to produce a metallacyclobutane intermediate. Retrocycloaddition then occurs to afford a new metal alkylidene and the olefin metathesis product. In this variant of the process, the fundamental steps are frequently reversible and the reaction is under ther-

modynamic control. In carbonyl olefination (eq 4), however, an oxametallacyclobutane intermediate is formed. Subsequent breakdown of this intermediate results in a new olefin and a metal oxo species, which is stable and catalytically inactive. Whereas olefin metathesis can be effected with *catalytic* quantities of metal alkylidenes, carbonyl olefination typically requires *stoichiometric* quantities of a metal complex.

$$(3)$$

$$(4)$$
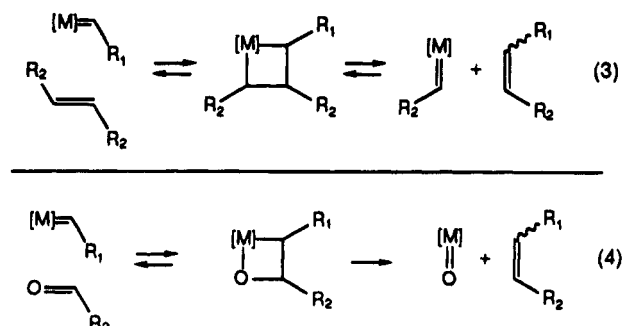
Background

Within the limitation of functional group tolerance, several applications of early transition metal based catalysts and catalyst systems to organic synthesis have been documented. For example, putative metal alkylidenes based on tungsten have been applied to the synthesis of several unfunctionalized hydrocarbon targets, including the pheromone 9-tricosene (eq 5).[4] However, this system suffers from the additional problem of poor selectivity in the cross metathesis reaction.

$$(5)$$

9-tricosene
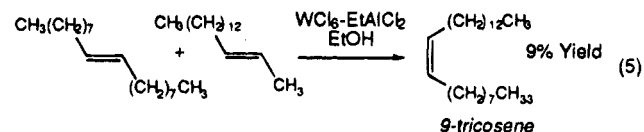
In addition, the titanium-based Tebbe reagent has been applied to the synthesis of $\Delta^{9,12}$ capnellane (Scheme 1).[5] In this case, combining alkene metathesis and carbonyl olefination causes a tandem reaction in which olefin metathesis results in a ring fragmen-

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(1) For leading references, see: (a) Feldman, J.; Schrock, R. R. *Prog. Inorg. Chem.* **1991**, *39*, 1–74. (b) Grubbs, R. H.; Tumas, W. *Science* **1989**, *243*, 907–915. (c) Ivin, K. J. *Olefin Metathesis*; Academic: New York, 1983.

(2) For a review, see: (a) Grubbs, R. H.; Pine, S. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 5, Chapter 9.3. For several related examples, see: (b) Trost, B. M.; Trost, M. K. *J. Am. Chem. Soc.* **1991**, *113*, 1850–1852. (c) Trost, B. M.; Trost, M. K. *Tetrahedron Lett.* **1991**, *32*, 3647–3650.

(3) Herrison, J. L.; Chauvin, Y. *Makromol. Chem.* **1970**, *141*, 161–176.

(4) Kupper, W.; Streck, R. *Chem.-Ztg.* **1975**, *99*, 464.

Scheme 1

$\Delta^{9,12}$ Capnellane
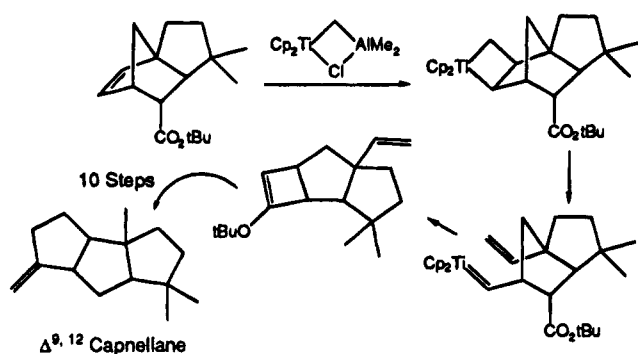
tation, followed by carbonyl olefination. Pivotal to the success of the reaction in this special case is the kinetic preference of the Tebbe reagent for the alkene over the ester. Titanium oxo formation during the carbonyl olefination necessitates that this reaction be stoichiometric in alkylidene precursor. The extensive use of the Tebbe reagent in organic synthesis has been reviewed elsewhere and will not be addressed here.[6]

Advances in catalyst design have contributed to increased functional group tolerance, which has expanded the scope of the olefin metathesis reaction. The key to functional group tolerance in alkene metathesis is the heightened affinity of metal alkylidenes for olefins relative to Lewis basic functionality. Early advances along these lines were reported by Schrock[7] and Basset.[8] Successful cross metathesis of methyl oleate to the corresponding diester illustrates some measure of success in the development of an alkene-selective alkylidene in the presence of ester functionality (eq 6).
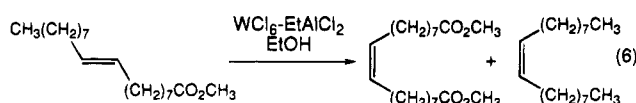
A complementary olefin metathesis based approach to organic synthesis is ring-closing metathesis (RCM, Scheme 2). In this process, a diene is treated with a metal alkylidene. Two competing pathways are then available to the intermediate metal alkylidene: (a) RCM can occur to afford cyclic adducts (path A), or (b) intermolecular reaction can occur to form polymeric adducts (acyclic diene metathesis polymerization, AD-

