Expanding the Applications of Transition Metal Alkylidenes and Alkylidynes to Organic Synthesis

Thesis by

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On a more personal note, I would also like to thank my fiancee, Melinda Wells. She has been incredibly supportive of me since we started dating, and I can't remember what I did without her. Her willingness to move to wherever I got a job was very helpful, and her willingness to come down here and hang out while I worked was wonderful. She has been willing to proofread all my proposals, and has proofread my entire thesis twice, which is more than I've read it. Thank you so much for being there, Melinda.

Finally, I must thank my family. They have always been there for support whenever I've needed it, and stayed in the background when I was too busy for them.

Even if they don't understand why I haven't gotten a real job yet, I wouldn't have made it without my parents. Thanks, Mom and Dad.

Abstract

The application of olefin and acetylene metathesis to organic synthesis has increased greatly since its introduction. The research in this thesis describes the Ring-Closing Metathesis (RCM) of substituted olefins and enynes, the metathesis of internal acyclic olefins and the conversion of acid chlorides to acetylenes with tungsten alkylidynes.

In Chapter 1, the activity of ruthenium alkylidenes and molybdenum alkylidenes for the RCM of dienes containing *gem*-disubstituted olefins was investigated. Dienes with sterically-demanding and/or electron-withdrawing substituents were cyclized successfully with only the molybdenum alkylidene. Dienes with allylic functional groups yielded functionalized cyclic olefins when treated with either alkylidene.

In Chapter 2 the cyclization of enyne and endiyne substrates using ruthenium alkylidenes was discussed. The effects of ring size and methyl substitution on the conversion were determined. A mechanism in which the alkylidene reacts with the olefin first, followed by an intramolecular reaction with the acetylene on an enyne substrate is described.

The RCM of acyclic dienes containing vicinally substituted olefins was described in Chapter 3. Water-soluble ruthenium alkylidenes did not cyclize α,ω-dienes due to the instability of the resulting methylidene. The incorporation of a phenyl substituent resulted in nearly quantitative cyclization. RCM of a water-soluble diene has been achieved in aqueous solution using this methodology. This methodology has also been successfully applied to increase RCM yields in organic solvents.

The stereoselectivity of metathesis of acyclic olefins was investigated for several ruthenium alkylidenes in Chapter 4. This was primarily done using *cis*-2-pentene metathesis. Data from *cis*-2-pentene metathesis was also used to determine relative metathesis rates for various alkylidenes and reaction conditions. An alkylidene bearing tricyclopentyl phosphines (**13**) was significantly more *cis* selective than one with tricyclohexyl phosphines (**8**). Alkylidene **8** was moderately *cis* selective for *cis*-2-pentene metathesis and slightly *cis* selective for *trans*-2-pentene metathesis.

An investigation into the conversion of acid chlorides to substituted acetylenes using tungsten alkylidynes is discussed in Chapter 5. A new route to DIPP tungsten alkylidynes is described. Several aromatic acid chlorides were converted into acetylenes using these alkylidynes in good yields. Finally, attempts at the synthesis of $W_2(DIPP)_6$ are described.

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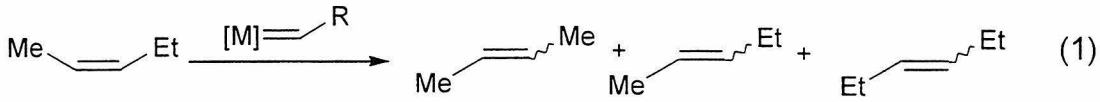
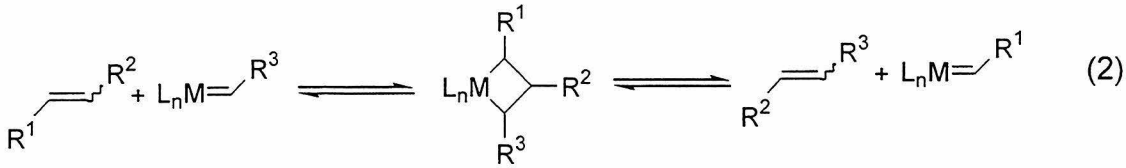
Introduction

Olefin Metathesis:

In 1967, the first report of olefin metathesis was presented by Calderon *et al.*[1] This reaction consists of the exchange of olefinic substituents in the presence of a transition metal catalyst, as described by the metathesis of *cis*-2-pentene to 2-butene, 2-pentene and 3-hexene (Eq. 1). No other products, including products arising from olefin isomerization are observed. Several studies were subsequently undertaken to elucidate the mechanism of this transformation, which is shown in Equation 2.[2] This mechanism involves the formation of a metallacyclobutane through reaction of a metal alkylidene with an olefin, followed by the formation of a new olefin and a new alkylidene.



(1)

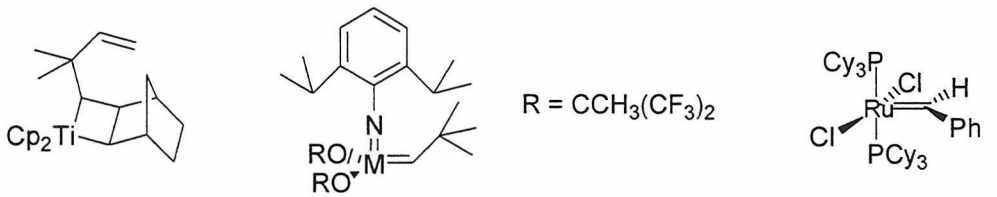


(2)

Initially, metathesis reactions were initiated using transition metal salts, usually in combination with a Lewis Acid.[3] As there is no transition metal alkylidene present at the start of these reactions, it is assumed that one is generated in small quantities during the reaction. This alkylidene is the only active catalytic species, and the salts are inactive. For this reason, these mixtures are called ill-defined catalysts. Because the alkylidene forms in an unknown manner, initiation in these systems tends to be slow and poorly reproducible. However, these systems can be highly active once they have initiated. In addition, catalysts based on early transition metals are highly intolerant of functional groups as well as traces of air and water.[3]

The development of well-defined transition metal alkylidenes and metallacyclobutanes greatly expanded the application of metathesis (Figure 1). The first generation of metathesis catalysts is typified by Tebbe's reagent (**1**) and Schrock's tungsten neopentylidene (**2**).[4] These catalysts are highly active for metathesis, and react with olefins in a well-defined manner, which eliminates many of the initiation problems observed with ill-defined catalysts. However, these catalysts are difficult to synthesize, extremely sensitive to air and water and functional group intolerant, making their application to organic chemistry problematic.

Figure 1:



1 **2** M = W **3** M = Mo **4**

The two primary members of the current generation of alkylidenes are Schrock's molybdenum neopentylidene (**3**)[5] and Grubbs' ruthenium benzylidene (**4**).[6] The functional group tolerance of these alkylidenes is increased compared to the first generation (Table 1). Tebbe's reagent (**1**) will react with all of the functionality shown in Table 1 before reacting with olefins, and thus cannot be used with any substrate containing these functionalities. The other alkylidenes shown in the table are more selective for olefins, and alkylidene **4** will react with olefins preferentially in the presence of the functional groups listed.[7] Because of the balance of reactivity and functional group

tolerance shown by alkylidenes **3** and **4**, these two alkylidenes have been used for nearly all of the organic applications of olefin metathesis.[3,8]

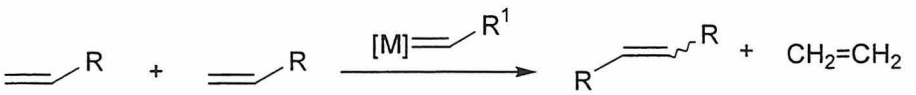
Table 1:

Titanium (**1**)	*Tungsten* (**2**)	*Molybdenum* (**3**)	*Ruthenium* (**4**)
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

Higher reactivity ↑ Lower reactivity

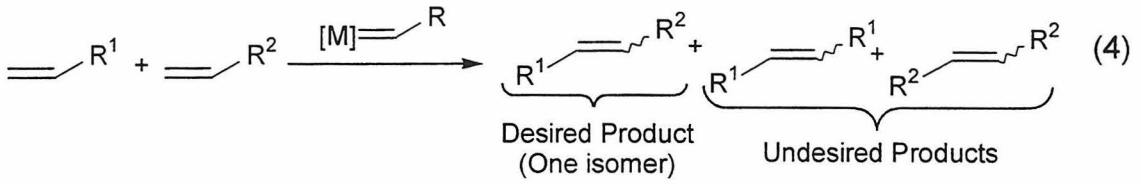
Organic Applications of Olefin Metathesis:

Although metathesis of acyclic olefins was the first reaction studied with metathesis catalysts, there has not been much success in applying this reaction to organic synthesis. The main difficulties have been controlling the product distribution and the stereoselectivity of this reaction. The most simple application of acyclic metathesis is the dimerization of two terminal olefins to give the dimer and ethylene (Eq. 3). Although the product is typically obtained as a mixture of *cis* and *trans* isomers, a number of symmetrical dimers have been synthesized using this methodology.[9]



(3)

A much broader extension of this methodology would be to react two different terminal olefins with a metathesis catalyst and obtain the heterodimer as one isomer (Eq. 4).[10] Ideally, conditions would be utilized where production of the two homodimers would not be observed. Although this ideal has not been achieved as a general reaction, significant steps have been made towards reducing the undesired byproducts of this reaction.

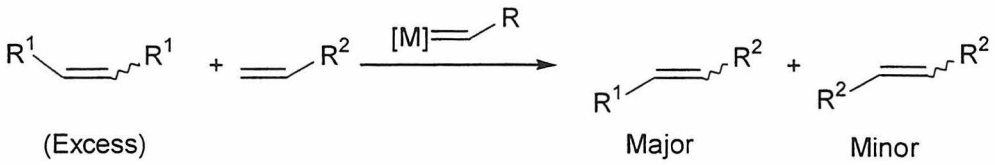


(4)

The first demonstration of cross metathesis in high yields involved the reaction of two olefins with significantly different electronic parameters. Thus, the reaction of conjugated olefins such as styrene and acrylonitrile with aliphatic olefins mediated by molybdenum alkylidene **3** provided the desired heterodimer in good yield.[11] This selectivity is attributed to the negligible homodimerization of the electron poor olefin. Using a similar principle, it has been demonstrated that highly substituted olefins will preferentially react with less hindered olefins instead of forming homodimers.[12]

Although these methods have given some cross metathesis products in high yields, this methodology is limited by requirements listed above. A more general method for cross metathesis was recently developed.[13] Reaction of an excess of a symmetrically substituted internal olefin with a terminal olefin often leads to high yields of the desired product (Eq. 5). Using the homodimerization of terminal olefins to generate the starting

materials for this reaction makes it the most general procedure yet developed for cross metathesis.

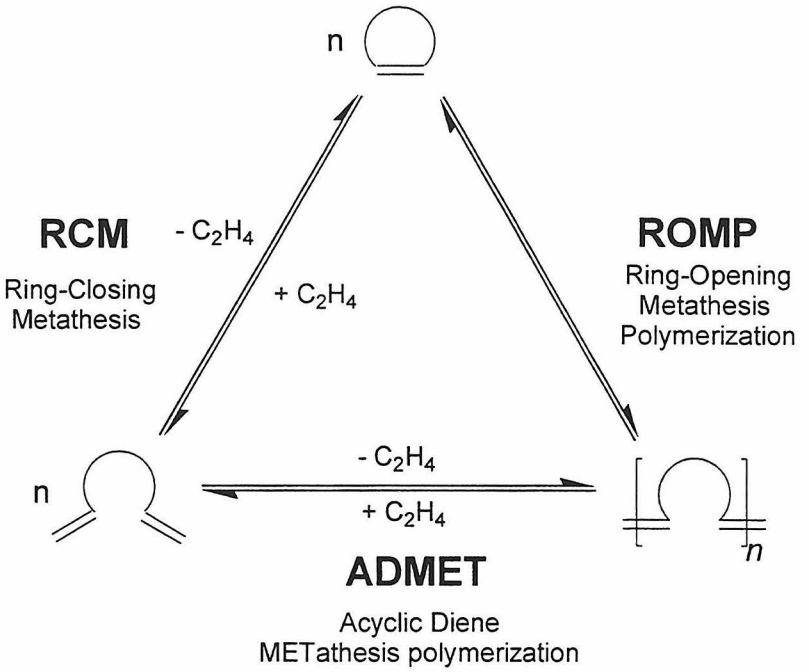


(5)

While these advances have greatly improved the yield of the desired cross metathesis product, the problem of stereoselectivity in these reactions remains largely unsolved. If the reaction is allowed to proceed to equilibrium, the selectivity is determined by the difference in the thermodynamic stability of the two isomers. However, if the reaction is stopped before equilibrium is reached, both the conditions and the catalyst used can influence the selectivity. Although some studies of this effect have been reported,[3,14] no method for completely controlling the stereoselectivity in these reactions has been developed.

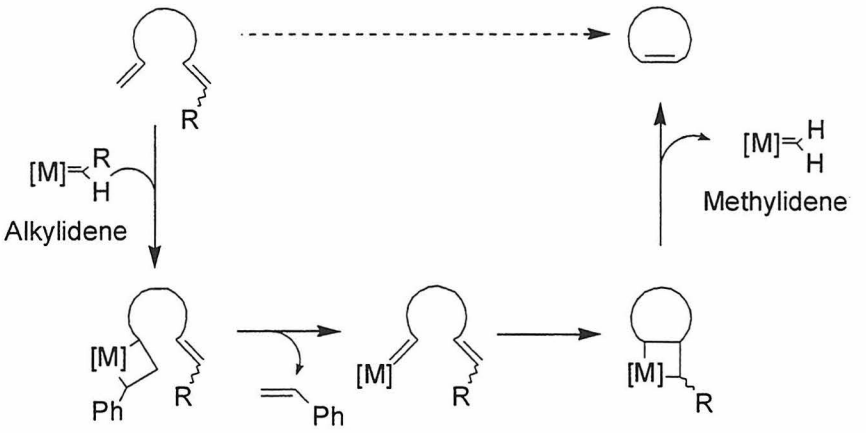
Although reaction with acyclic olefins is the simplest olefin metathesis reaction, most of the applications in organic and polymer chemistry involve more complex substrates (Scheme 1). The first widespread application of olefin metathesis was the Ring-Opening Metathesis Polymerization (ROMP) of cyclic olefins.[15] The driving force for this reaction comes from the release of ring strain, and only strained olefins can be used for this reaction. Polymers with similar structures are made through Acyclic Diene METathesis polymerization (ADMET), which is the application of cross metathesis to α,ω-dienes.[16] The driving force for this step growth polymerization is largely thermodynamic, generated by the removal of ethylene from the reaction.

Scheme 1:



The third side of the triangle in Scheme 1, Ring-Closing Metathesis (RCM), is the major contributor of olefin metathesis to organic chemistry.[8] The formation of a cyclic olefin through reaction of a diene with an ill-defined catalyst was demonstrated over twenty years ago.[2a,17] However, it was only with the development of well-defined alkylidenes **3** and **4** that a range of cyclic compounds with various functional groups could be synthesized through this technique.[7,18] The application of this technique to organic synthesis has increased steadily since that report. For example, there have been several reports describing RCM on solid support,[19] including using RCM as a technique to cleave compounds from solid support.[20] In addition, RCM has been one of the key steps in several syntheses of natural products, including the epothilones,[19a,21] Sch 38516,[22] Roseophillin,[23] and Manzamine A.[24]

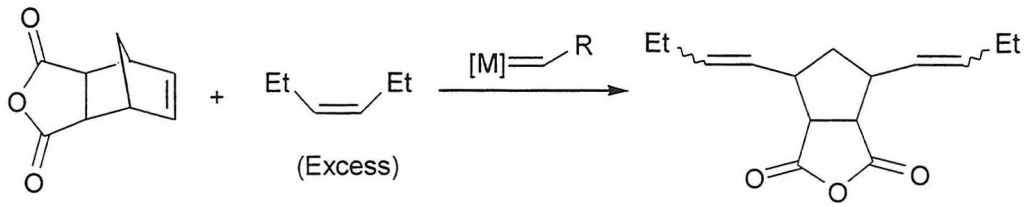
Scheme 2:



Unlike ROMP, the conversion of a diene to a cyclic olefin with the elimination of ethylene is entropically favored. However, the strain inherent in the ring being formed disfavors the cyclization, preventing the formation of three- and four- membered rings using this process. The mechanism for the first turnover in the RCM of an α,ω-diene is shown in Scheme 2. During this process, a substituted alkylidene is consumed, and a methylidene is generated. In all the subsequent cycles, the methylidene is the RCM catalyst. For this reason, the activity and stability of the methylidene of a transition metal alkylidene is quite important in RCM.[25]

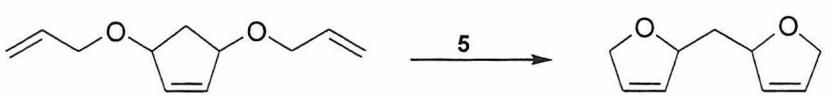
Since its development, the application of RCM to a variety of substrates has been reported. Macrocycle formation proceeds in high yield under dilute conditions, and rings consisting of over 40 atoms have been synthesized using RCM.[19b,26] However, problems with *cis/trans* selectivity are observed in macrocycle formation.[26] The synthesis of bicyclic systems with relatively low ring strain through RCM has also been demonstrated.[27]

The final significant application of olefin metathesis to organic synthesis is derived from ROMP and cross metathesis. When a strained, cyclic olefin is reacted with a metathesis catalyst in the presence of an excess of an acyclic olefin, this process is called Ring-Opening Metathesis (ROM) (Eq. 6).[10,28] This reaction is general for any strained cyclic olefin, and good selectivity has been achieved using both unsymmetrical acyclic and cyclic olefins.[28] Once again, *cis/trans* selectivity is a problem and mixtures are obtained in most of these reactions.



(6)

This reaction has been combined with other olefin metathesis processes to give tandem reactions. For example, the reaction of a substrate with two terminal olefins tethered to a cyclic olefin with alkylidene **4** gives a ring-opening, ring-closing process (Eq. 7).[29] This reaction has been demonstrated for a variety of cyclic olefins and tether lengths.[30] A similar method has also been reported with one tethered olefin and a cross metathesis partner.



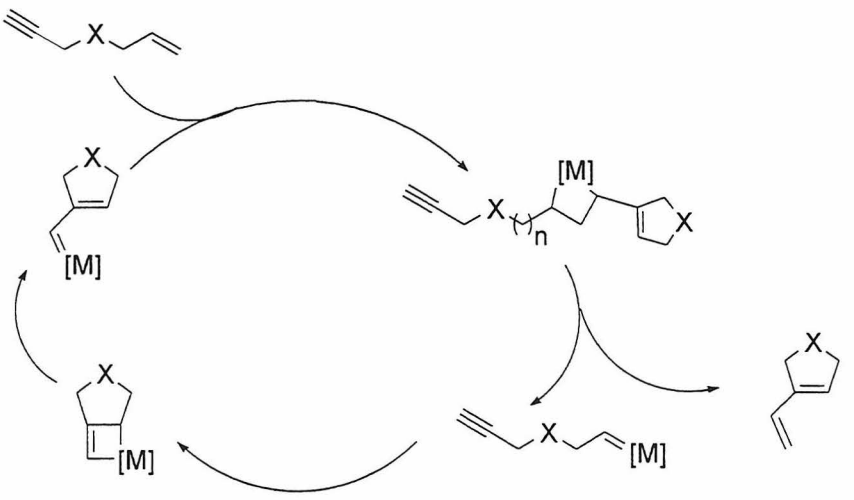
(7)

Organic Applications of Acetylene Metathesis:

Reaction of Acetylenes with Alkylidenes:

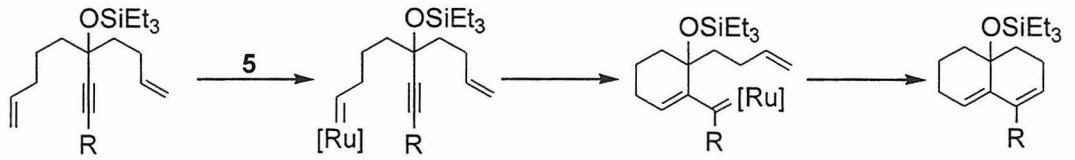
In addition to olefins, some metal alkylidenes will catalyze the metathesis of acetylenes, especially in an intramolecular fashion. The metathesis of an olefin followed by cyclization through reaction with a tethered acetylene is called enyne metathesis (Scheme 3).[31] This reaction has been used to synthesize a number of cyclic dienes, including the natural product stemoamide.[32] These cyclic dienes have been used for subsequent Diels-Alder reactions as well.[33] In addition, cross metathesis between an olefin and an acetylene has been performed using alkylidene **4**.[34]

Scheme 3:



Because the alkylidene remains attached to the substrate in enyne metathesis until it reacts with another substrate to continue the cycle, the addition of a pendant olefin allows a tandem cyclization. This dienyne metathesis is effective for the synthesis of bicyclics with several ring sizes and substituents (Eq. 8).[35] Following the development of

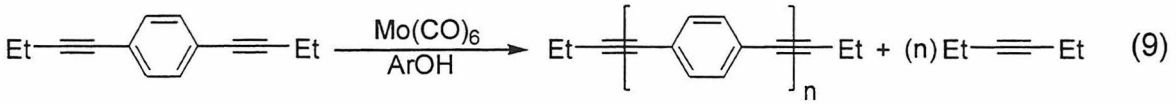
this methodology, cyclization cascades that formed up to 4 rings in one step were reported.[36] These multiple tandem cyclizations were also performed using cyclic olefins and acetylenes as tethers.[36]



(8)

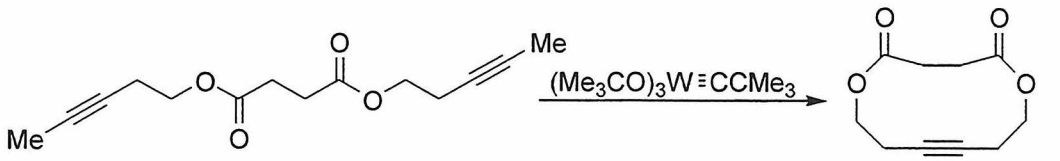
Reaction of Acetylenes with Alkylidynes:

Some transition metal alkylidynes will metathesize acetylenes with a mechanism similar to olefin metathesis.[37] Active, well-defined acetylene metathesis catalysts of the formula $(Me_3CO)_3W{\equiv}CR$ were developed almost twenty years ago.[38] Due to the sensitivity to functional groups and difficult syntheses of these tungsten-based alkylidynes, many applications of acetylene metathesis still depend on ill-defined systems,[39] such as the one shown in Equation 9.[40]



(9)

The reaction depicted in Equation 9 is an example of Acyclic DIyne METathesis polymerization (ADIMET),[40] which is analogous to the ADMET polymerization of dienes. In addition to ADIMET, the ROMP of cyclic acetylenes such as cyclooctyne has been demonstrated.[41] The RCM of macrocyclic acetylenes with a tungsten catalyst has recently been reported (Eq. 10).[42]



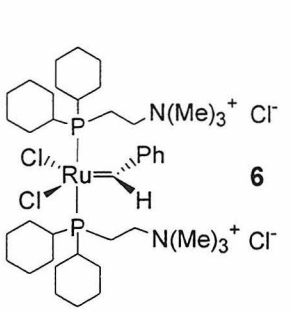
(10)

Thesis Research:

The development of ruthenium alkylidene **4** has led to research designed to take advantage of the stability and activity of that alkylidene, especially in the presence of polar and protic functional groups. In Chapter 1 of this thesis, the reactivity of both alkylidenes **3** and **4** with a variety of dienes containing *gem*-disubstituted olefins is described. It was discovered that dienes containing alkyl substituents smaller than *tert*-butyl would cyclize, but no substrates containing heteroatom substituted olefins were cyclized by alkylidene **4**. Alkylidene **3**, on the other hand, was much more active for the cyclization of substituted dienes, though it was also inactivated by the presence of some functional groups.

In Chapter 2, the synthesis of substituted cyclic olefins through enyne metathesis is discussed. As in Chapter 1, different ring sizes and substitution patterns were investigated. Substitution on the acetylene was tolerated while *geminal* substitution on the olefin prevented the reaction. This led to an examination of the mechanism of enyne metathesis. Contrary to some reports,[31,34,43] the evidence indicates that alkylidene **4** reacts with olefins preferentially, followed by reaction with a tethered acetylene. A preliminary investigation of the tandem cyclization of endiynes is also reported.

Following these investigations, the effects of 1,2-disubstituted olefins on the stability of the propagating species in RCM are described in Chapter 3. This study was prompted by the desire to perform RCM in water and methanol using the water-soluble



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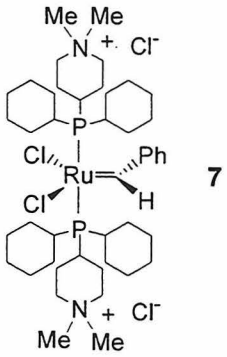

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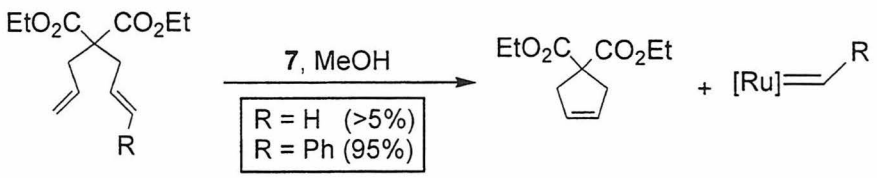
alkylidenes **6** and **7**. Through reactions with acyclic olefins, it was determined that the methylidenes derived from these benzylidenes are unstable. When the propagating species was the benzylidene instead of the methylidene, cyclic products were obtained in high yield in both methanol and water (Eq. 11). Although sporadically utilized, this technique is known to stabilize molybdenum and tungsten based alkylidenes during RCM.[18] A limited investigation of R substituents was also undertaken to optimize the activity of the propagating alkylidene.



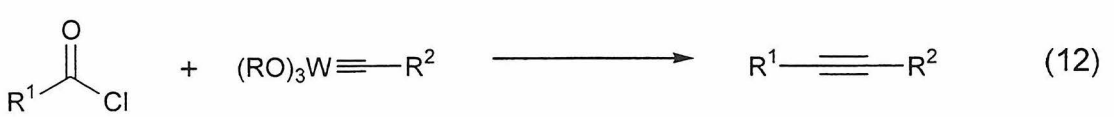
(11)

This methodology was subsequently demonstrated to be effective for improving RCM yields in organic systems. Although the ruthenium methylidene is typically stable, the benzylidene is more active and more stable. Therefore, in situations where the

stability of the methylidene is the limiting factor in an RCM reaction, addition of a phenyl substituent has been shown to significantly improve conversion. In a related manner, addition of $AlCl_3$ to an RCM reaction involving alkylidene **4** accelerates the reaction enormously but causes the methylidene to decompose. The use of phenyl substituted dienes improves the yield of $AlCl_3$ accelerated processes as well.

Following this discussion of RCM, the reaction of various olefin metathesis catalysts with acyclic olefins is described in Chapter 4. By reacting various alkylidenes with *cis*-2-pentene and analyzing the products by GC, it is possible to measure the relative activity of a catalyst under a particular set of conditions and analyze its *cis/trans* selectivity. The most selective conditions and alkylidenes will be identified, primarily for stereoselective cross metathesis reactions. Preliminary application of these parameters to the stereoselective synthesis of selected insect pheromones will also be described.

Finally, a preliminary investigation of the conversion of aliphatic and aromatic acid chlorides into substituted acetylenes using tungsten alkylidynes is discussed in Chapter 5 (Eq. 12). The reaction of tungsten alkylidynes with aldehydes, ketones and esters has also been described, along with a preliminary report of reaction with acetyl chloride to give the appropriate acetylene.[44] The reactivity of several acid chlorides and alkylidynes for this reaction will be described. Unlike most of the other reactions described in this introduction, this is a stoichiometric reaction. For this reason, investigations into easier syntheses of alkylidynes which are active for this reaction are described as well.



(12)

Summary:

Because transition metal alkylidenes have become so widespread in organic synthesis over the last few years, it is useful to have a systematic study of their reactivity. The reaction of these alkylidenes with RCM substrates containing a variety of substituents is expected to facilitate the application of these alkylidenes to the synthesis of more complex molecules. Similarly, the elaboration of the scope of enyne metathesis will assist in its application to organic synthesis. Although the RCM of dienes has been widely used in natural product synthesis, improving the stereoselectivity of the metathesis reaction will significantly increase the application of cross metathesis to organic synthesis. Application of these diverse techniques to olefin metathesis should further establish its place as an important technique in organic synthesis.

References:

[1] Calderon, N.; Chen, H. Y.; Scott, K. W. *Tetrahedron Lett.* **1967**, 3327-3329.

[2] For examples of these studies, see: a) Swetnick, S. J.; Grubbs, R. H. *J. Mol. Cat.* **1980**, *8*, 25-36. b) Katz, T. J.; McGinnis, J. *J. Am. Chem. Soc.* **1975**, *97*, 1592-1594. c) Grubbs, R.H.; Burk, P. L.; Carr, D. D. *J. Am. Chem. Soc.* **1975**, *97*, 3265-3267. d) Basset, J. M.; Bilhou, J. L.; Mutin, R.; Theolier, A. *J. Am. Chem. Soc.* **1975**, *97*, 7376-7377.

[3] For an overview of metathesis, see: Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Metathesis Polymerization*; Academic Press: London, **1997**.

[4] 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.

[5] Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875-3885.

[6] a) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.*, **1996**, *118*, 100-110. b) Schwab, P.; France, M. B.; Grubbs, R. H.; Ziller, J.W. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2039-2041.

[7] Fu, G. C.; Nguyen, S. T.; Grubbs, R. H.; *J. Am. Chem. Soc.* **1993**, *115*, 9856-9857.

[8] For some reviews of olefin metathesis in organic chemistry, see: a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413-4450. b) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371-388. c) Schuster, M.; Blechert, S. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2036-2056. d) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446-452.

[9] For some examples, see: a) Boger, D. L.; Chai, W.; Jin, Q. *J. Am. Chem. Soc.* **1998**, *120*, 7220-7225. b) Diver, S. T.; Schreiber, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 5106-5109. c) Marcinec, B.; Pietraszuk, C.; Foltynowicz, Z. *J. Orgmet. Chem.* **1994**, *474*, 83-87 and references therein.

[10] Randall, M. L.; Snapper, M. L. *J. Mol. Catal.* **1998**, *133*, 29-40.

[11] For examples of this technique, see: a) Feng, J.; Schuster, M.; Blechert, S. *Synlett* **1997**, 129-130. b) Crowe, W. E.; Goldberg, D. R.; Zhang, Z. J. *Tetrahedron Lett.* **1996**, *37*, 2117-2120. c) Crowe, W. E.; Goldberg, D. R. *J. Am. Chem. Soc.* **1995**,

117, 5162-5163. d) Crowe, W. E.; Zhang, Z. J. *J. Am. Chem. Soc.* **1993**, *115*, 10998-10999.

[12] Brümmer, O.; Rückert, A.; Blechert, S. *Chem. Eur. J.* **1997**, *3*, 441-446.

[13] O'Leary, D. J.; Blackwell, H. E.; Washenfelder, R. A.; Grubbs, R. H. *Tetrahedron Lett.* **1998**, *39*, 7427-7430.

[14] a) Quignard, F.; Leconte, M.; and Basset, J.M. *J. Mol. Cat.* **1985**, *28*, 27-32. b) Bosma, R. H. A.; Xu, X. D.; Mol, J. C. *J. Mol. Cat.* **1982**, *15*, 187-192. c) Bilhou, J. L.; Basset, J. M.; Mutin, R.; Graydon, W. F. *J Am. Chem. Soc.* **1977**, *99*, 4083-4090 and references therein.

[15] For a recent review of ROMP, see: Ivin, K. J.; Mol, J. C. *Makromol. Chem., Macromol. Symp.* **1991**, *42-43*, 1-14.

[16] For a leading reference on ADMET polymerization, see: Wolfe, P. S.; Gómez, F. J.; Wagener, K. B. *Macromolecules* **1997**, *30*, 714-717 and references therein.

[17] Tsuji, J.; Hashiguchi, S. *Tetrahedron Lett.* **1980**, *21*, 2955-2958.

[18] a) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324-7325. b) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426-5427.

[19] For some recent examples, see: a) Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Ninkovic, S.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Giannakakou, P.; Hamel, E. *Nature* **1997**, *387*, 268-272. b) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606-9614.

[20] Veerman, J. J. N.; van Maarseveen, J. H.; Visser, G. M.; Kruse, C. G.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **1998**, 2583-2589.

[21] a) Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.; Roschangar, F.; Sarabia, F.; Ninkovic, S.; Yang, Z.; Trujillo, J. I. *J. Am. Chem. Soc.* **1997**, *119*, 7960-7973. b) Meng, D.; Bertinato, P.; Balog, A.; Su, D-S.; Kamenecka, T.; Sorensen, E. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10073-10092.

[22] Xu, Z.; Johannes, C. W.; Houri, A. F.; La, D. S.; Cogan, D. A.; Hofilena, G. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 10302-10316.

[23] Kim, S. H.; Figueroa, I.; Fuchs, P. L. *Tetrahedron Lett.* **1997**, *38*, 2601-2604.

[24] a) Martin, S. F.; Humphrey, J. M.; Ali, A.; Hillier, M. C. *J. Am. Chem. Soc.* **1999**, *121*, 866-867. b) Magnier, E.; Langlois, Y. *Tetrahedron Lett.* **1998**, *39*, 837-840. c) Pandit, U. K.; Borer, B. C.; Bieräugel, H. *Pure. Appl. Chem.* **1996**, *66*, 659-662.

[25] Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, In Press.

[26] For some recent examples, see: a) Dietrich-Buchecker, C.; Sauvage, J-P. *Chem. Commun.* **1999**, 615-616 and references therein. b) Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792-803.

[27] Morehead, A.; Grubbs, R. H. *Chem. Commun.* **1998**, 275-276.

[28] a) Schneider, M. F.; Lucas, N.; Valder, J.; Blechert, S *Angew. Chem. Int. Ed. Engl.* **1997**, *36*. 257-259. b) Snapper, M. L.; Tallarico, J. A.; Randall, M. L. *J. Am. Chem. Soc.* **1997**, *119*, 1478-1479. c) Schneider, M. F.; Blechert, S. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 411-412. d) Randall, M. L.; Tallarico, J. A.; Snapper, M. L. *J. Am. Chem. Soc.* **1995**, *117*, 9610-9611.

[29] Zuercher, W. J.; Hashimoto, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *116*, 634-6640.

[30] Stragies, R.; Blechert, S. *Synlett* **1998**, 169-170.

[31] Kinoshita, A.; Mori, M. *Synlett* **1994**, 1020-1022.

[32] a) Kinoshita, A.; Mori, M. *Heterocycles* **1997**, *46*, 287-299. b) Kinoshita, A.; Mori, M. *J. Org. Chem.* **1996**, *61*, 8356-8357.

[33] For some recent examples, see: a) Heerding, D. A.; Takata, D. T.; Kwon, C.; Huffman, W. F.; Samanen, J. *Tetrahedron Lett.* **1998**, *39*, 6915-6818. b) Kotha, S.; Sreenivasachary, N.; Bramachary, E. *Tetrahedron Lett.* **1998**, *39*, 2805-2808.

[34] Stragies, R.; Schuster, M.; Blechert, S. *Angew. Chem. Int. Engl. Ed.* **1997**, *36*, 2518-2520.

[35] Kim, S-H.; Zuercher, W. J.; Bowden, N. B.; Grubbs, R. H. *J. Org. Chem.* **1996**, *61*, 1073-1081.

[36] Zuercher, W. J.; Scholl, M.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 4291-4298.

[37] For some reviews of this process, see: a) Schrock, R. R. *Polyhedron* **1995**, *14*, 3177-3195. b) Engel, P. F.; Pfeffer, M. *Chem. Rev.* **1995**, *95*, 2281-2309. c) Mayr, A.; Hoffmeister, H. *Adv. Organomet. Chem.* **1991**, *32*, 227-324. d) Schrock, R. R. *Acc. Chem. Res.* **1986**, *19*, 342-348.

[38] a) Listemann, M. L.; Schrock, R. R. *Organometallics* **1985**, *4*, 74-83. b) Wengrovius, J. H.; Sancho, J.; Schrock, R. R. *J. Am. Chem. Soc.* **1981**, *103*, 3932-3934.

[39] Bencheick, A.; Petit, M.; Mortreux, A.; Petit, F. *J. Mol. Cat.* **1982**, *15*, 93-101 and references therein.

[40] Kloppenburg, L.; Song, D.; Bunz, U. H. F. *J. Am. Chem. Soc.* **1998**, *120*, 7973-7974.

[41] Krouse, S. A.; Schrock, R. R.; Cohen, R. E. *Macromolecules* **1987**, *20*, 904-906.

[42] Fürstner, A.; Siedel, G. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1734-1736.

[43] Stragies, R.; Schuster, M.; Blechert, S. *Chem. Commun.* **1999**, 237-238.

[44] Freudenberger, J. H.; Schrock, R. R. *Organometallics* **1986**, *5*, 398-400.

Chapter 1:

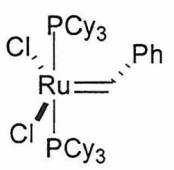
The Synthesis of Substituted Cyclic Olefins Through the Ring-Closing Metathesis of Substituted Dienes[†]

Abstract:

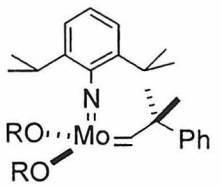
Ruthenium alkylidene **1** and molybdenum alkylidene **2** have been utilized in the ring-closing metathesis (RCM) of dienes containing *gem*-disubstituted olefins to yield tri- and tetrasubstituted cyclic olefins. Dienes with sterically-demanding and/or electron-withdrawing substituents such as Ph, CO_2Me and ^tBu were cyclized successfully with **2**, but did not cyclize with **1**. Tetrasubstituted cyclic olefins could be formed with **2**, but not with alkylidene **1**. Dienes with allylic functional groups yielded functionalized cyclic olefins when treated with **1**.

Introduction:

Ring-closing metathesis (RCM) is a versatile technique for the formation of five- to seven-membered carbocycles and heterocycles.[1] In addition, several examples of macrocycle formation through RCM have been reported.[2] Ruthenium alkylidene **1**[3] and molybdenum alkylidene **2**[4] are two of the most commonly used initiators for RCM (Scheme 1), and reports of their use in organic synthesis have



1

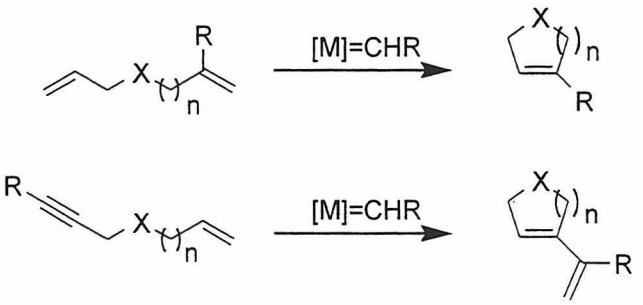


2

R = $C(CH_3)(CF_3)_2$

increased steadily.[1] However, there have been only sporadic reports of the synthesis of substituted cyclic olefins through RCM (Scheme 1).[5,6] This chapter focuses on the synthesis of substituted cyclic olefins through the RCM of substituted dienes, and Chapter 2 focuses on enyne metathesis. Since many protocols exist for the further elaboration of functionalized olefins, substituted cyclic olefins are attractive synthetic intermediates in organic synthesis.

Scheme 1:



Several examples of the RCM of alkyl-substituted dienes with highly active group VI alkylidenes have been reported. Molybdenum alkylidene **2** has been used

for the synthesis of a variety of methyl- and ethyl-substituted cyclic olefins through RCM.[5a,5b,5c,5g,5k,5l] Additionally, cyclic enol ethers have been synthesized from acyclic enol ethers using alkylidene **2**.[5a,5i,7] The high activity displayed by alkylidene **2** is accompanied by both a lack of tolerance for some common functional groups and the requirement that substrates and solvents be rigorously purified, dried and degassed.[8] Ruthenium alkylidene **1** will perform RCM in the presence of most of the functional groups commonly used in organic synthesis and requires far less rigorous conditions than **2**.[1d,3,8]

An alternative method for synthesizing functionalized cyclic olefins via olefin metathesis is through the RCM of acetylene containing substrates, which has been explored with several alkylidenes (Scheme 1).[5d,5h,5j,9] However, formation of substituted cyclic olefins through metathesis of *substituted dienes* has not been reported for alkylidene **1** and has been confined to the few examples listed above with alkylidene **2**. In this chapter, the synthesis of a variety of substituted dienes and their reactivities with these two common metathesis-active alkylidenes is presented. The substrates were chosen to test the limits of reactivity of both alkylidenes and to provide guidelines for their use in constructing complex synthetic targets.