Scheme 2
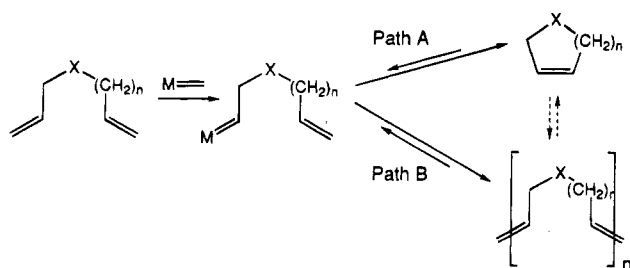
(5) (a) Stille, J. R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1986**, *108*, 855–856. (b) Stille, J. R.; Santarsiero, B. D.; Grubbs, R. H. *J. Org. Chem.* **1990**, *55*, 843–862.

(6) See refs 1b and 2a.

(7) Schrock, R. R.; Krouse, S. A.; Knoll, K.; Feldman, J.; Murdzek, J. S.; Yang, D. C. *J. Mol. Catal.* **1988**, *46*, 243–253.

(8) Quignard, F.; Leconte, M.; Basset, J.-M. *J. Chem. Soc., Chem. Commun.* **1985**, 1816–1817.

MET, path B). The reaction is also complicated by the possibility of ring-opening metathesis polymerization (ROMP). Which products are obtained is the result of an interplay of thermodynamic and kinetic parameters.

Among the first investigators to exploit RCM in organic synthesis was Tsuji in the synthesis of macrocycles (eq 7).[9] Application of the multiple-component tungsten-based catalysts to an α,ω-diene resulted in RCM to afford the illustrated macrocycle in 18% yield.

18% Yield
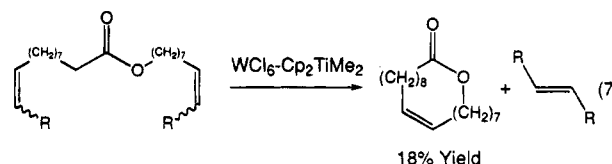
In addition to these examples, several advances were made in the area of catalyst design, including the use of systems based on later transition metals, such as rhenium.[10] Comprehensive coverage of this history will not be undertaken here, but many of these examples contributed to the steady evolution of olefin metathesis catalysts. Nevertheless, with the exception of the Tebbe system, it is noteworthy that most of the systems contain multiple components and are mechanistically ill-defined. It is fair to say that the search for and discovery of single-component catalysts has initiated a new period in the evolution of olefin metathesis catalysis.

Recent Developments

Molybdenum-Based Alkylidenes. Parallel discoveries in the development of metathesis catalysts for polymer synthesis suggested that well-defined, single-component metathesis catalysts could hold great promise for applications in organic synthesis. For example, the discovery of the highly active Mo-based catalyst **1** and its application to 7-oxanorbornene polymerization illustrated that these catalysts retained their high activities in the presence of a large excess of ether-containing monomers.[11] This level of activity, in addition to a reasonable level of tolerance of Lewis basic functionality, suggested that applications to RCM were possible.

R = CMe(CF$_3$)$_2$

1
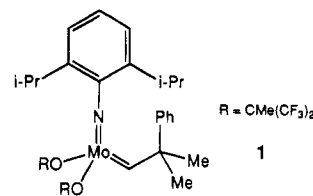
Cyclic ethers represent a class of heterocycles which are of great importance in natural products, and these oxygen heterocycles represented our initial goal for

(9) Tsuji, J.; Hashiguchi, S. *Tetrahedron Lett.* **1980**, *21*, 2955–2958.

(10) For a study employing a heterogeneous Re-based system, see: (a) Warwel, S.; Katzker, H.; Rauenbusch, C. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 702–703. For homogeneous Re-based systems, see: (b) Toreki, R.; Schrock, R. R. *J. Am. Chem. Soc.* **1990**, *112*, 2449–2451. (c) Toreki, R.; Schrock, R. R.; Davis, W. M. *J. Am. Chem. Soc.* **1992**, *114*, 3367–3380.