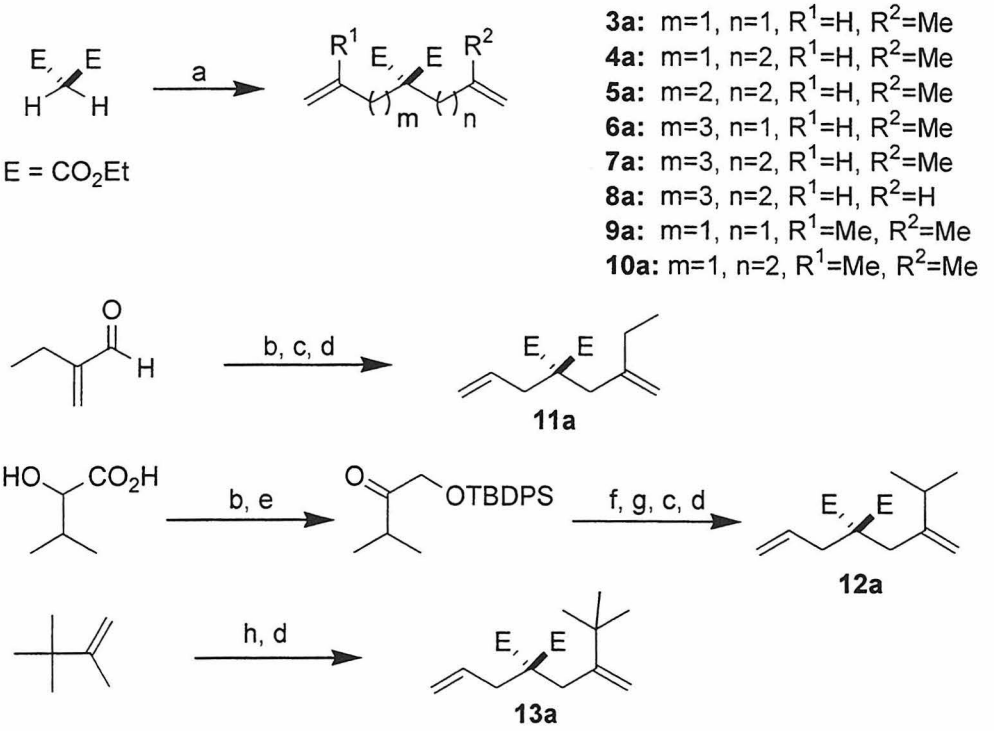
Results and Discussion:

Substrate Synthesis:

Standard alkylation of diethyl malonate with alkyl halides was used to prepare the alkyl-substituted dienes **3a-10a** (Scheme 2).[10] Halides used in the syntheses of these dienes were either commercially available or obtained from the corresponding alcohol.[11] Reduction of ethyl acrolein, subsequent conversion of the

alcohol to the bromide,[12] and coupling to diethyl allylmalonate provided diene **11a**. Synthesis of 2-(bromomethyl)-3-methyl-1-butene[13] (Scheme 2) followed by coupling to diethyl allylmalonate afforded diene **12a**. Allylic bromination of 2,2,3-trimethylbutene[14] followed by coupling to diethyl allylmalonate yielded diene **13a**.

Scheme 2:



3a: m=1, n=1, R^1=H, R^2=Me
4a: m=1, n=2, R^1=H, R^2=Me
5a: m=2, n=2, R^1=H, R^2=Me
6a: m=3, n=1, R^1=H, R^2=Me
7a: m=3, n=2, R^1=H, R^2=Me
8a: m=3, n=2, R^1=H, R^2=H
9a: m=1, n=1, R^1=Me, R^2=Me
10a: m=1, n=2, R^1=Me, R^2=Me

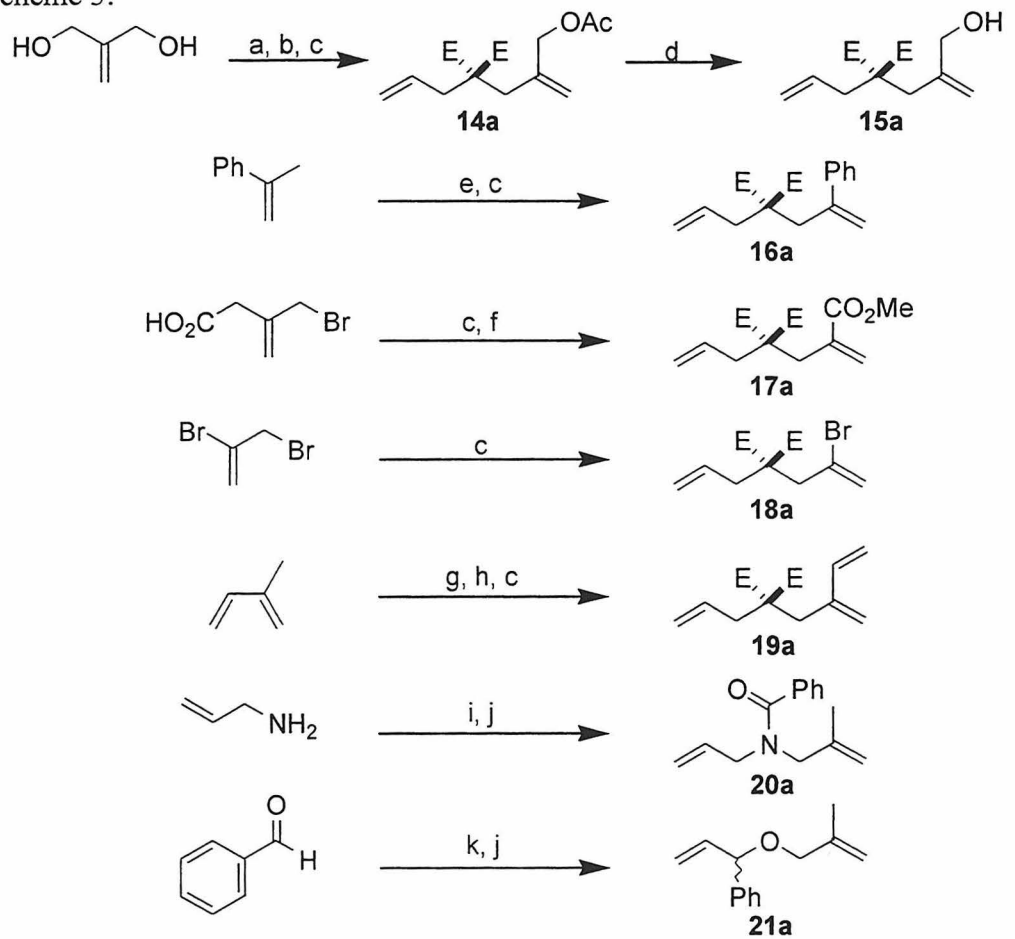
11a **12a** **13a**

(a) CH_2=$CHR^{1,2}(CH_2)_{m,n}Br$, NaOEt, DMF, 33-72%; (b) $LiAlH_4$, Et_2O, 79%; (c) PPh_3, CBr_4, CH_2Cl_2, 65-90%; (d) $(EtO_2C)_2CHCH_2CH$=CH_2, NaOEt, DMF, 33-75%; (e) TBDPSiCl, NEt_3, CH_2Cl_2, then PCC, CH_2Cl_2, 83%; (f) Ph_3PCH_3Br, BuLi, THF, 93%; (g) TBAF, THF, 65%; (h) NBS, CCl_4, 66%.

Functionalized dienes **14a-21a** were prepared in a similar manner to the alkyl-substituted dienes (Scheme 3). Bromination of 2-(acetoxymethyl)-3-propen-1-ol followed by coupling to diethyl allylmalonate gave diene **14a**, and subsequent deprotection afforded diene **15a**. Diene **16a** was prepared by allylic bromination of

α-methylstyrene[15] followed by coupling to diethyl allylmalonate. Reaction of 2-(bromomethyl)acrylic acid with diethyl allylmalonate followed by esterification afforded diene **17a**. The coupling of 2,3-dibromopropene to diethyl allylmalonate yielded diene **18a**. 2-(Bromomethyl)-1,3-butadiene[16] was reacted with diethyl allylmalonate to yield **19a**. Amide **20a** and ether **21a** were synthesized through standard alkylation reactions.

Scheme 3:



(a) Ac_2O (1eq), NEt_3, CH_2Cl_2, 48%; (b) PPh_3, CBr_4, CH_2Cl_2, 75%;
(c) $(EtO_2C)_2CHCH_2CH=CH_2$, NaOEt, DMF, 54-96%; (d) Na, EtOH, 57%; (e) NBS, CCl_4, 27%; (f) CH_3I, K_2CO_3, acetone, 55%; (g) SO_2, benzoquinone, CH_3OH, 47%;
(h) NBS, $CHCl_3$, then 160°C, neat, 62%; (i) PhCOCl, NEt_3, CH_2Cl_2, 64%;
(j) $CH_2=C(CH_3)CH_2Cl$, NaH, DMF, 38-78%; (k) $CH_2=CHMgBr$, THF, 56%.

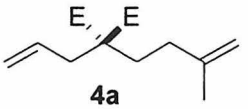
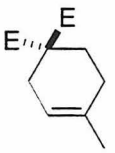
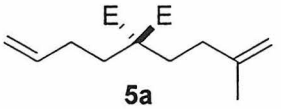
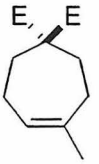
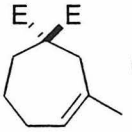
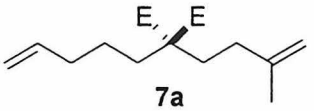
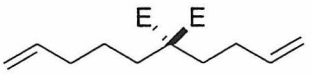
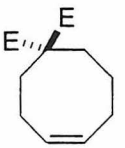
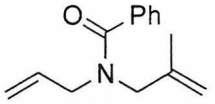
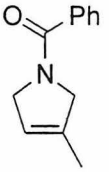
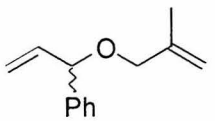
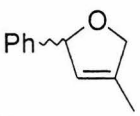
RCM of Methyl-Substituted Dienes:

Initially, it was necessary to determine if ruthenium alkylidene **1** was active for the RCM of dienes containing a *gem*-disubstituted olefin. When diene **3a** (0.01M, CH_2Cl_2)[17] was exposed to 5 mol% **1** for 24 h, cyclopentene **3b** was obtained in 93% isolated yield with no side products detected (Table 1, Entry 1). A relatively low concentration of substituted diene is required for optimized yields when RCM is performed with alkylidene **1**. Upon addition of **1** to a 0.1M solution of **3a**, significant formation of another species is observed. This species is postulated to be the dimer formed through acyclic diene metathesis of the monosubstituted olefins of two molecules of **3a**.[18] This was not surprising, as several examples of dimerization have been seen in other RCM applications of **1**.[19] However, no dimerization could be detected upon analysis of all of the reactions using **1** at a substrate concentration of 0.01M. Therefore, the first set of conditions reported above were used as the standard conditions for RCM with **1** for all of the reactions reported.

Exposure of **3a** (0.1M, C_6D_6)[17] to the molybdenum alkylidene **2** (5 mol%) also showed high reactivity in converting this substrate to **3b**. Upon examining the reactions of trisubstituted dienes with alkylidene **2** at this concentration, no dimer formation was detected. In addition, RCM of some substituted dienes which are unreactive with **1** can be carried out in good synthetic yield with alkylidene **2**.

The difference in reactivity between **1** and **2** can be understood through an examination of the kinetics of formation of trisubstituted cyclic olefins through RCM (Figure 1). From this analysis, it can be seen that the catalyst dependent term for productive RCM *vs* dimer formation is k_{more}/k_{less}. Because this ratio is much

Table 1:

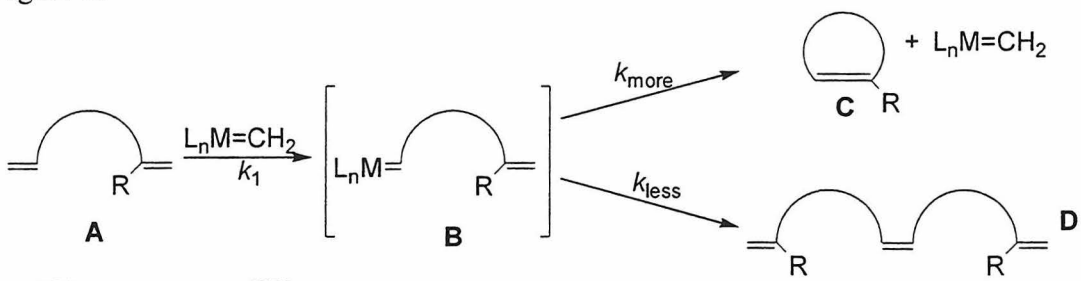
Entry	Substrate	Product	Yield With **1**	Yield With **2**
1	 **3a**	 **3b**	93%	(100%)[a]
2	 **4a**	 **4b**	97%	(100%)
3	 **5a**	 **5b**	96%	(100%)
4	 **6a**	 **6b**	(25%)	96%
5	 **7a**	 **7b**	No RCM product[b]	No RCM product[b]
6	 **8a**	 **8b**	No RCM product[b]	No RCM product[b]
7	 **21a**	 **21b**	97%	(100%)
8	 **22a**	 **22b**	98%	(100%)

[a]Numbers in parentheses represent the conversion to product as measured by ^{1}H NMR.

[b]In these cases, only starting material and a product which was assigned as an acyclic dimer based on ^{1}H NMR and TLC were observed.

smaller for the more selective ruthenium alkylidene ($k_{less} >> k_{more}$ for **1**), dimer formation is frequently competitive with RCM. Since the rate of dimer formation is dependent upon the concentration of substrate but the rate of RCM is independent of substrate concentration, performing RCM reactions under dilute conditions can reduce the rate of dimerization to the point where it is not observed. Because the molybdenum alkylidene **2** is much less selective than **1**, the intramolecular reaction occurs much faster than any intermolecular reaction under the range of concentrations examined in this study. For this reason, no dimeric products were observed in reactions using alkylidene **2**.

Figure 1:



$\frac{d[C]}{dt} = k_{more}[B]$ $\frac{d[D]}{dt} = k_{less}[B][A]$

k_{more} = rate of metathesis of the more substituted olefin
k_{less} = rate of metathesis of the less substituted olefin

The kinetic ratio of product to dimer at time = t

$$\frac{[C]}{[D]} = \frac{k_{more}[B]}{k_{less}[B][A]} = \frac{k_{more}}{k_{less}[A]}$$

$\frac{k_{more}}{k_{less}}$ for $L_nRu=CH_2$ is smaller than $\frac{k_{more}}{k_{less}}$ for $L_nMo=CH_2$.

In order to explain the increased conversion observed when the concentration of substrate is increased in molybdenum-mediated cyclizations, another kinetic term involving the methylidene[20] must be considered. Due to the limited stability of the

molybdenum methylidene,[4] the decomposition of the catalytic species is competitive with the rate of RCM. Because the rate of RCM increases with the concentration of substrate, the increased yield results from higher turnover of substrate before catalyst decomposition. This problem is significantly reduced in the case of the ruthenium methylidene, which is much more stable in solution and can even be isolated as a solid which is stable indefinitely at room temperature.[3] However, in cases where reaction with the more substituted olefin is extremely slow for the ruthenium alkylidene, the rate of catalyst decomposition exceeds the rate of RCM and little or no conversion to product is observed. In these cases decreasing the substrate concentration and increasing catalyst loading can significantly increase the conversion of substrate to product for the reasons outlined above.

A comparison of the conversion obtained at a variety of temperatures for substrate **3a** showed that while RCM was somewhat faster at elevated temperatures, the accelerated decomposition of the ruthenium methylidene led to a decrease in overall conversion. In some other studies with alkylidene **1** involving different conditions, increased temperature has resulted in higher overall conversions, notably at higher substrate concentrations.[5b,19a] This discrepancy is observed because the ruthenium methylidene undergoes unimolecular decomposition while substituted ruthenium alkylidenes undergo bimolecular decomposition.[21] Therefore, the decomposition of the active catalytic species in these reactions depends only on temperature and not on concentration. For this reason, all of the subsequent RCM reactions with alkylidene **1** were performed at room temperature in order to extend the lifetime of the methylidene. In contrast, elevated temperatures resulted in the

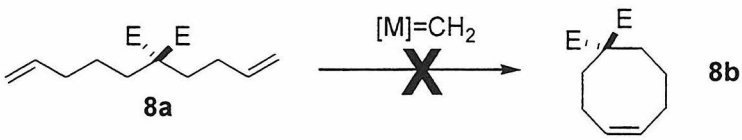
increased conversion of **10a** to **10b** with alkylidene **2**, and 65°C was eventually chosen as the optimal temperature for all RCM reactions with **2**.

Under the standard conditions discussed previously, alkylidenes **1** and **2** converted diene **4a** to the substituted cyclohexene **4b** in good yield (Table 1, Entries 2-4). Formation of the seven membered cyclic **5b** with alkylidene **1** required extended reaction times (4 days) to achieve a 96% yield. However, formation of the structural isomer **6b** was less favorable, with only 25% conversion to **6b** observed after 5 days. Quantitative conversion of both **5a** and **6a** to the respective cycloheptenes is seen with alkylidene **2**.

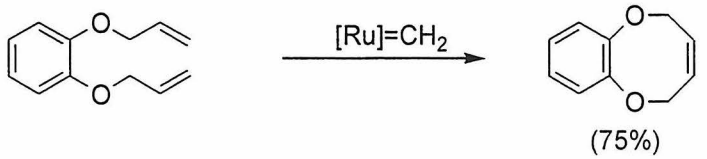
Differences in the rates of formation of isomeric cycloheptenes have been reported elsewhere,[22] although the reason for this drop in reactivity is unclear. In the case of substrates derived from malonic acid, the *gem*-diesters on the backbone of the substrate favor cyclization due to a Thorpe-Ingold effect.[23] Thus, the higher reactivity of **5a** may be due to the *gem*-diesters biasing the substrate to adopt a conformation which is favorable for cyclization. This bias may be less in the asymmetrical substrate **6a**. Another possible explanation is that the esters in **6a**, being closer to the disubstituted olefin, hinder the tethered alkylidene as it approaches the disubstituted olefin to form the cyclic product. The higher conversion observed with alkylidene **2** is believed to be due to the higher reactivity of this alkylidene, which overrides the factors inhibiting alkylidene **1** discussed above.

Exposure of the diene **7a** to alkylidene **1** or **2** under standard conditions yielded only dimeric products (Table 1, Entry 5). In order to determine if the methyl

group substituent on **7a** had prevented productive RCM from occurring, the analogous diene **8a** without olefinic substituents was synthesized (Table 1, Entry 6). Again, only dimeric products were observed upon exposure to both alkylidenes (Eq. 1). This result is in good agreement with previous work from these laboratories,[24] showing that formation of eight membered cyclics through RCM only occurs in systems where the dienes are conformationally predisposed for ring formation as in the catechol derivative shown below (Eq. 2). Unconstrained systems failed to yield eight-membered cyclics through RCM in almost all cases, and it has been demonstrated for several other systems that the formation of eight-membered rings is generally less favorable than formation of any other ring size.[25] Clearly, the diester moiety does not provide enough conformational bias to favor RCM in the cases of **7a** and **8a**.



(1)



(2)

In order to demonstrate that this methodology is general to a variety of substituted dienes, amide **20a** and ether **21a** were examined (Table 1, Entries 7 and 8). Alkylidene **1** cyclized amide **20a** and ether **21a** to the corresponding heterocycles **20b** and **21b** in 97% and 98% yield respectively. In accordance with previous reports from this laboratory,[5k,5l] it was found that the molybdenum alkylidene **2** also converted **20a** and **21a** to the expected cyclic products quantitatively.

Effect of Olefin Substitution:

Once it had been established that formation of substituted cyclics with **1** was feasible, attention was turned towards the olefinic substituent (Table 2, Entries 1-3). The steric bulk tolerated by each alkylidene was examined through the use of dienes **11a**, **12a** and **13a**. The cyclization of ethyl-substituted diene **11a** with **1** proceeded in 93% yield over 24 h. Reaction of isopropyl-substituted diene **12a** with **1** required 48 h for 98% yield of **12b** to be achieved, presumably due to the presence of additional steric bulk on the olefin. Alkylidene **1** showed no reaction with *tert*-Butyl-substituted diene **13a** over 5 days, demonstrating that further increasing the steric bulk on the olefin inhibits RCM with **1**. Due to the more active nature of alkylidene **2**, it was presumed that **2** would be more active towards the RCM of more hindered dienes such as **12a** and **13a**. In fact, **2** converts all three of these alkyl-substituted dienes into the corresponding cyclopentenes in high yield over 24 h.

After examining the steric bulk tolerated by these alkylidenes, substituents which affect the electronic nature of the olefin were examined. Previous reports from this laboratory had shown that enol ethers did not undergo RCM when exposed to **1**.[5i] For this reason we turned our attention away from electron-donating substituents and toward electron-withdrawing substituents (Table 2, Entries 4 and 5). When the phenyl substituted **16a** was subjected to RCM conditions with **1**, only 25% conversion to cyclized product was observed. In the case of the more electron-deficient diene **17a**, 5% conversion was observed. The failure of **16a** and **17a** to give the desired product in higher yield when exposed to alkylidene **1** is postulated to be a combination of the steric effect of the substituent and the electron-withdrawing effects of the phenyl and methyl ester groups. Alkylidene **1** is capable of cyclizing

Table 2:

Entry	Substrate		Product		Yield With **1**	Yield With **2**
1	R = Et	(**11a**)	R = Et	(**11b**)	93%	(100%)[a]
2	R = ^{i}Pr	(**12a**)	R = ^{i}Pr	(**12b**)	98%	(100%)
3	R = ^{t}Bu	(**13a**)	R = ^{t}Bu	(**13b**)	NR	96%
4	R = Ph	(**16a**)	R = Ph	(**16b**)	(25%)	97%
5	R = CO_2Me	(**17a**)	R = CO_2Me	(**17b**)	(5%)	89%
6	R = Br	(**18a**)	R = Br	(**18b**)	NR	NR
7	R = CH_2OH	(**15a**)	R = CH_2OH	(**15b**)	98%	decomp
8	R = CH_2OAc	(**14a**)	R = CH_2OAc	(**14b**)	97%	(100%)

[a]Numbers in parentheses represent the conversion to product as measured by ^{1}H NMR.

substrates that contain substituents of approximately equal steric demand to these substituents, such as the isopropyl group in diene **12a**. Examples have been reported of α,β-unsaturated carbonyl and phenyl substituted acetylenes[5d] and dienes[8,22b,26] reacting with alkylidene **1** to form cyclic products. However, when both the steric bulk and electron withdrawing character are combined in the same diene substituent, the rate of RCM with alkylidene **1** becomes so slow that catalyst decomposition is competitive with RCM and high yields are not obtained.

In contrast to **1**, alkylidene **2** was able to convert substrates **16a** and **17a** to the expected cyclopentenes in good yield (Table 2, Entries 4 and 5). The higher

reactivity exhibited by **2** towards olefins containing both electron-withdrawing and electron-donating substituents such as enol ethers[5d] underscores its generally higher activity towards *gem*-disubstituted olefins.

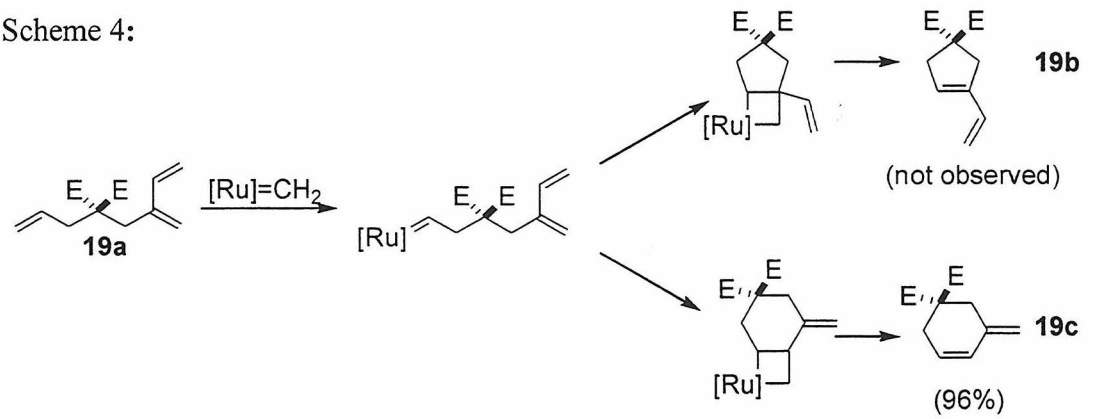
Next, diene **18a** containing a vinyl bromide was examined. Exposure of **18a** to either alkylidene **1** or **2** afforded no cyclic product (Table 2, Entry 6). In all cases, only **18a** and alkylidene decomposition products were detected upon examination of the reaction mixtures. The explanation for this lack of reactivity with alkylidene **1** is presumed to be the same as for dienes **16a** and **17a**. Acetylenic halides have been shown to react with alkylidene **1** through halide exchange, but will not undergo RCM.[5d] It has also been shown that vinyl chlorides do not react productively with alkylidene **1**.[27] The explanation for the failure of alkylidene **2** to react with **18a** has not been determined.

Due to the failure of alkylidene **1** to effectively cyclize dienes containing substituents in conjugation with an olefin, functional groups which do not electronically deactivate the substrate but could be used to efficiently derivatize the cyclic olefin after RCM were investigated. Allylic alcohol **15a** was the target molecule for this approach. Because the alcohol should have only an inductive effect on the olefin, it was hoped that the diene would not be deactivated for RCM with **1**. The reactivity of **1** towards **15a** was therefore presumed to be similar to its reactivity towards the ethyl substituted diene **11a**, due to the similar steric bulk of these two substituents. In fact, both the alcohol **15a** and the acetate **14a** react with **1** to yield the expected cyclopentenes in excellent yields (Table 2, Entries 7 and 8). As expected, molybdenum alkylidene **2** decomposes in the presence of the primary

alcohol present in **15a** to give no ring-closed product, although it does convert protected diene **14a** to the cyclized product.

In order to further examine the effects of olefin substitution on alkylidenes **1** and **2**, the RCM of triene **19a** was examined. Reaction of **19a** with either alkylidene could yield either cyclopentene **19b** or cyclohexene **19c** (Scheme 4). Based on the kinetic scheme described previously (Figure 1), it was predicted that alkylidene **1** would preferentially react with the two less substituted olefins on **19a** to give **19c**. This prediction proved correct, and **19c** is formed in 96% yield upon treatment of **19a** with **1**.[28,29] Due to the lower selectivity of molybdenum alkylidene **2** for monosubstituted olefins, it was believed that a mixture of **19b** and **19c** might be formed. However, reaction of **19a** with **2** also showed quantitative conversion to cyclohexene **19c** with none of the cyclopentene **19b** detected. This result suggests that while **2** is not as selective for less substituted olefins as **1**, both alkylidenes will preferentially react with the less substituted olefin when two olefins with different substitution are present.[30] This formation of *exo*-methylene ring systems such as **19c** represents a complementary diene system to the vinyl systems afforded through enyne metathesis, which are described in Chapter 2.

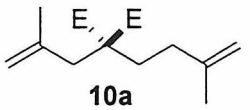
Scheme 4:



Synthesis of Tetrasubstituted Olefins:

Having demonstrated the formation of a variety of trisubstituted cyclic olefins, formation of tetrasubstituted cyclic olefins through the RCM of dienes **9a** and **10a** was investigated. Formation of cyclopentenes with tetrasubstituted olefins analogous to **9b** with molybdenum alkylidene **2** has been reported.[5k,31] Indeed, when **9a** was exposed to **2** under standard RCM conditions, **9b** was obtained in 93% yield (Table 3). Formation of the cyclohexene **10b** using alkylidene **2** proceeded in 61% yield.

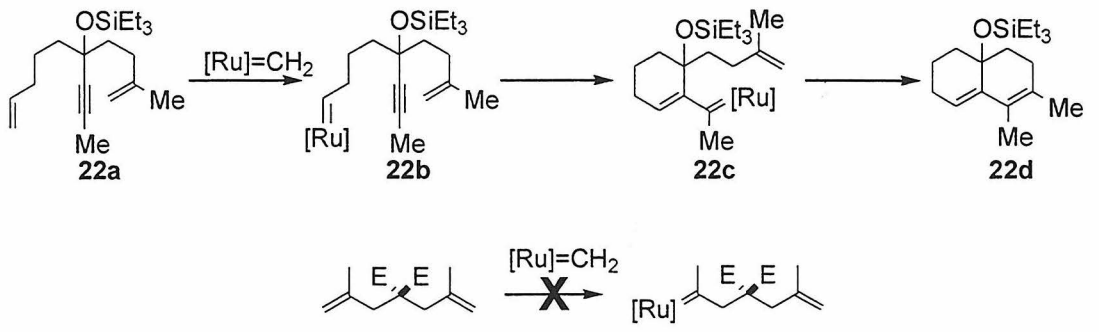
Table 3:

Entry	Substrate	Product	Yield With **1**	Yield With **2**
1	 **9a**	 **9b**	No Reaction	93%
2	 **10a**	 **10b**	No Reaction	61%

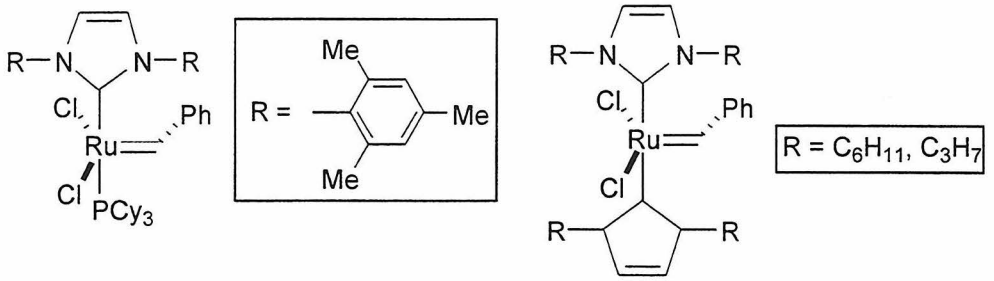
Exposure of **9a** or **10a** to alkylidene **1** afforded no cyclic product under standard RCM conditions, and the benzylidene was observed unchanged throughout the course of these reactions, indicating that initiation had not taken place. Even when the concentration of substrate was increased tenfold, neither ring-closed product nor dimerization were observed. However, previous studies in this laboratory have shown that tetrasubstituted cyclic olefins can be generated through reaction of **1** with acetylene containing substrates.[5d] The key difference between

these two systems lies in the initial reaction of alkylidene with the substrate. In acetylene containing substrates such as **22a**, the monosubstituted olefin is the site of initiation (Scheme 5). Once the alkylidene has initiated to yield intermediate **22b**, the intramolecular reaction is favored to form intermediate **22c**. The new alkylidene present in **22c** performs another intramolecular reaction with the disubstituted olefin at the end of the tether to form the fused bicyclic compound **22d** containing a tetrasubstituted olefin. As discussed earlier, an intramolecular reaction is also observed in the formation of trisubstituted dienes through metathesis of *gem*-disubstituted olefins, although only at high dilution. Initiation occurs through the less substituted olefin and the new alkylidene undergoes the intramolecular reaction providing the desired product. When no monosubstituted olefin is present on the RCM substrate, however, reaction with **1** is not observed (Scheme 5). In fact, the isolation of disubstituted alkylidenes of ruthenium which are metathesis active has not been reported.[32] The low intermolecular reactivity of **1** with *gem*-disubstituted olefins indicates that formation of tetrasubstituted cyclic olefins through dienes such as **9a** is not feasible using alkylidene **1**.

Scheme 5:



Following the completion of this research, a new class of ruthenium based olefin metathesis catalysts has been synthesized, typified by alkylidenes **23**[33] and **24**.[34] Alkylidene **23** is significantly more active for the RCM of highly substituted dienes than alkylidene **1**. Good conversion for the RCM of substrates **13a**, **9a** and **9b** were reported using this alkylidene.[33] The higher activity of this alkylidene combined with the superior functional group tolerance of ruthenium alkylidenes make this alkylidene well suited for the RCM of extremely hindered substrates.



23 **24**

Conclusions:

The formation of trisubstituted and tetrasubstituted olefins has been demonstrated *via* ring-closing metathesis of *gem*-disubstituted olefins. This is a general reaction for the formation of five-, six- and seven-membered carbocycles and heterocycles. The reactivities of all substrates examined support the general observation that five-membered ring formation is the most kinetically favorable and eight-membered ring formation is the least favorable regardless of the alkylidene used. Ruthenium alkylidene **1** will cyclize dienes with olefinic substituents as sterically demanding as isopropyl in good yield, but will not cyclize a *tert*-butyl substituted diene. In addition, dienes containing an electron-withdrawing olefinic

substituent do not undergo RCM when exposed to **1**. The more active and less selective molybdenum alkylidene **2** does catalyze the RCM of many of the substrates for which **1** was not active. Both alkylidenes **1** and **2** are shown to efficiently convert trienes such as **19a** to the *exo*-methylenecyclohexene **19c**. Tetrasubstituted cyclic olefins can be synthesized from bis-*gem*-disubstituted dienes using the more active alkylidene **2**, but **1** is unreactive towards that class of dienes. However, alkylidene **1** does perform RCM in excellent yield to form a carbocycle containing an allylic alcohol.

The differing reactivities of alkylidenes **1** and **2** suggest that both have a role in the synthesis of complex molecules through RCM. The more active molybdenum alkylidene **2** is required for the RCM of highly substituted dienes. However, RCM using **2** frequently requires a substantial number of substrate protection and deprotection steps which are not required with alkylidene **1**. Another advantage of ruthenium alkylidene **1** is that rigorous purification, drying and degassing of substrates is not required for RCM. Therefore, total syntheses of many densely-functionalized targets may be more simply and efficiently carried out using **1**. Alkylidene **23** may be effective for substrates requiring a combination of these properties due to its higher activity.

Acknowledgements:

Professor Scott Miller and Dr. Osamu Fujimura are gratefully acknowledged for many helpful discussions in this work. Dr. Delwin Elder is acknowledged for supplying alkylidene **2**. This research was generously supported through a grant from the NIH.

Experimental Section:

General. NMR spectra were recorded on either a General Electric QE-300 (300.1 MHz ^{1}H; 75.49 MHz ^{13}C) or a Jeol GX-400 (399.65 MHz ^{1}H; 100 MHz ^{13}C) spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane with reference to internal solvent. In cases where more than one rotamer is observed, both rotamers are reported. Infrared spectra were obtained on a Perkin-Elmer Paragon 1000 FT-IR. High-resolution mass spectra were provided by either the Chemistry and Biology Mass Spectrometry Facility (Caltech) or the Southern California Mass Spectrometry Facility (University of California, Riverside). Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Flash column chromatography was performed using silica gel 60 (230-400 mesh) from EM Science.[35] Alkylidenes **1** and **2** were prepared according to published procedures.[3,4]

4,4-Dicarboethoxy-2-methyl-1,6-heptadiene (3a). To a suspension of sodium ethoxide (5.09 g, 74.9 mmol) in DMF (100 mL) was added diethyl allylmalonate (10.0 g, 49.9 mmol). After 15 min, methallyl chloride was added (4.52 g, 49.9 mmol). After stirring for 24 h at room temperature, the reaction was quenched with water (100 mL) and extracted with Et_2O (4 × 50 mL). Purification of the resultant orange oil on silica gel (10% EtOAc in hexanes) yielded **3a** (8.26 g, 65%) as a clear, colorless oil as first reported by Doran:[10] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.79-5.68 (m, 1H), 5.05-4.96 (m, 2H), 4.80 (s, 1H), 4.77 (s, 1H), 3.95-3.92 (m, 4H), 2.85-2.80 (m, 4H), 1.59 (s, 3H), 0.93 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$,

75 MHz) δ 170.9, 141.1, 133.4, 118.8, 115.9, 61.1, 57.2, 40.6, 37.4, 23.3, 14.0; IR (neat, cm^{-1}) 3079, 2982, 1731, 1644, 1446, 1367; HRMS calcd for $C_{14}H_{22}O_4$ (M^+) 254.1507, found 254.1518.

4,4-Dicarboethoxy-1-methylcyclopentene (3b). To a solution of catalyst **1** (16 mg, 0.02 mmol) in dry, degassed methylene chloride (40 mL) was added diene **3a** (102 mg, 0.4 mmol). After stirring at room temperature for 24 h the reaction was concentrated and purified on silica gel (5% EtOAc in hexanes) to yield the product **3b** (83 mg, 91%) as a clear, colorless oil. The spectral data are in good agreement with that first reported by Schweizer.[36]

5,5-Dicarboethoxy-2-methyl-1,7-octadiene (4a). The diester **4a** was prepared in a manner similar to **3a** using 1-bromo-3-methyl-3-butene.[11] **4a** was isolated as a clear, colorless oil (50%) in good agreement with the spectral data reported by Sato.[37]

4,4-Dicarboethoxy-1-methylcyclohexene (4b). Cyclohexene **4b** was obtained as a clear, colorless oil (97%) under conditions analogous to the reaction producing **3b.** The spectral data are in good agreement with those first reported by Schweizer.[36]

5,5-Dicarboethoxy-2-methyl-1,8-nonadiene (5a). The diester **5a** was prepared in a manner similar to **3a** using 1-bromo-3-methyl-3-butene and 1,1-

dicarboethoxy-4-pentene. 1,1-Dicarboethoxy-4-pentene was also synthesized in a manner similar to **3a** using diethyl malonate and 1-bromo-3-butene. **5a** was isolated as a clear, colorless oil (50%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.77-5.66 (m, 1H), 5.05-4.89 (m, 2H), 4.80 (s, 1H), 4.74 (s, 1H), 3.95 (q, J = 7.7 Hz, 4H), 2.32-2.20 (m, 4H), 2.13-2.04 (m, 4H), 1.60 (s, 3H), 0.92 (t, J = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.3, 145.0, 137.9, 115.1, 110.7, 60.9, 57.4, 32.7, 32.2, 31.4, 28.9, 22.4, 14.0; IR (neat, cm^{-1}) 3077, 2797, 2939, 1732, 1643, 1454, 1367; HRMS calcd for $C_{16}H_{27}O_4$ (MH^+) 283.1900, found 283.1909.

5,5-Dicarboethoxy-1-methylcycloheptene (5b). To a solution of catalyst **1** (16 mg, 0.02 mmol) in dry, degassed methylene chloride (40 mL) was added diene **5a** (113 mg, 0.4 mmol). After stirring at room temperature for 4 days the reaction was concentrated and purified on silica gel (5% EtOAc in hexanes) to yield the product **5b** (98 mg, 96%) as a clear, colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.40 (s, 1H), 4.15 (q, J = 7.1 Hz, 4H), 2.19-2.12 (m, 8H), 1.65 (s, 3H), 1.22 (t, J = 7.9 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.4, 138.9, 124.9, 61.3, 58.3, 32.2, 31.1, 29.7, 25.9, 25.9, 23.8, 14.2; IR (neat, cm^{-1}) 2966, 2853, 1732, 1447, 1367, 1292, 1180, 1035; HRMS calcd for $C_{14}H_{23}O_4$ (MH^+) 255.1588, found 255.1596.

5,5-Dicarboethoxy-2-methyl-1,9-decadiene (7a). The diester **7a** was synthesized in a similar manner to **3a** using 1,1-dicarboethoxy-5-hexene, which was prepared from diethyl malonate and 1-bromo-4-pentene. **7a** was isolated as a clear, colorless oil (33%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.78-5.69 (m, 1H), 5.01-4.90 (m,

2H), 4.67-4.66 (m, 2H), 4.14 (q, J = 7.1 Hz, 4H), 2.06-1.95 (m, 4H), 1.89-1.83 (m, 4H), 1.68 (s, 3H), 1.23-1.18 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.8, 145.0, 138.2, 115.1, 110.3, 61.2, 57.3, 33.9, 31.7, 31.5, 30.6, 23.6, 23.2, 14.2; IR (neat, cm^{-1}) 3078, 2980, 2938, 1731, 1643, 1447, 1380, 1255, 1181, 1030; HRMS calcd for $C_{17}H_{29}O_4$ (MH^+) 297.2054, found 297.2066.

5,5-Dicarboethoxy-1,9-decadiene (8a). The diester **8a** was synthesized in a similar manner to **3a** using 1,1-dicarboethoxy-5-hexene and 1-bromo-4-pentene. **8a** was isolated as a clear, colorless oil (44%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.76-5.65 (m, 1H), 4.99-4.87 (m, 4H), 4.11 (q, J = 7.2 Hz, 4H), 2.03-1.80 (m, 8H), 1.25-1.15 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.6, 138.1, 137.7, 115.05, 114.98, 61.1, 57.2, 33.8, 31.7, 31.5, 28.4, 23.3, 14.1; IR (neat, cm^{-1}) 3079, 2980, 2874, 1732, 1642, 1447, 1368, 1260, 1032, 913; HRMS calcd for $C_{16}H_{27}O_4$ (MH^+) 283.1914, found 283.1909.