(11) (a) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875–3886. (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. *J. Am. Chem. Soc.* **1990**, *112*, 8378–8387. (c) Bazan, G. C.; Oskam, J. H.; Cho, H.-N.; Park, L. Y.; Schrock, R. R. *J. Am. Chem. Soc.* **1991**, *113*, 6899–6907.
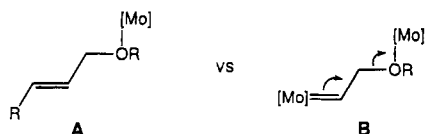
Figure 1. Possible modes of catalyst inhibition with **1**.

synthesis by RCM.[12] In addition to the problems of competing polymerization of the acyclic substrate (ADMET) and cyclic product (ROMP), there were several problems associated with allylic oxygen functionality and the Lewis acidity of the metal center (Figure 1). Not only was there the possibility for activation of the substrate by the metal (A), but also β-elimination threatened to consume the propagating catalytic species (B).[13,14] These problems were not encountered, and Scheme 3 presents a mechanism which is consistent with the observed results.[15] It is noteworthy that the intermediate undergoes ring closure prior to any β-elimination pathway.

Scheme 3
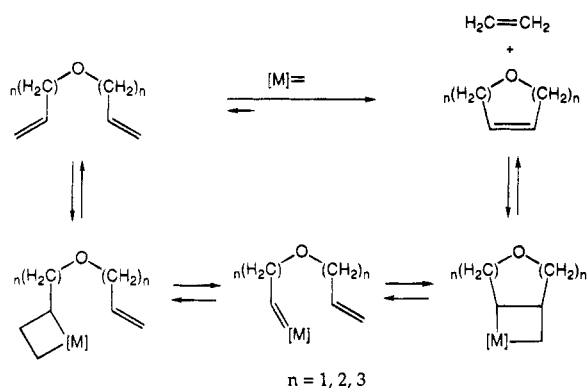
$$n = 1, 2, 3$$

The scope is illustrated in Scheme 4. It is significant to note that di-, tri-, and tetrasubstituted olefins are accessible by this method as are ring sizes of five to seven members. Reaction rates were found to correlate with olefin substitution and ring size; the more substituted olefins required longer reaction times, as did the seven-membered rings. Nevertheless, each of the substrates in Scheme 4 was obtained in synthetically useful yield.[16]

Cycloalkenes containing ethers were also accessible by this method (Scheme 5). Benzyl ethers, silyl ethers, and ester moieties were incorporated to illustrate the generality of the method in the presence of functionality commonly employed in organic synthesis. In addition, a tertiary alcohol was found not to interfere with the course of the reaction.

(12) For the leading references to the synthesis and structures of this class of natural products, see: (a) Belen'kii, L. I. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic: New York, 1988; Vol. 44, Chapter 4. (b) *Comprehensive Heterocyclic Chemistry*; Meth-Cohn, O., Ed.; Pergamon: New York, 1984. For an early application of RCM to the synthesis of cyclic ethers, see: Bogolopova, E. I.; Fridman, R. A.; Bashkirov, A. N. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1978**, *27*, 2429.

(13) For precedent concerning these competing reaction pathways in other metathesis systems, see: Levisalles, J.; Rudler, H.; Villemin, D. J. *J. Organomet. Chem.* **1979**, *164*, 251–257.

(14) In intermolecular cases employing highly reactive W-based catalysts, the competing β-elimination has been observed: Hillmyer, M. A.; Grubbs, R. H. *Macromolecules* **1993**, *26*, 872–874.
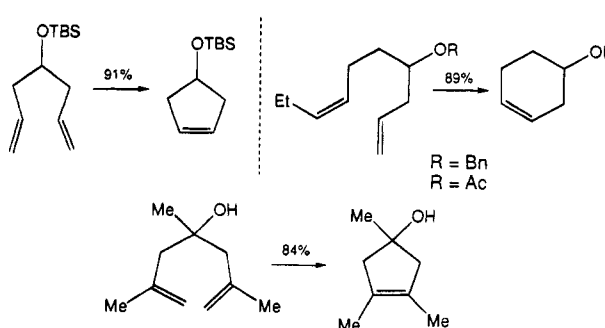
(15) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426–5427.

(16) Forbes et al. subsequently reported the RCM of a number of linear dienes exploiting the Thorpe–Ingold effect employing catalyst **1**. Forbes, M. D. E.; Patton, J. T.; Myers, T. L.; Maynard, H. D.; Smith, W. D., Jr.; Schulz, G. R.; Wagener, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 10978–10980.

Scheme 4
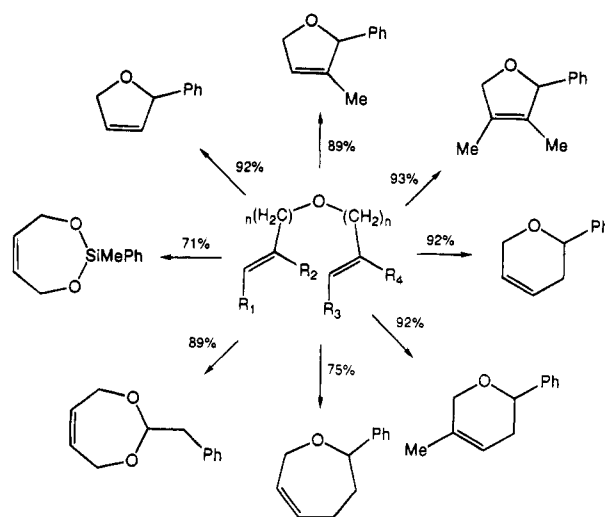
Scheme 5

In a significant extension of the methodology, the reaction was found to be applicable to nitrogen-containing heterocycles (eq 8).[17] This set the stage for application of RCM technology to the important alkaloid class of natural products.[18] Amines and amides were incorporated into the substrates, and RCM was found to proceed with rates and yields comparable to those observed with the cyclic ethers (Table 1). This
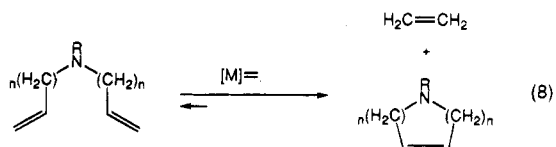
$$(8)$$