4,4-Dicarboethoxy-2,6-dimethyl-1,6-heptadiene (9a). The diester **9a** was synthesized in a similar manner to **3a** using diethyl methallylmalonate. **9a** was isolated as a clear, colorless oil (72%) as first reported by Doran:[10] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.88-4.85 (m, 4H), 3.95 (q, J = 7.1 Hz, 4H), 3.01 (s, 4H), 1.68 (s, 6H), 0.91 (t, J = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.3, 141.6, 115.3, 61.1, 57.1, 41.0, 23.7, 13.9; IR (neat, cm^{-1}) 3078, 2981, 2937, 1732, 1446, 1367; HRMS calcd for $C_{15}H_{25}O_4$ (MH^+) 269.1755, found 269.1753.

4,4-Dicarboethoxy-1,2-dimethylcyclopentene (9b). A solution of **9a** (107 mg, 0.4 mmol) in dry, degassed benzene (4 mL) was added to alkylidene **2** (12.0 mg, 0.02 mmol) and heated to 65°C. After stirring for 24 h the reaction was concentrated and purified on silica gel (10% EtOAc in hexanes) to yield **9b** as a clear, colorless oil (89mg, 93%):[38] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.16 (q, J = 7.0 Hz, 4H), 2.90 (s, 4H), 1.57 (s, 6H), 1.22 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.8, 128.2, 61.6, 57.2, 45.9, 14.2, 13.5; IR (neat, cm^{-1}) 3468, 2981, 2859, 1732, 1446, 1366, 1253, 1076, 1020; HRMS calcd for $C_{13}H_{20}O_4$ (M^+) 240.1362, found 240.1362.

4,4-Dicarboethoxy-2,7-dimethyl-1,7-octadiene (10a). The diester **10a** was synthesized in a similar manner to **3a** using diethyl methallylmalonate and 1-bromo-3-methyl-3-butene. Diene **10a** was isolated as a clear, colorless oil (65%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.79 (s, 1H), 4.68 (s, 1H), 4.62 (s, 2H), 4.17-4.10 (m, 4H), 2.66 (s, 2H), 1.99-1.93 (m, 2H), 1.84-1.79 (m, 2H), 1.65 (s, 3H), 1.59 (s, 3H), 1.19 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.5, 144.9, 140.6, 115.6, 110.3, 61.2, 56.6, 40.0, 32.2, 30.4, 23.1, 22.5, 14.1; IR (neat, cm^{-1}) 3077, 2981, 2940, 1732, 1650, 1448, 1368, 1259, 1093, 1031; HRMS calcd for $C_{16}H_{27}O_4$ (MH^+) 283.1915, found 283.1909.

4,4-Dicarboethoxy-1,2-dimethylcyclohexene (10b). Cyclohexene **10b** was obtained as a clear colorless oil (61%) under conditions analogous to the reaction producing **9b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.16 (q, J = 7.1 Hz, 4H), 2.43 (s, 2H),

2.11-2.07 (m, 2H), 1.99-1.97 (m, 2H), 1.63 (s, 3H), 1.57 (s, 3H), 1.22 (t, J = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.9, 124.7, 123.0, 61.3, 54.0, 36.6, 28.8, 28.2, 19.2, 18.9, 14.3; IR (neat, cm^{-1}) 2982, 2913, 1732, 1446, 1367, 1297, 1177, 1090, 1031; HRMS calcd for $C_{14}H_{22}O_4$ (M^+) 254.1513, found 254.1518.

4,4-Dicarboethoxy-2-ethyl-1,6-heptadiene (11a). The diester **11a** was synthesized in a similar manner to **3a** using 2-(bromomethyl)-1-butene.[12b] **11a** was isolated as a clear, colorless oil (50%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.65-5.53 (m, 1H), 5.02-4.97 (m, 2H), 4.80 (s, 1H), 4.70 (s, 1H), 4.14-4.03 (m, 4H), 2.62 (s, 2H), 2.57 (d, J = 7.4 Hz, 2H), 1.84 (q, J = 7.4 Hz, 2H), 1.16 (t, J = 7.1 Hz, 6H), 0.91 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.2, 146.1, 132.8, 118.9, 113.1, 61.2, 57.1, 38.3, 36.8, 29.3, 14.1, 12.4; IR (neat, cm^{-1}) 3080, 2982, 2879, 1732, 1642, 1446, 1368, 1288, 1096, 1042; HRMS calcd for $C_{15}H_{25}O_4$ (MH^+) 269.1751, found 269.1753.

4,4-Dicarboethoxy-1-ethylcyclopentene (11b). Cyclopentene **11b** was obtained as a clear, colorless oil (93%) under conditions analogous to the reaction producing **3b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.18-5.16 (m, 1H), 4.15 (q, J = 7.1 Hz, 4H), 2.95 (s, 2H), 2.89 (s, 2H), 2.06-1.99 (m, 2H), 1.23 (t, J = 7.1 Hz, 6H), 1.02 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.6, 143.7, 119.2, 61.6, 59.2, 43.2, 40.7, 23.8, 14.2, 12.2; IR (neat, cm^{-1}) 3057, 2969, 2878, 1732, 1464, 1367, 1252, 1183, 1097, 1015; HRMS calcd for $C_{13}H_{20}O_4$ (M^+) 240.1353, found 240.1362.

4,4-Dicarboethoxy-2-phenyl-1,6-heptadiene (16a). The diester **16a** was synthesized in a manner similar to **3a** using α-(bromomethyl)styrene.[15] **16a** was isolated as a clear, colorless oil (74%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32-7.23 (m, 5H), 5.67-5.55 (m, 1H), 5.26 (s, 1H), 5.16 (s, 1H), 5.08-5.02 (m, 2H), 3.96-3.75 (m, 4H), 3.16 (s, 2H), 2.58 (d, J = 7.3 Hz, 2H), 1.13 (t, J = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.6, 144.6, 141.7, 132.6, 128.0, 127.5, 127.0, 119.2, 118.7, 61.1, 57.2, 37.2, 36.1, 14.0; IR (neat, cm^{-1}) 3082, 2983, 1732, 1642, 1627, 1601, 1575, 1446, 1368, 1287, 1047; HRMS calcd for $C_{19}H_{25}O_4$ (MH^+) 317.1743, found 317.1753.

4,4-Dicarboethoxy-1-phenylcyclopentene (16b). Cyclopentene **16b** was obtained as a clear, colorless oil (97%) under conditions analogous to the reaction producing **9b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45-7.25 (m, 5H), 6.03 (t, J = 2.1 Hz, 1H), 4.23 (q, J = 7.1 Hz, 4H), 3.44-3.42 (m, 2H), 3.24-3.22 (m, 2H), 1.28 (t, J = 7.1 Hz, 6H); ^{13}C NMR (C_6D_6, 75 MHz) δ 172.2, 140.2, 136.1, 129.0, 128.0, 126.4, 123.0, 61.9, 59.6, 42.0, 41.9, 14.4; IR (neat, cm^{-1}) 3058, 2982, 2867, 1732, 1600, 1576, 1447, 1367, 1258, 1183, 1073, 1017; HRMS calcd for $C_{17}H_{21}O_4$ (MH^+) 289.1431, found 289.1440.

2-Carbomethoxy-4,4-dicarboethoxy-1,6-heptadiene (17a). To a suspension of K_2CO_3 (1.09 g, 7.91 mmol) in acetone (50 mL) was added 4,4-dicarboethoxy-1,6-heptadiene 2-carboxylic acid (1.50 g, 5.28 mmol) and CH_3I (9.9 mL, 158.3 mmol). After stirring for 24 h at room temperature, the reaction was

quenched with $NaHCO_3$ (sat aq, 75 mL) and extracted with Et_2O (4 × 60 mL). After concentration, the yellow oil obtained was purified with silica gel (20% EtOAc in hexanes). 4,4-Dicarboethoxy-1,6-heptadiene-2-carboxylic acid was prepared in a manner similar to **3a** using 2-(bromomethyl)acrylic acid. **17a** was obtained as a pale yellow, colorless oil (1.02 g, 65%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.17 (s, 1H), 5.67-5.56 (m, 2H), 5.02-4.97 (m, 2H), 4.11-4.01 (m, 4H), 3.62 (s, 3H), 2.87 (s, 2H), 2.49 (d, J = 7.3 Hz, 2H), 1.15 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.5, 167.3, 135.9, 132.5, 129.3, 119.2, 61.3, 57.5, 51.8, 37.1, 33.6, 14.0; IR (neat, cm^{-1}) 3080, 2983, 2908, 1732, 1632, 1445, 1368, 1155, 1053, 1008; HRMS calcd for $C_{15}H_{23}O_6$ (MH^+) 299.1482, found 299.1495.

1-Carbomethoxy-4,4-dicarboethoxycyclopentene (17b). Cyclopentene **18b** was obtained as a clear, colorless oil (89%) under conditions analogous to the reaction producing **9b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.56 (s, 1H), 4.14 (q, J = 7.1 Hz, 4H), 3.67 (s, 3H), 3.20-3.19 (m, 2H), 3.13-3.12 (m, 2H), 1.20 (t, J = 7.1 Hz, 6Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.4, 164.5, 139.9, 133.5, 61.9, 58.7, 51.7, 41.1, 39.5, 14.1; IR (neat, cm^{-1}) 2984, 1732, 1644, 1436, 1367, 1246, 1184, 1069, 1015; HRMS calcd for $C_{13}H_{19}O_6$ (MH^+) 271.1180, found 271.1182.

2-(Acetoxymethyl)-4,4-dicarboethoxy-1,6-heptadiene (14a). To a solution of 2-methylene-1,3-propanediol (5.0 g, 56.7 mmol) in CH_2Cl_2 (150 mL) at 0°C was added Ac_2O (5.8 g, 56.7 mmol) and NEt_3 (8.6 g, 85.1 mmol). This solution was allowed to warm to RT for 5 h, then quenched with water (75 mL) and washed with

$NaHCO_3$ (sat aq, 75 mL). Upon concentration of the organic portion, a pale yellow oil was isolated and the crude acetate was used without further purification. To a solution of this 2-(acetoxymethyl)-3-propen-1-ol (3.6 g, 27.5 mmol) in CH_2Cl_2 (60 mL) at 0°C was added PPh_3 (10.8 g, 41.3 mmol) and CBr_4 (13.7 g, 41.3 mmol). After stirring for 40 min the solvent was removed and the red viscous oil was eluted through a plug of silica gel with Et_2O. Concentration of the resulting solution gave a clear, colorless oil, and this crude bromide was used without further purification. The triester **14a** was synthesized in a manner similar to **3a** using this 1-bromo-2-(acetoxymethyl)-2-propene. **14a** was isolated as a clear, colorless oil (28%, 3 steps): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.56-5.46 (m, 1H), 5.04-4.86 (m, 4H), 4.27 (s, 2H), 4.07-3.96 (m, 4H), 2.57 (s, 2H), 2.51 (d, J = 7.3 Hz, 2H), 1.92 (s, 3H), 1.09 (t, J = 7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.5, 170.1, 138.9, 132.2, 119.1, 117.2, 66.6, 61.2, 56.9, 37.0, 35.4, 20.7, 13.9; IR (neat, cm^{-1}) 3082, 2984, 2908, 1732, 1644, 1446, 1368, 1226, 1031, 922; HRMS calcd for $C_{16}H_{25}O_6$ (MH^+) 313.1641, found 313.1651.

1-(Acetoxymethyl)-4,4-dicarboethoxycyclopentene (14b). Cyclopentene **14b** was obtained as a clear, colorless oil (98%) under conditions analogous to the reaction producing **3b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.51 (br s, 1H), 4.54 (s, 2H), 4.14 (q, J = 7.1 Hz, 4H), 2.98 (s, 2H), 2.95 (s, 2H), 2.02 (s, 3H), 1.20 (t, J = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.9, 170.8, 136.3, 125.6, 62.3, 61.7, 59.1, 40.9, 40.5, 20.9, 14.1; IR (neat, cm^{-1}) 2984, 2909, 1732, 1446, 1367, 1242, 1097, 1022, 972; Calcd for $C_{14}H_{20}O_6$ (M^+) 284.1260, found 284.1260.

4,4-Dicarboethoxy-2-(hydroxymethyl)-1,6-heptadiene (15a). Lump Na (100 mg, 4.34 mmol) was added to anhydrous ethanol (50 mL). After the metal was no longer visible, **14a** (1.24 g, 3.95 mmol) was added to the solution. After stirring for approximately 30 min at room temperature, no starting material spot was observed by TLC (33% EtOAc in hexanes, anisaldehyde). The reaction was quenched with NH_4Cl (sat aq, 30 mL) and extracted with EtOAc (5 × 30 mL). After purification on silica gel (33% EtOAc in hexanes) **15a** was obtained as a clear, colorless oil (57%): ^1H NMR ($CDCl_3$, 300 MHz) δ 5.65-5.56 (m, 1H), 5.09-5.01 (m, 3H), 4.84 (s, 1H), 4.14-4.06 (m, 4H), 3.90 (s, 2H), 2.73 (s, 1H), 2.63-2.59 (m, 4H), 1.18 (t, J = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.3, 144.3, 132.3, 119.4, 114.7, 65.6, 61.5, 57.5, 38.0, 35.8, 14.1; IR (neat, cm^{-1}) 3544, 3080, 2983, 2937, 1738, 1644, 1446, 1418, 1368, 1046, 918; HRMS calcd for $C_{14}H_{22}O_5$ (M^+) 270.1469, found 270.1467.

4,4-Dicarboethoxy-1-(hydroxymethyl)cyclopentene (15b). Cyclopentene **15b** was obtained as a clear, colorless oil (97%) under conditions analogous to the reaction producing **3b**: ^1H NMR ($CDCl_3$, 300 MHz) δ 5.45-5.43 (m, 1H), 4.18-4.09 (m, 6H), 2.98-2.95 (m, 4H), 2.46 (br s, 1H), 1.20 (t, J = 7.1 Hz, 6H), ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.3, 141.6, 122.2, 61.7, 61.3, 59.2, 40.7, 40.5, 14.1; IR (neat, cm^{-1}) 3462, 2982, 2871, 1732, 1446, 1392, 1368, 1257, 1184, 1072, 1017; HRMS calcd for $C_{12}H_{18}O_5$ (M^+) 242.1148, found 242.1154.

4,4-Dicarboethoxy-2-isopropyl-1,6-heptadiene (12a). The diester **12a** was synthesized in a similar manner to **3a** using 2-(bromomethyl)-3-methyl-1-butene.[13] **12a** was obtained as a clear, colorless oil (33%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.69-5.58 (m, 1H), 5.08-5.01 (m, 2H), 4.86 (s, 1H), 4.70 (s, 1H), 4.18-4.08 (m, 4H), 2.69-2.62 (m, 4H), 2.03-1.98 (m, 1H), 1.21 (t, J = 7.1 Hz, 6H), 0.97 (d, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.4, 151.1, 133.0, 119.0, 111.0, 61.4, 57.5, 37.3, 37.3, 37.0, 33.8, 22.1, 14.2; IR (neat, cm^{-1}) 3082, 2964, 2874, 1732, 1641, 1443, 1366, 1288, 1209, 1050; HRMS calcd for $C_{16}H_{27}O_4$ (MH^+) 283.1912, found 283.1909.

4,4-Dicarboethoxy-1-isopropylcyclopentene (12b). To a solution of catalyst **1** (16 mg, 0.02 mmol) in dry, degassed methylene chloride (40 mL) was added diene **12a** (113 mg, 0.4 mmol). After stirring at room temperature for 2 days the reaction was concentrated and purified on silica gel (5% EtOAc in hexanes) to yield the product **12b** (100 mg, 98%) as a clear, colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.16-5.14 (m, 1H), 4.20-4.12 (m, 4H), 2.94 (s, 2H), 2.92 (s, 2H), 2.30-2.24 (m, 1H), 1.21 (t, J = 8.6 Hz, 6H), 1.00 (d, J = 8.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.5, 148.2, 118.2, 61.5, 59.3, 41.3, 40.4, 29.6, 21.3, 14.2; IR (neat, cm^{-1}) 3062, 2963, 1732, 1466, 1447, 1367, 1248, 1182, 1097, 1074; HRMS calcd for $C_{14}H_{22}O_4$ (M^+) 254.1519, found 254.1518.

4,4-Dicarboethoxy-2-*tert*-butyl-1,6-heptadiene (13a). The diester **13a** was synthesized in a similar manner to **3a** using 2-(bromomethyl)-3,3-dimethyl-1-

butene.[14] **13a** was obtained as a clear, colorless oil (75%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.70-5.61 (m, 1H), 5.09-5.03 (m, 2H), 4.92 (s, 1H), 4.62 (s, 1H), 4.17 (q, J = 7.2 Hz, 4H), 2.80 (d, J = 7.5 Hz, 2H), 2.72 (s, 2H), 1.23 (t, J = 7.1 Hz, 6H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.6, 152.2, 132.9, 118.9, 107.0, 61.4, 56.7, 36.8, 36.7, 32.8, 29.4, 14.2; IR (neat, cm^{-1}) 3080, 2970, 2873, 1732, 1639, 1466, 1445, 1365, 1298, 1220, 918; HRMS calcd for $C_{17}H_{29}O_4$ (MH^+) 297.2058, found 297.2066.

4,4-Dicarboethoxy-1-*tert*-butylcyclopentene (13b). Cyclopentene **13b** was obtained as a clear, colorless oil (96%) under conditions analogous to the reaction producing **9b**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.16 (br s, 1H), 4.16 (q, J = 7.0 Hz, 4H), 2.92 (s, 4H), 1.21 (t, J = 7.0 Hz, 6H), 1.02 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.3, 151.0, 117.5, 61.4, 59.6, 40.2, 39.8, 32.7, 28.9, 14.1; IR (neat, cm^{-1}) 2964, 2870, 1732, 1464, 1392, 1365, 1249, 1185, 1062; HRMS calcd for $C_{15}H_{25}O_4$ (MH^+) 269.1747, found 269.1753.

5,5-Dicarboethoxy-3-methylene-1,7-octadiene (19a). The diester **19a** was synthesized in a similar manner to **3a** using 2-(bromomethyl)-1,3-butadiene.[16] **19a** was isolated as a clear, colorless oil (54%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.25-6.16 (m, 1H), 5.64-5.55 (m, 1H), 5.20-5.10 (m, 2H), 5.03-4.91 (m, 3H), 4.11-3.98 (m, 4H), 2.76 (s, 2H), 2.57 (d, J = 7.2 Hz, 2H), 1.15 (t, J = 6.9 Hz, 6H); ^{13}C NMR (C_6D_6, 75 MHz) δ 170.7, 142.1, 139.5, 133.5, 118.91, 118.89, 113.8, 61.1, 57.6,

37.3, 34.0, 14.0; IR (neat, cm^{-1}) 3085, 2982, 1732, 1641, 1595, 1446, 1367, 1296, 1207, 907; HRMS calcd for $C_{15}H_{23}O_4$ (MH^+) 267.1607, found 267.1596.

5,5-Dicarboethoxy-3-methylenecycloxene (19c). Cyclohexene **19c** was obtained as a clear, colorless oil (96%) under conditions analogous to the reaction producing **3b**: ^1H NMR ($CDCl_3$, 300 MHz) δ 6.11 (d, J = 9.8 Hz, 1H), 5.78-5.73 (m, 1H), 4.88 (br s, 2H), 4.19-4.08 (m, 4H), 2.82 (t, J = 1.5 Hz, 2H), 2.65-2.63 (m, 2H), 1.19 (t, J = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.0, 139.2, 129.0, 126.6, 113.6, 61.6, 54.0, 36.0, 31.1, 14.1; IR (neat, cm^{-1}) 3083, 2982, 1732, 1642, 1603, 1446, 1367, 1299, 1187, 1074, 1016; HRMS calcd for $C_{13}H_{18}O_4$ (M^+) 238.1206, found 238.1205.