is particularly interesting in view of the fact that initial attempts to cyclize amide-containing substrates were unsuccessful due to the formation of stable, chelated substrate-alkylidene adducts (Figure 2).[19]
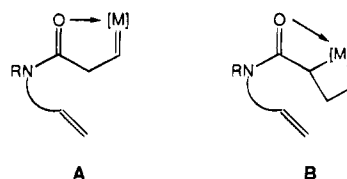

Figure 2. Possible modes of catalyst inhibition with **1**.

(17) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324–7325.

(18) For leading references to the synthesis and structure of natural products containing nitrogen heterocycles, see: (a) *The Alkaloids: Chemistry and Pharmacology; Brossi*, A., Cordell, G. A., Eds.; Academic: New York, 1992. (b) *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Eds.; Wiley-Interscience: New York, 1988. (c) See also refs 12a,b.

Ring-Closing Metathesis in Organic Synthesis

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The problem was solved by introducing olefin substitution to control the site of initial metathesis of the free metal alkylidene (Table 1, entry 1 vs entry 2). Steric effects regulate the site of initial metathesis, precluding the formation of unreactive chelate structures. This modification has resulted in the preparation of a range of ring sizes, in addition to varying degrees of olefin substitution. In addition, Martin's group has expanded the scope of this particular variant of RCM to include additional ring sizes relevant to natural product synthesis (*vide infra*).[20]

It is significant to note that carbonyl olefination is not observed when the propagating alkylidene can react intermolecularly with an additional olefin. When a second olefin is absent, however, intermolecular carbonyl olefination is possible (Scheme 6).[21] The key to successful olefination in this case is the initial metathesis of the metal alkylidene with the olefin (formation of **A**), followed by intramolecular metathesis with the carbonyl function (**B** to **C**). The second step is stoichiometric in metal, resulting in a stable metal−oxo species which is not catalytically active.

Scheme 6
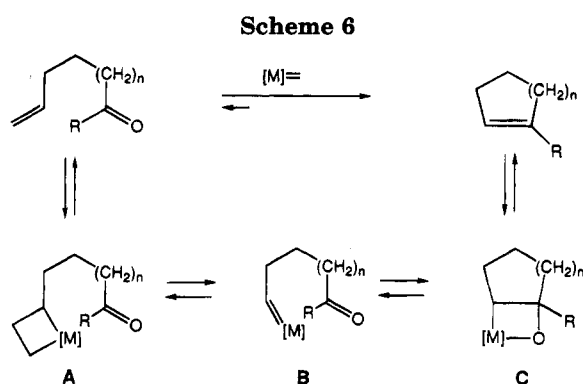
This pathway was also found to by a synthetically useful reaction, and the results are presented in Table 2.

Ring sizes of five, six, and seven are accessible through this reaction. The intramolecular ketone olefination is faster than the RCM of alkenes in certain situations where a pendant olefin is present (entry 2). Carbonyl olefination is limited to ketones with Mo alkylidene **1**, as esters were found to be inert under these conditions. Esters will undergo carbonyl olefination, however, with the more reactive tungsten analogue [W(CHCMe₃)(NAr)(OCMe(CF₃)₂)₂].[22]

A combined carbonyl olefination/ring-closing metathesis approach was introduced which expanded the synthetic scope of the processes described above.[23] In this case, stoichiometric ester carbonyl olefination was effected using inexpensive titanium reagent based olefination. Subsequent catalytic RCM of the resulting enol ether substrates led to cyclic enol ether products,

Table 1

Entry	Substrate	Product	Yield
1			0%
2			80%
3		n = 1, 2, 3 73-86%

Table 2

Entry	Substrate	Product	Yield
1			86%
2			84%
3			86%

which are often constituents of bioactive compounds. This process is illustrated by the synthesis of the natural product *Sophora* compound I (Scheme 7).

Scheme 7

R = H
Sophora Compound I

72%   85%

Ruthenium-Based Alkylidenes. The advances described to this point in applying metal alkylidene catalyzed RCM and carbonyl olefination were made possible in large part by the active Mo-based alkylidene **1**. Although this complex exhibits some level of functional group tolerance, the extreme sensitivity of the system to O₂, H₂O, and additional polar functional groups, in addition to its difficult synthesis, made the ongoing search for less sensitive catalysts a worthwhile endeavor. The impetus for discovery once again came from parallel developments in the field of

(19) Related problems had been encountered in studies concerning the metal alkylidene mediated dimerization of α,β-unsaturated esters. Feldman, J.; Murdzek, J. S.; Davis, W. M.; Schrock, R. R. *Organometallics* **1989**, *8*, 2260−2265.