***N*-Allyl-*N*-methallylbenzamide (20a).** To a solution of allyl amine (0.89 g, 15.5 mmol) in CH_2Cl_2 (50 mL) was added benzoyl chloride (2.2 g, 15.5 mmol). After 7 h, the reaction was quenched with water (30 mL) and washed with NH_4Cl (sat aq, 30 mL). After concentration, a pale yellow oil was isolated and the crude amide was used without further purification. To a suspension of NaH (0.26 g, 10.9 mmol) in DMF (35 mL) was added this *N*-allylbenzamide (1.6 g, 9.9 mmol). After stirring for 15 min, methallyl chloride (0.98 mL, 9.9 mmol) was added. Once the reaction had stirred for 2 h, it was quenched with water (50 mL) and extracted with Et_2O (3 × 30 mL). After purification on silica gel (25% EtOAc in hexanes), **20a** was obtained as a clear, colorless oil (78%): ^1H NMR ($CDCl_3$, 300 MHz, RT, not coalesced) δ 7.33-7.23 (m, 5H), 5.84-5.76, 5.64-5.55 (2m, 1H), 5.13-5.00 (m, 2H),

4.86-4.75 (m, 2H), 4.04 (s, 2H), 3.70-3.64 (m, 2H), 1.68, 1.48 (2s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, RT, not coalesced) δ 171.6, 140.3, 140.0, 136.1, 132.9, 132.6, 129.3, 128.2, 126.3, 117.4, 112.1, 53.7, 50.2, 49.0, 46.8, 19.9; IR (neat, cm^{-1}) 3648, 3496, 3082, 2977, 2918, 1634, 1578, 1495, 1293, 1263, 1152, 923; HRMS calcd for $C_{14}H_{16}NO$ (M^+) 214.1230, found 214.1232.

***N*-Benzoyl-3-methyl-3-pyrroline (20b).** Pyrroline **20b** was obtained as a clear, colorless oil (97%) under conditions analogous to the reaction producing **12b**: ^1H NMR ($CDCl_3$, 300 MHz, RT, not coalesced) δ 7.46 (br s, 2H), 7.34 (br s, 3H), 5.45, 5.29 (2s, 1H), 4.36, 4.28 (2s, 2H), 4.10, 4.02 (2s, 2H), 1.76, 1.65 (2s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, RT, not coalesced) δ 169.8, 136.8, 135.6, 134.8, 129.9, 128.4, 126.9, 119.6, 119.0, 59.1, 56.5, 56.3, 53.8, 14.34, 14.26; IR (neat, cm^{-1}) 3545, 3062, 2914, 2858, 1674, 1634, 1576, 1418, 1334, 1226, 1149, 1025, 967; HRMS calcd for $C_{12}H_{13}NO$ (M^+) 187.0997, found 187.0997.

4,4-Dicarboethoxy-2-methyl-1,8-nonadiene (6a). The diester **6a** was synthesized in a manner similar to **3a** using 1,1-dicarboethoxy-5-hexene. **6a** was isolated as a clear, colorless oil (68%): ^1H NMR ($CDCl_3$, 300 MHz) δ 5.72-5.62 (m, 1H), 4.94-4.83 (m, 2H), 4.75 (s, 1H), 4.64 (s, 1H), 4.12-4.05 (m, 4H), 2.62 (s, 2H), 1.96 (q, J = 7.1 Hz, 2H), 1.83-1.77 (m, 2H), 1.56 (s, 3H), 1.26-1.14 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.6, 140.7, 138.1, 115.4, 114.9, 61.1, 56.8, 40.1, 33.8,

31.6, 23.5, 23.2, 14.0; IR (neat, cm^{-1}) 3078, 2981, 2938, 1732, 1643, 1446, 1368, 1262, 1196, 1027; HRMS calcd for $C_{16}H_{27}O_4$ (MH^+) 283.1911, found 283.1909.

6,6-Dicarboethoxy-1-methylcycloheptene (6b). Cycloheptene **6b** was obtained as a clear, colorless oil (96%) under conditions analogous to the reaction producing **9b**: ^1H NMR ($CDCl_3$, 300 MHz) δ 5.55 (br s, 1H), 4.14 (q, J = 7.5 Hz, 4H), 2.61 (s, 2H), 2.18-2.14 (m, 2H), 2.04-2.00 (m, 2H), 1.72 (s, 3H), 1.61-1.58 (m, 2H), 1.21 (t, J = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.0, 135.2, 127.7, 61.2, 55.7, 37.6, 36.9, 28.0, 26.8, 22.9, 14.2; IR (neat, cm^{-1}) 2937, 2862, 1732, 1446, 1367, 1311, 1224, 1033, 857; HRMS calcd for $C_{14}H_{23}O_4$ (MH^+) 255.1601, found 255.1596.

2-Bromo-4,4-dicarboethoxy-1,6-heptadiene (18a). The diester **18a** was synthesized in a manner similar to **3a** using 2,3-dibromopropene. **18a** was obtained as a clear, colorless oil (96%): ^1H NMR ($CDCl_3$, 300 MHz) δ 5.61-5.50 (m, 3H), 5.04-5.01 (m, 2H), 4.15-4.07 (m, 4H), 3.05 (s, 2H), 2.67 (d, J = 7.4Hz, 2H), 1.17 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.9, 132.1, 127.2, 122.0, 119.5, 61.5, 56.7, 42.8, 35.9, 14.0; IR (neat, cm^{-1}) 3081, 2983, 2938, 1732, 1641, 1626, 1445, 1367, 1287, 1218, 1149, 1041; HRMS calcd for $C_{13}H_{20}O_4Br$ (M^+) 319.0545, found 319.0545.

Methallyl (1-phenylallyl) ether (21a). To a solution of benzaldehyde (1.6 g, 14.9 mmol) in THF (100 mL) at 0°C was added vinylmagnesium bromide (1M in

THF, 15 mL). After 3 h, the reaction was quenched with water (100 mL) and extracted with Et_2O (3 × 75 mL). After concentration, a pale yellow oil was isolated and the crude alcohol was used without further purification. To a suspension of NaH (0.22 g, 9.10 mmol) in DMF (25 mL) was added this 1-phenyl-2-propen-1-ol (1.11 g, 8.27 mmol). After this mixture had stirred for 15 min, methallyl chloride (0.90 mL, 9.10 mmol) was added. After stirring for 2 h at room temperature, the reaction was quenched with water (25 mL) and extracted with Et_2O (3 × 30 mL). After purification on silica gel (25% toluene in hexanes), **21a** was obtained as a clear, colorless oil (21%, 2 steps): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36-7.28 (m, 5H), 6.00-5.89 (m, 1H), 5.31-5.18 (m, 2H), 4.99 (s, 1H), 4.90 (s, 1H), 4.77 (d, J = 6.6Hz, 1H), 3.89 (s, 2H), 1.75 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.4, 141.3, 139.1, 128.6, 127.7, 127.0, 116.2, 112.2, 81.9, 72.2, 19.8; IR (neat, cm^{-1}) 3078, 3030, 2977, 2918, 2856, 1657, 1452, 1092, 1070, 991, 925, 900, 701; HRMS calcd for $C_{13}H_{16}O$ (M^+) 188.1202, found 188.1201.

4-Methyl-2-phenyl-2,5-dihydrofuran (21b). Dihydrofuran **21b** was obtained as a clear, colorless oil (98%) under conditions analogous to the reaction producing **21b**:[39] ^{1}H NMR (C_6D_6, 300 MHz) δ 7.27-7.24 (m, 2H), 7.17-7.03 (m, 3H), 5.76-5.74 (m, 1H), 5.16-5.14 (m, 1H), 4.49-4.41 (m, 2H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.8, 136.6, 128.6, 127.8, 126.5, 124.2, 88.6, 78.6, 12.4; IR (neat, cm^{-1}) 3064, 3030, 2837, 2630, 1668, 1491, 1453, 1258, 1061, 970, 760, 699; HRMS calcd for $C_{11}H_{11}O$ (M-H^+) 159.0806, found 159.0810.

References:

† Portions of this chapter have been published as: Kirkland, T. A.; Grubbs R. H. *J. Org. Chem.* **1997**, *62*, 7310-7318.

[1] For some reviews of RCM, see: a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413-4450. b) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371-388. c) Schuster, M.; Blechert, S. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2036-2056. d) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446-452.

[2] Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792-803.

[3] Schwab, P. E.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100-110.

[4] Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875-3886.

[5] a) Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 127-130. b) Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 123-126. c) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 3942-3943. d) Kim, S.-H.; Zuercher, W. J.; Grubbs, R. H. *J. Org. Chem.* **1996**, *61*, 1073-1081. e) Hölder, S.; Blechert, S. *Synlett* **1996**, 505-506. f) Maier, M. E.; Langenbacher, D.; Rebien, F. *Liebigs. Ann.* **1995**, 1843-1848. g) Houri, A. F.; Xu, Z.; Cogan, D.; Hoyveda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 2943-2944. h) Kim, S.-H.; Bowden, N.; Grubbs, R. H. *J. Am. Chem. Soc.* **1994**, *116*, 10801-10802. i) Fujimura, O.; Fu, G. C.; Grubbs, R. H. *J. Org. Chem.* **1994**, *59*, 4029-4031. j) Kinoshita, A.; Miwako, M. *Synlett.* **1994**, 1020-1022. k) Fu, G. C.; Grubbs, R. H. *J. Am.*

Chem. Soc. **1992**, *114,* 5426-5427. l) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114,* 7324-7325.

[6] Some examples have been reported after the completion of this work: a) Bujard, M.; Gouverneur, V.; Mioskowski, C. *J. Org. Chem.* **1999**, *64*, 2119-2123. b) Clark, J. S.; Kettle, J. G. *Tetrahedron* **1999**, *55*, 8231-8248. c) Burke, S. D.; Quinn, K. J.; Chen, V. J. *J. Org. Chem.* **1998**, *63*, 8626-8627. d) Renaud, J.; Ouellet, S. G. *J. Am. Chem. Soc.* **1998**, *120*, 7995-7996. e) Hanson, P. R.; Stoianova, D. S. *Tetrahedron Lett.* **1998**, *39*, 3939-3942. f) Alexander, J. B.; La, D. S.; Cefalo, D. R.; Hoyveda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 4041-4042. g) Miller, J. F.; Termin, A.; Koch, K.; Piscopio, A. D. *J. Org. Chem.* **1998**, *63*, 3158-3159.

[7] Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38,* 123-126.

[8] Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115,* 9856-9857.

[9] a) Katz, T. J.; Sivavec, T. M. *J. Am. Chem. Soc.* **1985**, *107,* 737-738. b) Kinoshita, A.; Mori, M. *J. Org. Chem.* **1996**, *61,* 8356-8357.

[10] Doran, W. J.; Shonle, H. A. *J. Am. Chem. Soc.* **1937**, *59,* 1625-1626.

[11] Bhanot, O. S.; Dutta, P. C. *J. Chem. Soc. (C)* **1968**, 2583-2588.

[12] a) Borg, R. M.; Heuckeroth, R. O.; Lan, A. J. Y.; Quillen, S. L.; Mariano, P. S. *J. Am. Chem. Soc.* **1987**, *109,* 2728-2737. b) Takano, S.; Hirama, M.; Araki, T.; Ogasawara, K. *J. Am. Chem. Soc.* **1976**, *98,* 7084-7085.

[13] Barton, D. H. R.; Shioiri, T.; Widdowson, D. A. *J. Chem. Soc. (C)* **1971**, 1968-1974.

[14] White, W. N.; Norcross, B. E. *J. Am. Chem. Soc.* **1961**, *83,* 3265-3269.

[15] Reed, S. F. *J. Org. Chem.* **1965**, *30,* 3258.

[16] a) Frank, R. L.; Seven, R. P. *Org. Syntheses Coll. Vol. 3* **1955**, *3,* 499-500. b) Thomas, A. F. *J. Am. Chem. Soc.* **1969**, *91,* 3281-3289. c) Krug, R. C.; Yen, T. F. *J. Org. Chem.* **1956**, *21,* 1082-1084.

[17] CH_2Cl_2 was chosen as the optimal solvent for reactions with **1** based on slightly lower yields obtained in other solvents employed (C_6H_6, $CHCl_3$). C_6H_6 was used as the solvent for reactions with **2** based on previous work done in this laboratory.[5k,5l]

[18] Tentative assignment of the species which did not correspond to the desired product in the reaction mixture as dimeric was done through ^1H NMR.

[19] a) Zuercher, W. J.; Hashimoto, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118,* 6634-6640. b) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118,* 9606-9614.

[20] The methylidene ($L_nM=CH_2$) is the active catalytic species in RCM of dienes which contain only mono- and *gem*-disubstituted olefins. It is formed through reaction of the starting alkylidene with one molecule of substrate. After this, the methylidene is the propagating species for the remainder of the catalytic cycles.

[21] Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, In Press.

[22] a) Hammer, K.; Undheim, K. *Tetrahedron* **1997**, *53,* 2309-2322. b) Rutjes, F. P. J. T.; Shoemaker, H. E. *Tetrahedron Lett.* **1997**, *38,* 677-680.

[23] a) Forbes, M. D. E.; Patton, J. T.; Myers, T. L.; Maynard, H. D.; Smith, D. W.; Schulz, G. R.; Wagener, K. B. *J. Am. Chem. Soc.* **1992**, *114,* 10978-10980. b)

Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113,* 224-232, and references contained therein.

[24] Miller, S. J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117,* 2108-2109.

[25] Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14,* 95-102.

[26] Overkleeft, H. S.; Pandit, U. K. *Tetrahedron Lett.* **1996**, *37,* 547-550.

[27] Kim, S-H. Unpublished results.

[28] The product of the metathesis of **19a** was determined not to be **19b** through comparison to the spectral data of **19b** as reported.[29]

[29] Chatani, N.; Morimoto, T.; Muto, T.; Murai, S. *J. Am. Chem. Soc.* **1994**, *116,* 6049-6050.

[30] Although the mechanism presented explains the formation of **19c** (Scheme 4), there are two other obvious means by which **19c** could be formed from **19a**. If the alkylidene initiates at the conjugated terminal olefin, the only possible RCM product is **19c**. Additionally, it is possible that cyclopentene **19b** is formed initially and undergoes subsequent reaction to produce the thermodynamically more stable cyclohexene **19c**. However, in NMR experiments formation of **19b** is not observed.

[31] Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115,* 3800-3801.

[32] Reaction of alkylidene **1** with isobutylene does occur, though only under forcing conditions and the reaction does not go to completion, preventing isolation of the alkylidene.

[33] Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247-2250.

[34] Weskamp, T.; Schattenmann, W. C.; Spiegler, M.; Herrmann, W. A. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 2490-2493.

[35] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43,* 2923.

[36] Schweizer, E. E.; O'Neill, G. J. *J. Org. Chem.* **1965**, *30,* 2082-2083.

[37] Yamakazi, T.; Kasatkin, A.; Kawanaka, Y.; Sato, F. *J. Org. Chem.* **1996**, *61,* 2266-2267.

[38] Grigg, R.; Mitchell, T. R. B.; Ramasubbu, A. *J. Chem. Soc., Chem. Commun.* **1980**, 27-28.

[39] Kunishima, M.; Hioki, K.; Tani, S.; Kato, A. *Tetrahedron Lett.* **1994**, *35,* 7253-7254.

Chapter 2:

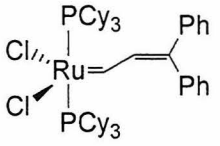
Investigations into Enyne and Endiyne Metathesis

Abstract:

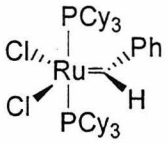
The cyclization of enyne and endiyne substrates using ruthenium alkylidenes is presented. Five- and six-membered cyclics were synthesized quantitatively, while a seven-membered cyclic was only formed in moderate conversion. Methyl substitution is tolerated on the acetylene and vicinally on the olefin, but not geminally on the olefin. This suggests a mechanism in which the alkylidene reacts with the olefin first, followed by an intramolecular reaction with the acetylene on an enyne substrate. Endiyne substrates were cyclized to provide biscyclopentenes, but attempts to cyclize homologues of these substrates met with failure.

Introduction:

Group VI Fischer carbenes were the first reagents demonstrated to react with enynes to give a metathesis type product.[1] Later, it was discovered that certain "unstabilized" Group VI alkylidenes will metathesize acetylenes catalytically. Extremely reactive alkylidenes will polymerize acetylenes,[2] and certain specialized alkylidenes have been developed for this purpose.[3] Other Group VI alkylidenes do not perform acetylene metathesis.[4] However, all of the Group VI alkylidenes proved to be poor at catalyzing enyne metathesis.[4]

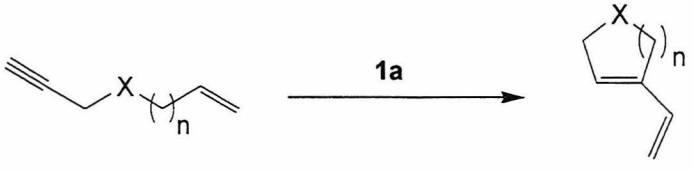


1a

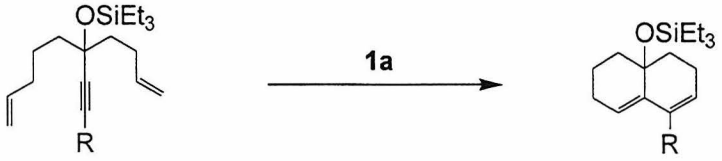


1b

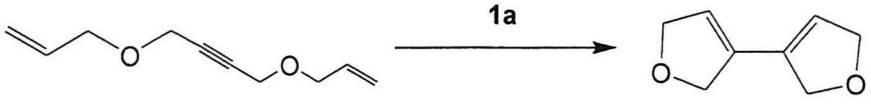
Well-defined ruthenium alkylidenes **1a**[5] and **1b**,[6] on the other hand, have been demonstrated to cyclize enynes in high yield (Eq. 1).[7] This methodology has been extended through the use of the acetylene as a tether in order to effect two tandem cyclizations.[4,8] Depending on the connectivity of the olefins and the



(1)



(2)

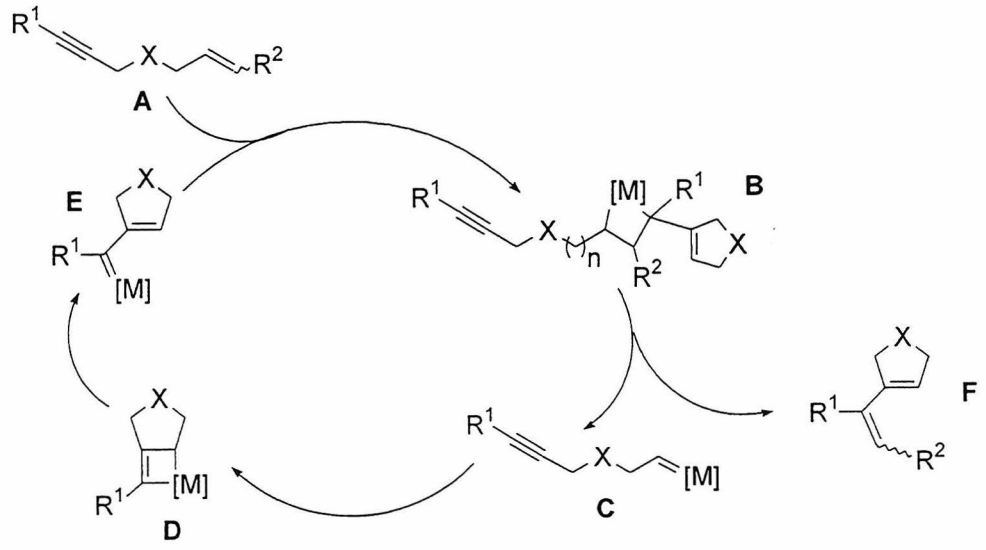


(3)

acetylene, this technique, called dienyne metathesis, could synthesize two separate or fused cyclics from an acyclic precursor (Eqs. 2 and 3). Extension of this methodology has allowed the cyclization of three or four fused rings in one step from an appropriately substituted acyclic precursor.[9]

The mechanism of enyne metathesis is quite similar to the Ring-Closing Metathesis (RCM) of dienes.[10] However, in enyne metathesis the alkylidene is transferred from one substrate to another (Scheme 1, **B** to **C**). For this reason, the concentration at which these reactions are run is critical. If the concentration is too low, the rate of the intermolecular alkylidene transfer is slow and alkylidene decomposition can occur. However, at high concentrations the intermediate alkylidene **C** can dimerize, especially when the rate of cyclization is slow due to substitution or increased ring size, as detailed in Chapter 1.[11] An atmosphere of ethylene over the reaction mixture has been shown to alleviate this problem in some cases.[12] This allows alkylidene **E** to react with ethylene, forming the ruthenium

Scheme 1:

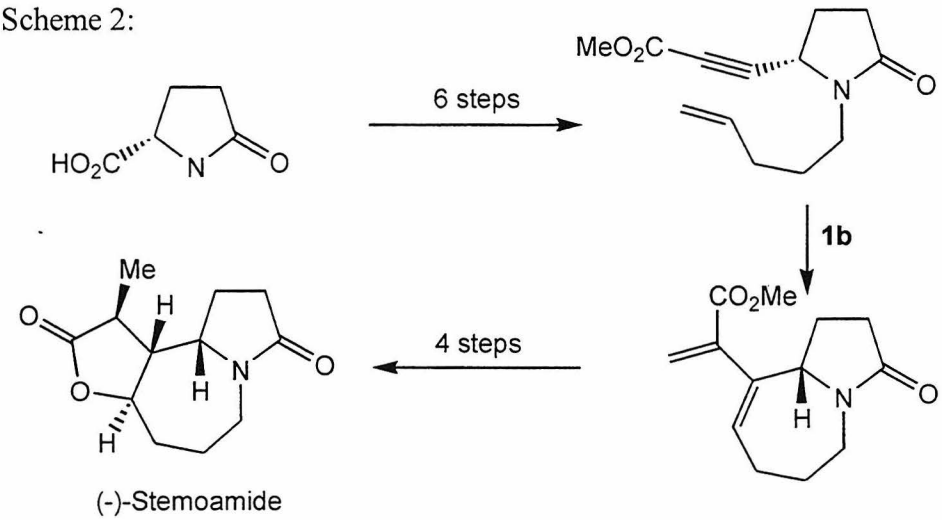


methylidene and diene **F** (Scheme 1). The methylidene can then react with another molecule of **A** to form **C** directly.