(20) Martin, S. F.; Liao, Y.; Chen, H. J.; Patzel, M.; Ramser, M. N. *Tetrahedron Lett.* **1994**, *35*, 6005−6008.

(21) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 3800−3801.

(22) (a) Schrock, R. R.; DePue, R. T.; Feldman, J.; Schaverien, C. J.; Dewan, J. C.; Liu, A. H. *J. Am. Chem. Soc.* **1988**, *110*, 1423−1435. (b) Schrock, R. R.; DePue, R. T.; Feldman, J.; Yap, K. B.; Yang, D. C.; Davis, W. M.; Park, L.; DiMare, M.; Schofield, M.; Anhaus, J.; Walborsky, E.; Evitt, E.; Kruger, C.; Betz, P. *Organometallics* **1990**, *9*, 2262−2275.

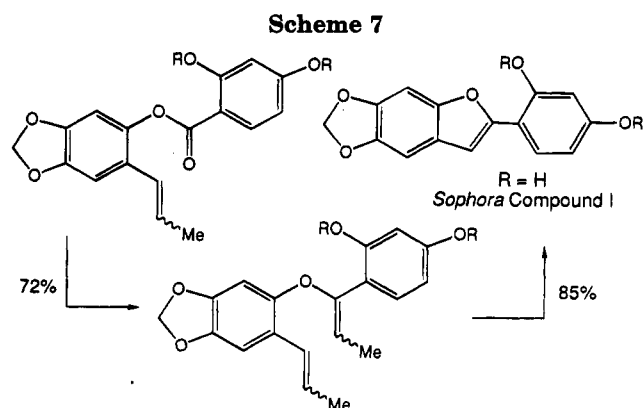(23) Fujimura, O.; Fu, G. C.; Grubbs, R. H. *J. Org. Chem.* **1994**, *59*, 4029−4031.
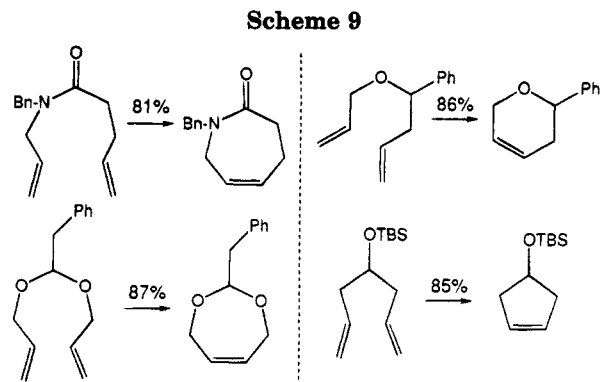
polymer synthesis. For example, it had been demonstrated that 7-oxanorbornene and related monomers could be polymerized using classical, several-component catalysts based on Ru and Os.[24] The fact that these catalyst systems retain activity in the presence of ethers and other functional groups, in addition to the fact that they *function in aqueous media*, suggested that applications to functionalized substrates in organic synthesis were reasonable to consider.

A significant breakthrough was achieved with the discovery of the well-defined ruthenium catalyst **2** and its activity in the polymerization of norbornenes. The key step in the synthesis of **2** is the transition metal catalyzed rearrangement of cyclopropenes, initially discovered in the context of the synthesis of group IV based alkylidenes[25] and later applied to the synthesis of well-defined W-,[26] and Re-,[27] and Ir-based alkylidenes[28] (Scheme 8). Although the initially developed bis(PPh3) complex **2** was found to be inactive for RCM, varying the phosphine ligands was found to increase the activity of the catalyst. In particular, exchanging the PPh3 ligands for P(Cy)3 ligands afforded complex **3**, which not only was much more reactive in ROMP but also exhibited sufficient activity for RCM.[29]

Scheme 8
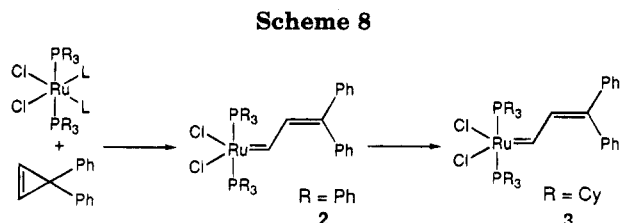
It quickly became clear that the Ru-based systems possessed the desired balance between functional group tolerance and high catalyst activity. The applications of these systems in polymer synthesis will not be elaborated on here,[30] except to mention that catalysts **2** and **3** were active in the ROMP of monomers containing multiple functional groups. Carbonyl olefination was not observed under any circumstances. In addition, catalyst activity was retained even under reaction conditions which did not include rigorous exclusion of H2O and O2. More recently, catalysts **2** and **3** have been found to retain polymerization activity even under aqueous emulsion conditions.[30c]

In the initial study of **3** as a RCM catalyst, most of the substituents used in the previous studies with the Mo-based catalyst **1** were reexamined with the goal of comparing activity and functional group tolerance. Alkylidene **3** was found to be an extremely efficient catalyst for the RCM of cycloalkenes, cyclic ethers, and

(24) (a) Novak, B. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1988**, *110*, 960. (b) Novak, B. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1988**, *110*, 7542. (c) McGrath, D. V.; Grubbs, R. H. *J. Am. Chem. Soc.* **1991**, *113*, 3611–3613.

(25) Binger, P.; Muller, P.; Benn, R.; Mynott, R. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 610–611.

(26) Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 8130–8145.

(27) Flatt, B. T.; Grubbs, R. H.; Blanski, R. L.; Calabrese, J. C.; Feldman, J. *Organometallics* **1994**, *13*, 2728–2732.

(28) Li, R. T.; Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1994**, *116*, 10032–10040.

(29) (a) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3974–3975. (b) Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 9858–9859.

(30) For example, see: (a) Grubbs, R. H. *J. Macromol. Sci., Pure Appl. Chem.* **1994**, *A31*, 1829–1833. (b) Wu, Z.; Benedicto, A. D.; Grubbs, R. H. *Macromolecules* **1993**, *26*, 4975–4977. (c) Lynn, D.; Kanaoka, S.; Grubbs, R. H. Submitted to *Macromolecules*.

Scheme 9

amides (Scheme 9). Ring sizes of five to seven members were handled quite efficiently, and rates were not too different from those of the Mo-based systems.[31] In addition, catalyst **3** was tolerant of an expanded range of functional groups (eq 9). For example, neither carboxylic acids nor aldehydes destroyed catalyst activity. Furthermore, amine hydrochloride salts were found to be suitable as substrates for the RCM reactions.[32]

$$X = CO_2H, CH_2OH, CHO$$
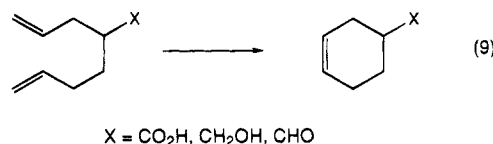
A notable limitation for RCM had proven to be the synthesis of carbocycles and heterocycles of more than seven atoms. In particular, eight-membered rings, ubiquitous in biologically active natural products, have proven to be a special case for RCM. In fact, this is not surprising, given the use of eight-membered-ring compounds as useful monomers for ROMP-based polymer synthesis. Among the problems for RCM and advantages for ROMP is the existence of a high degree of strain energy present in the cyclic substrate. However, the scope of RCM for eight-membered-ring synthesis using **3** was delineated in a study which found that the presence of conformational contraints in substrates made the synthesis of these cyclic alkanes possible. A delicate balance between RCM and ROMP was found. The relative facility of ring closures for diastereomeric eight-membered rings could be correlated with the calculated thermodynamics of the process.[33] For example, the cis and trans bis(allyl) ethers derived from the corresponding cis- and trans-cyclohexanediols were found to have strikingly different reactivity in RCM reactions (Scheme 10). Whereas the trans [4.0.6] ring system could be prepared in good yield (75%), the corresponding cis-bicycle was obtained in only 25% yield. The calculated strain energies of the reactants and products were consistent with these observations. Nevertheless, representatives of several classes of substrates relevant to natural products synthesis were cyclized in reasonable yield employing **3**. The method was highlighted by the application of

(31) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856–9857.

(32) Sita has recently applied RCM employing **1** to the synthesis of a cyclopentene monomer: Sita, L. R. *Macromolecules* **1995**, *28*, 656–657.

(33) Chen, Z.-R.; Claverie, J. P.; Grubbs, R. H.; Kornfield, J. A. *Macromolecules* **1995**, *28*, 2147–2154.

Scheme 10

Ring Closed Product/
Acyclic Starting Material

3:1

1:3
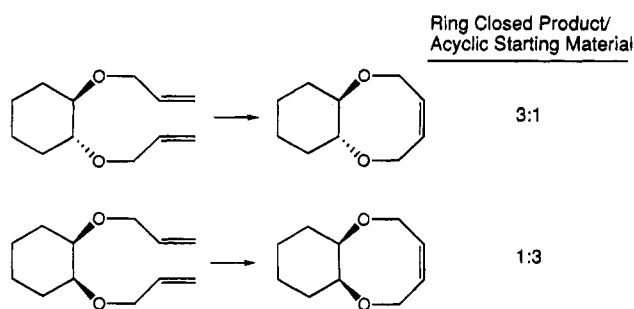
catalyst **3** to a precursor to the core fragment of the antitumor agent FR900482 (eq 10).[34,35]

59%   (10)
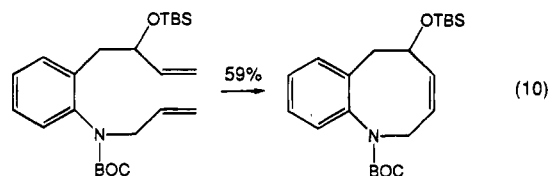
FR900482 Core Fragment Precursor

Larger rings and the limits of functional group tolerance of catalyst **3** are now under study in the context of constrained peptide structures, which contain multiple functional groups.[36] The synthesis of a covalently stabilized β-turn structure in a peptide was introduced by replacing cysteine residues with the allylglycines (eq 11). In these macrocyclizations, the presence of intramolecular hydrogen bonding may be crucial for efficient ring closure in the face of the competing intermolecular oligomerization pathways.