The field of enyne metathesis did not expand quickly following these initial reports. However, several applications of enyne metathesis to organic synthesis have been published recently.[13] For example, this methodology was a key step in the total synthesis of (-)-stemoamide, which is outlined in Scheme 2.[14] This synthesis also takes advantage of the versatile diene which is obtained as the product of enyne metathesis reactions. Another common method of elaborating the products of enyne metathesis is through a Diels-Alder reaction.[15]

The recent interest in enyne metathesis has prompted an examination of the scope of enyne metathesis catalyzed by alkylidenes **1a** and **1b**. The research outlined below contains an investigation into the effect of ring-size and substrate substitution on enyne metathesis, as well as a discussion of the mechanism of this transformation. In addition, initial investigations into endiyne metathesis are presented.

Scheme 2:

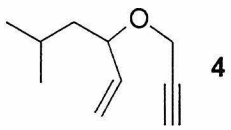


(-)-Stemoamide

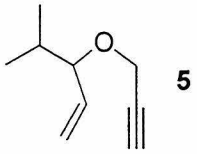
Results and Discussion:

Enyne Metathesis:

The simple enyne **2a** was the first substrate examined for this study (Table 1). Alkylidenes **1a** and **1b** were both effective in converting it to diene **2b**. The synthesis of heterocycles was demonstrated through the quantitative conversion of protected amine **3a** to **3b**, and other reported studies have also shown the versatility of this technique.[13] The synthesis of furan derivatives has also been demonstrated through the quantitative cyclization of isobutyl substituted substrate **4.**[16] The isopropyl substituted substrate **5** failed to cyclize under identical conditions, which can be attributed to the increased steric demand in substrate **5**. The quantitative synthesis of two isomeric cyclohexenes was demonstrated through the cyclization of substrates **6a** and **7a**.



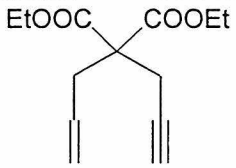
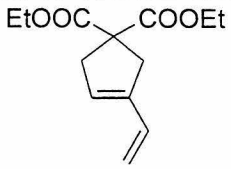
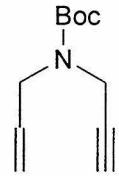
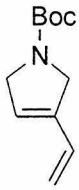
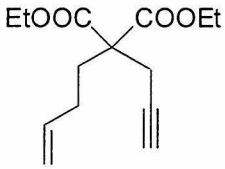
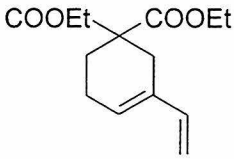
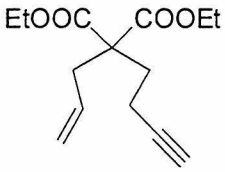
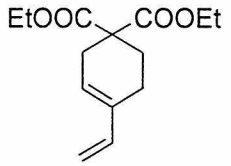
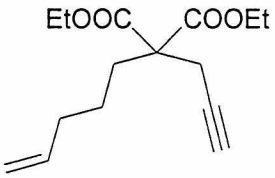
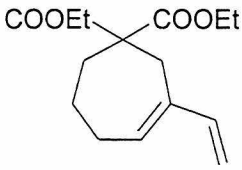
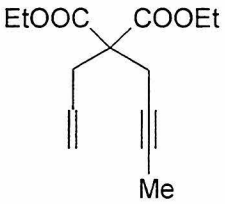
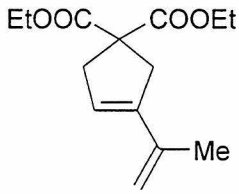
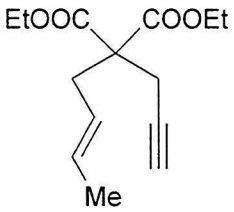
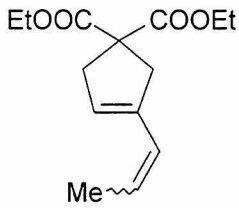
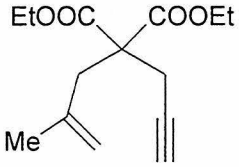
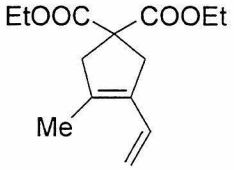
4



5

The cyclization of **8a** was considerably lower yielding, and quite dependent upon temperature, solvent and concentration.[17] For this reason, optimization of conditions for enyne metathesis was done for this substrate. As described in the experimental section, performing the reaction under dilute conditions (0.01M) and room temperature was critical for the obtained conversion (Table 1). When this reaction was run in CH_2Cl_2 or $CHCl_3$ equivalent conversions were obtained, but running the reaction in C_6H_6 gave reduced conversions (<20%). Based on the

Table 1:

Substrate		Product		Conversion[a]
	**2a**		**2b**	>95%
	**3a**		**3b**	>95%
	**6a**		**6b**	>95%
	**7a**		**7b**	>95%
	**8a**		**8b**	60%
	**9a**		**9b**	>95%
	**10a**		**10b**	>95%
	**11a**		**11b**	No Reaction

[a]The conversions were measured using ^{1}H NMR.

disappointing conversion of substrate **8a** and previous difficulty encountered in synthesizing eight-membered rings through RCM,[18] the synthesis of an eight-membered cyclic diene through enyne metathesis was not attempted.

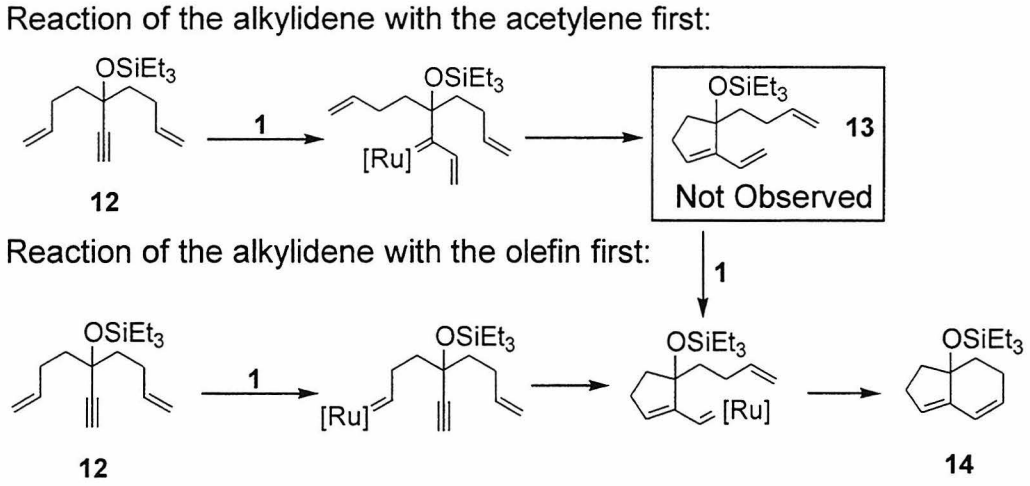
The effects of methyl substitution were examined through the RCM of substrates **9a**, **10a** and **11a**. The RCM of substrate **9a** proceeded quantitatively to give cyclopentene **9b** (Table 1). Alkyl substitution is generally tolerated on the acetylene, and has been shown to improve the yields for the RCM of some classes of enynes.[19] However, the presence of a sterically demanding or heteroatomic substituent prevents enyne metathesis.[4]

The RCM of enyne **10a**, which contains an internal olefin, proceeds quantitatively to give **10b**. The methyl group migration occurs as shown for substituent R^2 in Scheme 1. The reaction of alkylidene **E** with substrate **A** transfers the substituent to the product **F**. This transfer will not occur in enyne metathesis reactions performed under an atmosphere of ethylene, however.[12] In the RCM of dienes containing an analogously substituted olefin, which is discussed in Chapter 3, the methyl group would be eliminated as propene instead of appearing in the final product. The enyne metathesis of substrates substituted in the manner of **9a** and **10a** is an effective method for the synthesis of highly substituted cyclic dienes.

On the other hand, with substrates containing a *gem*-disubstituted olefin (**11a**) no reaction occurs. In Chapter 1, it was demonstrated that alkylidene **1b** is quite unreactive with *gem*-disubstituted olefins when the reaction is intermolecular. The lack of reaction with **11a** therefore indicates that the alkylidene reacts with the olefin first, followed by reaction with the acetylene. Additional evidence for this proposed mechanism comes from dienyne metathesis (Scheme 3).[4,8] As an example, if in the

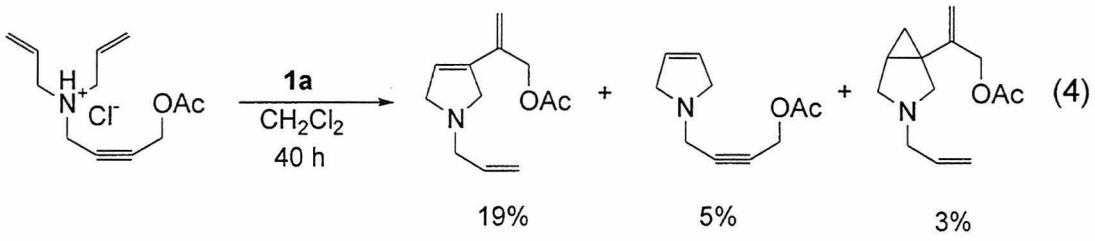
RCM of substrate **12** the alkylidene reacted with the acetylene faster than the olefin, there should be an observable concentration of intermediate **13**. Intermediate **13** would then undergo RCM to give the observed product **14** at a slower rate. In all of the reactions performed of this type, no intermediates of the structure **13** have been observed. The general rate decrease observed when comparing the RCM of dienes to the RCM of enynes also supports the mechanism proposed here.

Scheme 3:



However, reports have appeared supporting the mechanism in which alkylidene **1b** reacts with acetylenes before reacting with olefins in certain substrates. The first piece of evidence for this claim is shown in Equation 4, where the major product of this reaction is the triene resulting from enyne metathesis.[7] Alkylidene **1a** is unstable in the presence of amine hydrochlorides over the length of this reaction, and this is indicated through the poor combined yield. The presence of cyclopropanated product attests to the fact that other active ruthenium species are present in this reaction as well.[20] Furthermore, ruthenium salts have been shown to

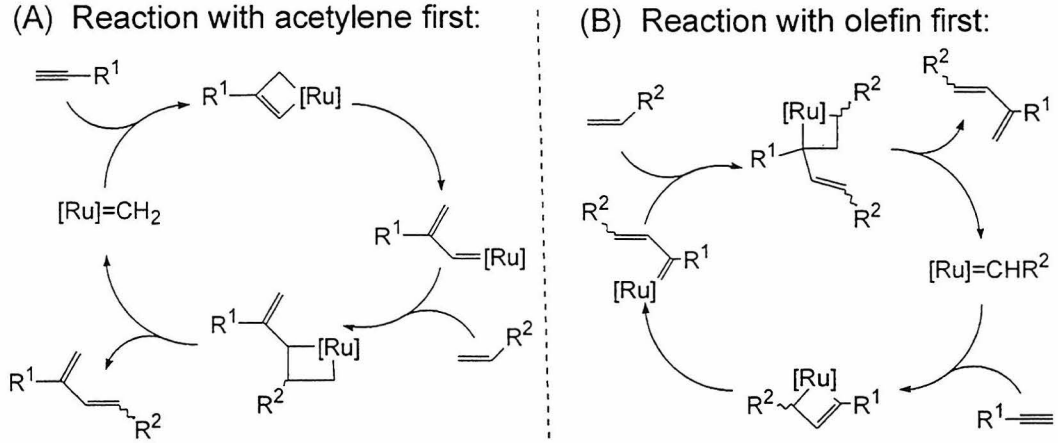
catalyze the cyclization of enynes and not dienes.[21] In addition, the final product distribution does not indicate the kinetic product, only the thermodynamic product. For example, diene cyclization could be occurring faster than enyne cyclization, followed by subsequent opening of the cyclopentene in the minor product to give the major product, and this trisubstituted cyclic olefin is then inactive under the reaction conditions.



(4)

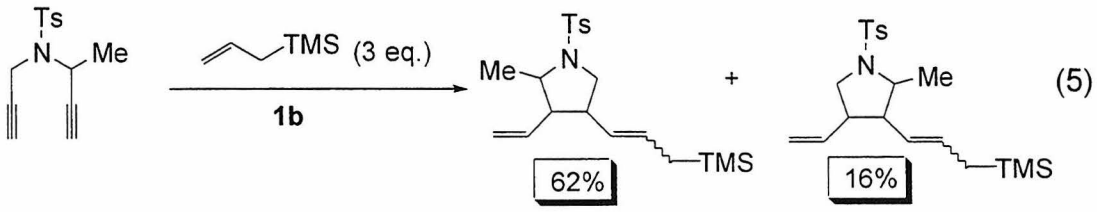
In a separate publication, it has been claimed that olefin metathesis may be faster than acetylene metathesis for intramolecular metathesis, but that alkylidene **1b** reacts with terminal acetylenes faster than terminal olefins during a cross metathesis reaction (Scheme 4A).[22] Unfortunately, little experimental evidence is given to support this claim. In addition, qualitative measurements of the rate of reaction of

Scheme 4:



alkylidene **1b** with 1-hexene and 1-hexyne showed that reaction with the terminal olefin was significantly faster.[23] All of the reactivity patterns reported can also be explained by assuming that **1b** reacts with the terminal olefin first to give an appropriately substituted alkylidene (Scheme 4B). This substituted alkylidene is the propagating species for the cross metathesis instead of the methylidene, giving the same product.

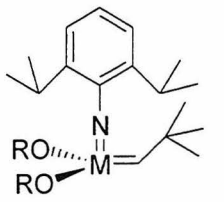
In fact, strong additional evidence that alkylidene **1b** initially reacts with olefins comes from a subsequent report by the same authors (Eq. 5).[24] In this reaction, an unsymmetrical diyne is cyclized and this divinylcyclopentene undergoes cross metathesis with a terminal olefin. The proposed mechanism for this transformation is an extension of the methodology shown in Scheme 4A. In the mechanism proposed by the authors, the methylidene adds into one acetylene of the diyne and then cyclizes the diyne through an intramolecular reaction with the tethered acetylene. The resultant alkylidene would then react with the terminal olefin to generate the observed product and regenerate the methylidene. However, because the steric bulk of the methyl group is the cause of the selectivity observed for this substrate (Eq. 5), the free alkylidene clearly reacts with the olefin first to generate a substituted alkylidene (Scheme 4B). Because either alkylidene will preferentially react with the acetylene possessing the least steric hindrance, the formation of the



(5)

major product can only be explained through reaction of the silylated alkylidene with the diyne.[25] Based on the accumulated evidence presented here, ruthenium alkylidenes will react with olefins preferentially in the presence of acetylenes.

The failure of alkylidene **1a** to cyclize substrate **11a** led to an examination of the more active Group VI alkylidenes **15** and **16**. Because the molybdenum alkylidene **15**[26] was shown to be significantly more reactive with substituted olefins than alkylidene **1b**, it was thought that it might cyclize substrate **11a**. However, none of the desired product was observed, and the alkylidene quickly decomposed. This surprising result was confirmed through reaction with several other substrates in Table 1, all of them causing complete decomposition of the molybdenum alkylidene. The related tungsten alkylidene **16**[27] also proved to be ineffective in cyclizing these simple enynes, though it was considerably more stable in their presence. The inability of these alkylidenes to cyclize simple enynes was unexpected in light of their activity towards acetylenes in other substrates, and no suitable explanation has been proposed.



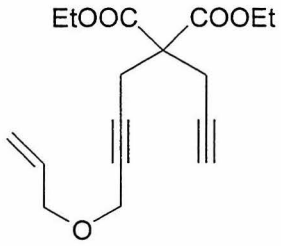
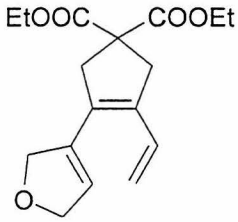
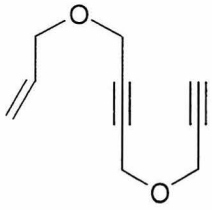
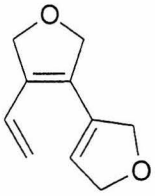
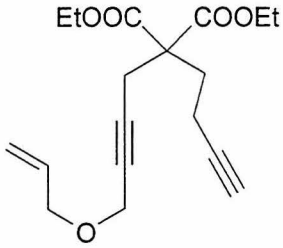
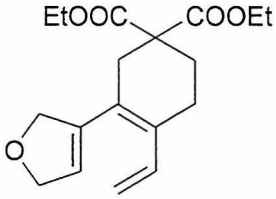
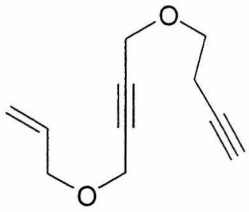
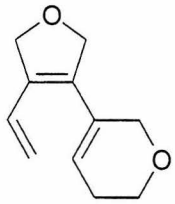
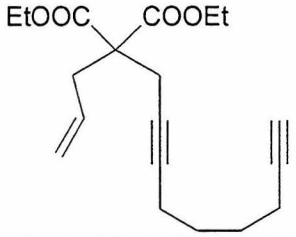
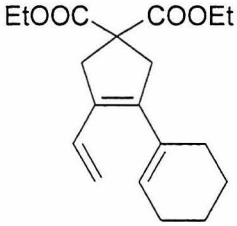
R = $CCH_3(CF_3)_2$

15 M = Mo
16 M = W

Endiyne Metathesis:

Having established the effectiveness of alkylidenes **1a** and **1b** for the RCM of enynes, the RCM of endiynes was examined (Table 2). This tandem cyclization was expected to be analogous to the previously reported dienyne cyclizations,[4,9] and

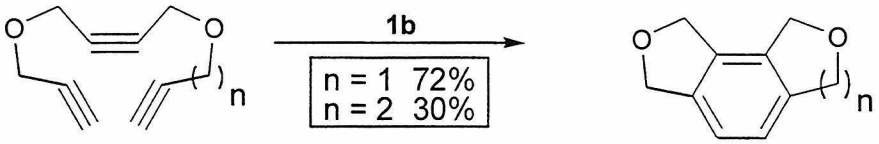
Table 2:

Substrate		Product		Conversion[a]
	**17a**		**17b**	>95%
	**18a**		**18b**	>95%
	**19a**		**19b**	No Reaction
	**20a**		**20b**	No Reaction
	**21a**		**21b**	No Reaction

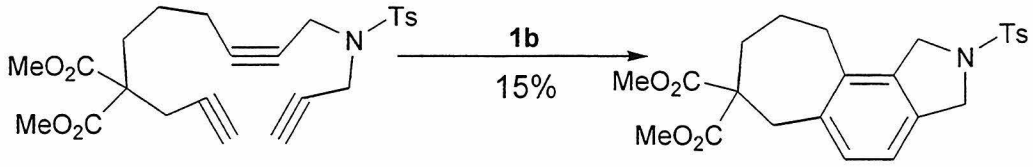
[a]The conversions were measured using ^{1}H NMR.

indeed cyclization of substrates **17a** and **18a** to give biscyclopentenes **17b** and **18b** proceeded quantitatively.