60%   (11)
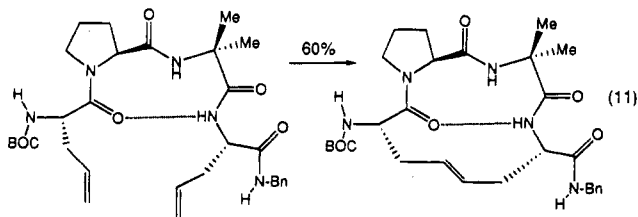
Tandem Reactions. The remarkable activity of the catalysts in organic synthesis set the stage for the applications in tandem reactions employing alkynes as olefin metathesis relays. An important precedent for this transformation was found in the work of Katz and co-workers (eq 12).[37] In this case, the illustrated

30-50%   (12)
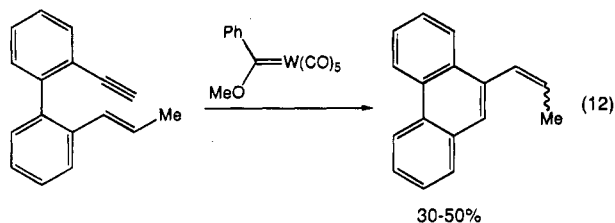
enyne undergoes W alkylidene catalyzed metathesis to afford the illustrated tricyclic product.[38]

(34) Miller, S. J.; Kim, S. H.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108−2109.

(35) Professor S. F. Martin has employed the Mo-based alkylidene **1** to a related cyclization in studies directed toward the total synthesis of FR900482. Martin, S. F.; Wagman, A. S. *Tetrahedron Lett.* **1995**, *36*, 1169−1170.

(36) Miller, S. J.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 5855−5856.
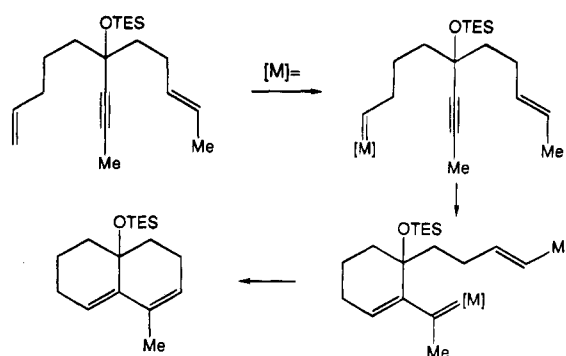
Scheme 11

[M]=

Table 3

Entry	Substrate	Product	Yield
1			78%
2			88%

This precedent suggested the possibility of performing bicyclization reactions by placing an alkyne in an intervening position between two olefins.[39] This reaction significantly expands the scope of olefin metathesis in natural products chemistry due to the large number of bicyclic structures in biologically relevant molecules. The strategy is illustrated by the mechanism in Scheme 11. Initial metathesis of the sterically less substituted double bond, followed by intramolecular metathesis with the alkyne and final metathesis with the remaining exocyclic alkene, leads to the illustrated 6,6 bicyclic structure.

When appropriate dienyne substrates were submitted to the metathesis conditions employing catalyst **3**, the desired bicyclic products were obtained. Two additional examples are included in Table 3. Many fused-ring systems were accessible through the method. Incorporation of an ether unit allowed the synthesis of fused hetero-carbocyclic systems. Interestingly, both Mo-based catalyst **1** and the related W-based analogue afforded inferior results in these tandem bicyclizations.[40]

Additional Applications in Natural Products Synthesis. Olefin metathesis is now starting to take hold as a powerful method for C−C bond formation in organic synthesis. Important applications have been documented by both the Martin and Pandit groups in applications to the polycyclic structure manzamine A (Scheme 12). Interestingly, in this case the larger 13-membered ring is formed with the Ru

(37) Katz, T. J.; Sivavec, T. M. *J. Am. Chem. Soc.* **1985**, *107*, 737−738.

(38) See ref 2b.

(39) (a) Kim, S. H.; Bowden, N.; Grubbs, R. H. *J. Am. Chem. Soc.* **1994**, *116*, 10801−10802. (b) Full paper submitted.

(40) Recently a related report on enyne metathesis employing catalyst **3** has appeared: Kinoshita, A.; Mori, M. *Synlett* **1994**, 1020−1022.

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Scheme 12

Manzamine A:
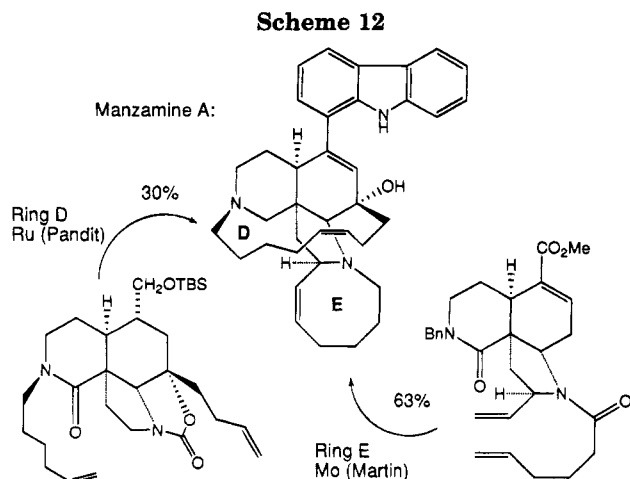
catalyst **3**, while the eight-membered ring is formed through catalysis by the Mo alkylidene **1**.[41]

More recently, Hoveyda and co-workers have prepared the aglycon of Sch 38516 through the formation of a trisubstituted olefin employing the Mo catalyst (eq 13).[42] These applications and others help to illustrate the emerging importance of olefin metathesis chemistry in the construction of complex natural products.[43–45]

(13)
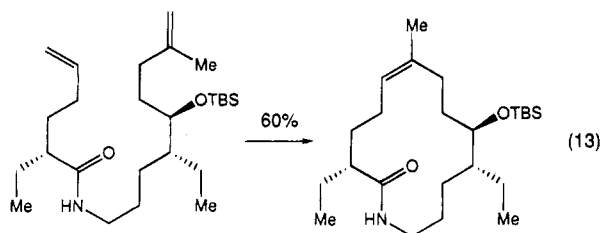
New Catalysts. The frontier in the application of these methods to organic synthesis remains the development of new catalysts with the appropriate

(41) (a) Martin, S. F.; Liao, Y.; Rein, T. *Tetrahedron Lett.* **1994**, *35*, 691–694. (b) Borer, B. C.; Deerenberg, S.; Bieraugel, H.; Pandit, U. K. *Tetrahedron Lett.* **1994**, *35*, 3191–3194.

(42) Houri, A. F.; Xu, Z.; Cogan, D.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 2943–2844.

(43) For an application of a tungsten-based catalyst to the dimerization of functionalized carbohydrates, see: Descotes, G.; Ramza, J.; Basset, J. M.; Pagano, S. *Tetrahedron Lett.* **1994**, *35*, 7379–7382.

(44) Nugent, W. A.; Feldman, J.; Calabrese, J. C. *J. Am. Chem. Soc.* **1995**, *117*, 8992–8998. The complex *trans*-WOCl₂(OAr)₂ upon treatment with tetraethyllead affords an active, functional group tolerant RCM catalyst. Private communication from Nugent, W. A., Feldman, J., and Calabrese, J. C.

(45) Morken, J. P.; Didiuk, M. T.; Visser, M. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1994**, *116*, 3123–3124.

(46) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem. Int., Ed. Engl.*, in press.

(47) Catalysts **1** and **4b** are commercially available from Strem Chemicals, Inc.

Scheme 13
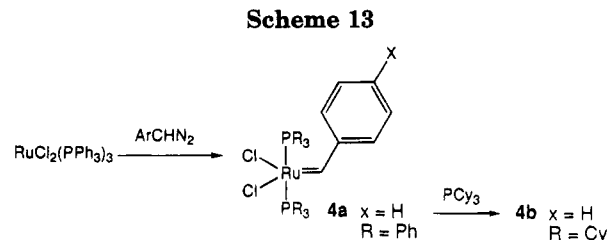
activities, coupled to the required functional group tolerance for applications in the arena of natural products synthesis. Ease of catalyst synthesis also plays a role in the application of these reactions to natural products chemistry. It is therefore appropriate to close this Account with a look at the state of catalyst discovery.

The success of the vinyl carbene **3** in organic synthesis has stimulated an ongoing search for the next generation of Ru-based alkylidenes. Along these lines, a family of aryl-substituted carbenes has been discovered which demonstrate remarkable activities in norbornene polymerization while retaining the stability toward functionality exhibited by **3**.[46] Catalysts **4a** and **4b** have proven the most active, and each is readily prepared by treatment of the appropriate Ru species with phenyl-substituted diazomethane (Scheme 13). Phosphine exchange converts **4a** to **4b**. Mechanistic studies have revealed that the heightened reactivity of **4** relative to **3** may be ascribed to a faster catalyst initiation rate, which may be coupled to the less effective binding properties of styrene relative to 1,1-diphenylbutadiene.

Conclusions

The evolution of olefin metathesis as a practical method for organic synthesis has been the result of a fruitful interplay of synthetic chemistry with the fields of organometallic, polymer, inorganic, and organic chemistry. The identification of catalysts based on the later transition metals has provided an increased range of functional group tolerance for these catalysts. In addition, the most recently described catalysts **1**–**4** based on Mo and Ru exhibit activities which are sufficient for a broad range of applications in organic synthesis.[47] The future will no doubt involve the discovery of more active and more tolerant catalysts, coupled to the simultaneous determination of the optimum catalyst for the specific application of this powerful C—C bond forming reaction.