However, all attempts to extend this methodology to the synthesis of cyclohexenes met with failure. Exposure of substrates **19a**, **20a** or **21a** to alkylidene **1b** under a variety of conditions resulted in either no reaction or decomposition. The reasons for this drastic change in reactivity are still unclear. However, a recent report describing the cyclization of triynes to fused aromatics using alkylidene **1b** showed a similar reactivity pattern.[28] The construction of 5,6,5-tricyclics proceeded in good yields, but the yields dropped significantly for the construction of 5,6,6-tricyclics (Eq. 6). The synthesis of a 5,6,7-tricyclic through this method proceeded in only 15% yield (Eq. 7). The higher driving force for the formation of an aromatic ring may permit the formation of these higher analog compounds, albeit in low yield, when they do not form at all with the endiyne systems examined.



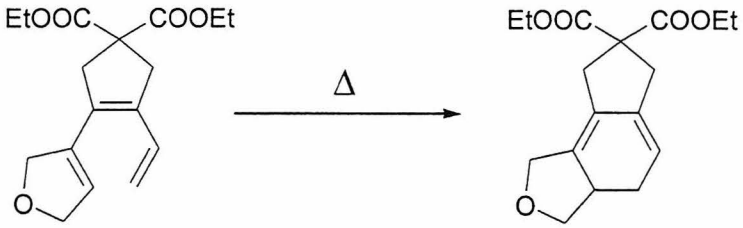
(6)



(7)

Following the isolation of triene **17b**, it was heated in an attempt to cause it to undergo an electrocyclic rearrangement to the fused tricyclic **17c** (Eq. 8). As **17b** decomposes upon sitting, it was hoped that this would improve the stability of the

compound. Heating to 140°C caused **17b** to be converted to a new compound, but analysis of this compound showed that it was not **17c**, and the identity of the compound was not determined. Compound **18b** was also converted to an unknown compound instead of the desired tricyclic **18c** upon heating. It is unclear why the desired product was not isolated in these cases, but it is likely that these cyclohexadienes are unstable.



17b **17c** (8)

Conclusions:

The synthesis of several enynes enabled the investigation of many of the factors which influence their cyclization with alkylidenes **1a** and **1b**. Five- and six-membered cyclics are formed in high yields through this methodology, but cyclization to give vinyl cycloheptenes only proceeds to moderate conversion. Methyl substitution is also tolerated on the acetylene and vicinally on the olefin, but substrates containing *gem*-disubstituted olefins were not cyclized. This result was taken as strong evidence that alkylidenes **1a** and **1b** react with the olefin preferentially over the acetylene. Finally, several endiynes were synthesized and exposed to **1b**. Biscyclopentenes were formed in quantitative yield, but cyclization to give higher homologues was not observed.

Although enyne metathesis is significantly less developed than diene RCM, its usefulness has already been demonstrated for the synthesis of natural products and compound libraries. In addition, the products of enyne metathesis are cyclic dienes, which are valuable synthetic intermediates. The elaboration of these through Diels-Alder reactions and electrocyclic rearrangements is expected to allow the synthesis of complex ring systems from simple enynes. The reactivity profiles described in this chapter are expected to assist in the development of enyne metathesis.

Acknowledgements:

First and foremost, Dr. Soong-Hoon Kim is gratefully acknowledged for starting this project and providing enormous intellectual and technical assistance throughout. In addition, he is acknowledged for the synthesis of substrates **3a-11a**, **17a**, **19a** and **21a**, as well as performing many of the initial RCM experiments. Gordon Kwan is also gratefully acknowledged for technical assistance in performing many of the substrate syntheses as well as the RCM reactions. This research was generously funded by a grant from the NIH.

Experimental Section:

General. NMR spectra were recorded on either a General Electric QE-300 (300.1 MHz ^{1}H; 75.49 MHz ^{13}C) or a Jeol GX-400 (399.65 MHz ^{1}H; 100 MHz ^{13}C) spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane with reference to internal solvent. In cases where more than one rotamer is observed, both rotamers are reported. Infrared spectra were obtained on a Perkin-Elmer Paragon 1000 FT-IR. High-resolution mass spectra were provided

by either the Chemistry and Biology Mass Spectrometry Facility (Caltech). Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Flash column chromatography was performed using silica gel 60 (230-400 mesh) from EM Science.[29] Alkylidene **1**,[6] substrates **2a**,[30] **3a**,[31] **6a**,[32] **9a**,[30] **10a**,[30] **11a**,[21] **18a**[33] and products **2b**,[21] **6b**,[32] **9b**,[21] and **10b**[32] have been previously prepared and reported.

4,4-Dicarboethoxyoct-1-en-7-yne (7a). Diethyl but-3-ynylmalonate (0.73 g, 3.49 mmol) was added to a suspension of sodium methoxide (0.20 g, 3.84 mmol) in dimethyl formamide (25 mL). After the cloudiness disappeared, allyl bromide (0.46g, 3.84 mmol) was added and the reaction was allowed to stir overnight. It was then quenched with water (30 mL), extracted with Et_2O (3 × 30 mL) and purified over silica gel (10% EtOAc in hexanes) to afford **7a** as a colorless oil (71%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.69-5.57 (m, 1H), 5.15-5.09 (m, 2H), 4.22-4.13 (m, 4H), 2.66 (d, J = 7.4 Hz, 2H), 2.17 (br s, 4H), 1.96 (s, 1H), 1.25 (t, J = 6.7 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.6, 132.0, 119.3, 83.1, 69.0, 68.4, 61.4, 56.7; 37.0, 31.2, 14.0; IR (neat, cm^{-1}) 3292, 3081, 2983, 2361, 2121, 1732, 1642, 1447, 1368, 925, 860, 649.

4,4-Dicarboethoxy-1-vinylcyclohexene (7b). Enyne **7a** (10 mg, 0.040 mmol) was added to a solution of alkylidene **1b** (1.6 mg, 1.9 μmol) in $CDCl_3$ (4 mL), and the reaction was allowed to proceed overnight. Analysis of the ^{1}H NMR showed that starting material had disappeared and a new set of peaks had grown in which were

assigned as **7b** (>95% conversion): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.4-6.3 (m, 1H), 5.7 (br s, 1H), 5.1-4.8 (m, 2H), 4.3-4.1 (m, 4H), 2.6 (s, 2H), 2.2-2.1 (m, 4H), 1.3-1.2 (m, 6H).

6,6-Dicarboethoxynon-1-en-8-yne (8a). Diester **8a** was synthesized in a manner similar to **7a** from 1,1-dicarboethoxy-5-hexene and propargyl bromide. It was obtained as a clear, colorless oil: ^{1}H NMR (C_6D_6, 300 MHz) δ 5.74-5.61 (m, 1H), 4.98-4.90 (m, 2H), 3.94 (q, J = 7.0 Hz, 4H), 3.04 (s, 2H), 2.40-2.32 (m, 2H), 1.97-1.91 (m, 2H), 1.70 (t, J = 2.7 Hz, 1H), 1.41-1.31 (m, 2H), 0.87 (t, J = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.2, 137.9, 115.0, 78.9, 71.2, 61.6, 56.6, 33.7, 31.2, 23.2, 22.6, 14.0; IR (neat, cm^{-1}) 3287, 3079, 2982, 2939, 2869, 1732, 1642, 1446, 1368, 941, 859, 647; HRMS calcd for $C_{15}H_{23}O_4$ (MH^+) 267.1608, found 267.1596.

4,4-Dicarboethoxy-2-vinylcycloheptene (8b). Diester **8a** (10.0 mg, 0.035 mmol) was added to a solution of alkylidene **1b** (2.9 mg, 3.5 μmol) in $CDCl_3$ (4 mL) and the reaction was left overnight. Analysis of the reaction by ^{1}H NMR showed that new peaks had grown in consistent with the desired product, but starting material remained. Integration of the peaks at 2.8 ppm (SM) and 2.9 ppm (product) showed that the conversion was 60%. Many other conditions for this cyclization were examined, and these proved optimal.

N-*tert*-butyl carbamyl-3-vinyl-3-pyrroline (3b). Enyne **3a** (30 mg, 0.15 mmol) was added to a solution of alkylidene **1b** (7.0 mg, 7.5 μmol) in C_6D_6 (0.75 mL), and

this reaction was heated to 65°C. Analysis of the ^{1}H NMR showed that starting material had disappeared and a new set of peaks had grown in which were assigned as **3b** (>95% conversion): ^{1}H NMR (C_6D_6, 300 MHz) δ 6.20-6.10 (m, 1H), 5.09 (s, 1H), 4.84 (d, J = 10.8 Hz, 1H), 4.76-4.68 (m, 1H), 4.28-3.89 (m, not coalesced, 4H), 1.49 (s, 9H).

5,5-Dicarboethoxyoct-2,7-diyn-1-ol, allyl ether (17a). Diester **17a** was synthesized in an analogous manner to **7a** from diethyl propargylmalonate and 4-iodo-2-butynylallylether. Endiyne **17a** was isolated as a clear, colorless oil (37%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.97-5.82 (m, 1H), 5.33-5.19 (m, 2H), 4.23 (q, J = 7.3 Hz, 4H), 4.08-4.06 (m, 2H), 4.03-4.00 (m, 2H), 3.06-2.98 (m, 4H), 2.03-2.01 (m, 1H), 1.27 (t, J = 7.2 Hz, 6H).

4,4-Dicarboethoxy-1-[2,5-dihydrofuranyl]-2-vinylcyclopentene (17b). Endiyne **17a** (30 mg, 0.10 mmol) was added to a solution of alkylidene **1b** (4.6 mg, 5.0 μmol) in $CDCl_3$ (0.5 mL) and the reaction was allowed to sit for 1.5 h. Although analysis of the ^{1}H NMR showed >95% conversion to the desired product, after purification on silica gel (30% Et_2O in petroleum ether) **17b** was isolated as a white solid in only 70% yield. This compound was found to be unstable as a solid, and was used quickly in benzene solution in subsequent reactions. Preliminary characteristics are as follows: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.42-6.33 (m, 1H), 5.32 (s, 1H), 5.02 (d, J = 18 Hz, 1H), 4.91 (d, J = 7 Hz, 1H), 4.83-4.77 (m, 2H), 4.41 (s, 2H), 3.95 (q, J = 8

Hz, 4H), 3.46 (d, J = 10 Hz, 2H), 1.24 (t, J = 7 Hz, 6H); GC/MS analysis gave a total mass peak of 306, corresponding to the desired product.

1-[2,5-Dihydrofuranyl]-2-vinyl-2,5-dihyrdofuran (18b). Endiyne **18a** (99 mg, 0.60 mmol) was added to a solution of alkylidene **1b** (25 mg, 0.030 mmol) in C_6H_6 (60 mL), and the reaction was heated to 45°C. After 14 h the solvent was removed and the brown solid was purified over silica gel (10% EtOAc in hexanes) to give a white solid (68%). This material is unstable in the solid state, and analysis of an NMR reaction showed quantitative formation of triene **18b**. Preliminary characteristics of **18b** are as follows: ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 6.51 (dd, J = 17.4 Hz, 11.0 Hz, 1H), 5.76 (s, 1H), 5.23 (d, J = 10.8 Hz, 1H), 5.04 (d, J = 17.3 Hz, 1H), 4.93-4.80 (m, 6H), 4.66 (s, 2H); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 133.7, 132.6, 128.3, 125.9, 117.7, 77.8, 76.7, 75.5, 75.4; IR (neat, cm^{-1}) 2845, 1616, 1574, 1476, 1359, 1337, 1259, 1234, 1094, 1004, 931, 904, 746.

Thermal Rearrangement of Trienes 17b and 18b. The following is a typical reaction procedure. Triene **18a** (45 mg, 0.27 mmol) was dissolved in chlorobenzene (5.5 mL) in a sealed tube, the solution was degassed and heated to 140°C. After 24 h there was no starting material left as determined by tlc (20% EtOAc in hexanes), and the solvent was removed. Purification on silica gel (20% EtOAc in CH_2Cl_2) gave a white solid. However, NMR analysis of this material did not match the desired tricyclic **18c**, and this material was not identified. Similar results were obtained with

17b also being completely converted to an unidentified material that was not **17c** upon heating.

5,5-Dicarboethoxynon-2,8-diyn-1-ol, allyl ether (19a). Diester **19a** was synthesized in an analogous manner to **7a** from diethyl but-3-ynylmalonate and 4-bromo-2-butynylallylether. Endiyne **19a** was isolated as a clear, colorless oil (20%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.97-5.82 (m, 1H), 5.36-5.19 (m, 2H), 4.25-4.17 (m, 4H), 4.12 (t, J = 4 Hz, 2H), 4.04-4.01 (m, 2H), 2.88 (t, J = 5 Hz, 2H), 2.38-2.17 (m, 4H), 1.96 (t, J = 3 Hz, 1H), 1.25 (t, J = 8 Hz, 6H).

4-(4-Allyloxy-but-2-ynyloxy)-but-1-yne (20a). 3-Butyn-1-ol (0.47 g, 6.63 mmol) was added to a suspension of NaH (0.18 g, 7.29 mmol) in dimethyl formamide (35 mL). After the alcohol was deprotonated, 4-bromo-2-butynylallylether (1.9g, 9.94 mmol) was added and the reaction allowed to stir overnight, quenched with water (40 mL) and extracted with Et_2O (4 × 50 mL). The resultant black oil was purified over silica gel (1% NEt_3 and 4% EtOAc in hexanes) to provide **20a** as a yellow oil (34%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.87-5.80 (m, 1H), 5.24 (d, J = 17.2 Hz, 1H), 5.14 (d, J = 10.6 Hz, 1H), 4.15 (d, J = 17.6 Hz, 4H), 3.98 (d, J = 5.5 Hz, 2H), 3.58 (t, J = 7.0 Hz, 2H), 2.42 (td, J^1 = 7.0 Hz, 2.6 Hz, 2H), 1.95 (t, J = 2.6 Hz, 1H); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 133.7, 117.5, 82.3, 81.8, 80.8, 70.4, 69.3, 67.6, 58.1, 57.1, 19.4.

4,4-Dicarboethoxytridec-1-en-6,12-diyne (21a). The diester was synthesized in an analogous manner to **7a** from 1-bromo-2,8-nonadiyne and diethyl allylmalonate. **21a**

was isolated as a clear, colorless oil (90%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.71-5.58 (m, 1H), 5.23-5.09 (m, 2H), 4.21 (q, J = 7 Hz, 4H), 2.81-2.74 (m, 2H), 2.23-2.14 (m, 2H), 1.95 (t, J = 3 Hz, 1H), 1.63-1.56 (m, 2H), 1.24 (t, J = 7 Hz, 6H).

References:

[1] For some examples, see: a)Watanuki, S.; Mori, M. *Organometallics* **1985**, *14*, 5054-5061. b) Watanuki, S.; Ochifuji, N.; Mori, M. *Organometallics* **1995**, *14*, 5062-5067. c) Katz, T. J.; Sivavec, T. M. *J. Am. Chem. Soc.* **1985**, *107*, 737-738.

[2] For some examples, see: a) Fox, H. H.; Wolf, M. O.; O'Dell, R.; Lin, B. L.; Schrock, R. R.; Wrighton, M. S. *J. Am. Chem. Soc.* **1994**, *116*, 2827-2843. b) Schrock, R. R. *Pure. Appl. Chem.* **1994**, *66*, 1447-1454. c) Schlund, R.; Schrock, R. R.; Crowe, W. E *J. Am. Chem. Soc.* **1989**, *111*, 8004-8006. d) Masuda, T.; Higashimura, T. *Acc. Chem. Res.* **1984**, *17*, 51-56.

[3] Schattenmann, F. J.; Schrock, R. R.; Davis, W. M. *J. Am. Chem. Soc.* **1996**, *118*, 3295-3296.

[4] Kim, S-H.; Zuercher, W. J.; Bowden, N. B.; Grubbs, R. H. *J. Org. Chem.* **1996**, *61*, 1073-1081.

[5] Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 9858-9859.

[6] a) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.*, **1996**, *118*, 100-110. b) Schwab, P.; France, M. B.; Grubbs, R. H.; Ziller, J.W. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2039-2041.

[7] Kinoshita, A.; Mori, M. *Synlett* **1994**, 1020-1022.

[8] Kim, S-H.; Bowden, N.; Grubbs, R. H. *J. Am. Chem. Soc.* **1994**, *116*, 10801-10802.

[9] Zuercher, W. J.; Scholl, M.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 4291-4298.

[10] For a recent review of these processes, see: Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413-4450.

[11] Kirkland, T. A.; Grubbs R. H. *J. Org. Chem.* **1997**, *62*, 7310-7318.

[12] Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, 6082-6083.

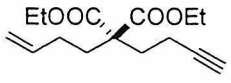
[13] For some recent examples, see: a) Leeuwenburgh, M. A.; Kulker, C.; Duynstee, H. I.; Overkleeft, H. S.; Van Der Marel, G. A.; Van Boom, J. H. *Tetrahedron* **1999**, *55*, 8253-8262. b) Clark, J. S.; Trevitt, G. P.; Boyall, D.; Stammen, B. *Chem. Commun.* **1998**, 2629-2630.

[14] a) Kinoshita, A.; Mori, M. *Heterocycles* **1997**, *46*, 287-299. b) Kinoshita, A.; Mori, M. *J. Org. Chem.* **1996**, *61*, 8356-8357.

[15] a) Schürer, S. C.; Blechert, S. *Tetrahedron Lett.* **1999**, *40*, 1877-1880. b) Heerding, D. A.; Takata, D. T.; Kwon, C.; Huffman, W. F.; Samanen, J. *Tetrahedron Lett.* **1998**, *39*, 6815-6818. c) Kotha, S.; Sreenivasachary, N.; Bramachary, E. *Tetrahedron Lett.* **1998**, *39*, 2805-2808.

[16] Kim, S-H.; Grubbs, R. H., Unpublished results.

[17] The cyclization of seven-membered rings through RCM can be highly dependent upon remote substituent effects. As with the substituted dienes described in

Chapter 1, it is believed that the substrate  would cyclize in significantly higher yield than is observed for substrate **8a**.

[18] Miller, S. J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117,* 2108-2109.

[19] Barrett, A. G. M.; Baugh, S. P. D.; Braddock, D. C.; Flack, K.; Gibson, V. C.; Procopiou, A. *Chem. Commun.* **1997**, 1375-1376.

[20] Although several 18 electron ruthenium species are known to catalyze cyclopropanation, no 16 electron ruthenium (II) species such as alkylidenes **1a** and **1b** have been reported to do so. Younkin, T.; Sanford, M. Unpublished results. The presence of a cyclopropanated product suggests that another ruthenium species is being generated during the course of this reaction.

[21] Chatani, N.; Morimoto, T.; Muto, T.; Murai, S. *J. Am. Chem. Soc.* **1994**, *116*, 6049-4050.

[22] Stragies, R.; Schuster, M.; Blechert, S. *Angew. Chem. Int. Engl. Ed.* **1997**, *36*, 2518-2520.

[23] Scholl, M.; Grubbs, R. H. Unpublished results.

[24] Stragies, R.; Schuster, M.; Blechert, S. *Chem. Commun.* **1999**, 237-238.

[25] The preference for olefins over alkylidenes is not necessarily defined by the 4:1 product ratio observed in Equation 5. Based on other studies, it is more likely that the energy difference for alkylidenes to react with olefins *vs.* acetylenes is much higher, and the ratio observed is merely a reflection of the directing ability of the methyl group for that particular reaction.

[26] Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875-3885.

[27] 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.

[28] Peters, J-U.; Blechert, S. *Chem. Commun.* **1997**, 1983-1984.

[29] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43,* 2923.

[30] Grigg, R.; Stevenson, P.; Worakun, T. *Tetrahedron* **1988**, *44*, 4967-4972.

[31] Becker, D. P.; Flynn, D. L. *Tetrahedron Lett.* **1993**, *34*, 2087-2090.

[32] Chatani, N.; Furukawa, N.; Sakurai, H.; Murai, S. *Organometallics* **1996**, *15*, 901-903.

[33] Grigg, R.; Scott, R.; Stevenson, P. *J. Chem. Soc. Perkin Trans. 1* **1988**, 1365-1370.

Chapter 3:

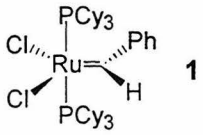
Increasing the Stability and Reactivity of Alkylidenes through the Substitution of Olefins in RCM Substrates[†]

Abstract:

The ring-closing metathesis (RCM) of acyclic dienes in both methanol and water has been achieved through the use of water-soluble ruthenium alkylidenes. These alkylidenes react readily with acyclic olefins in protic solvents, but they do not cyclize α,ω-dienes due to the instability of the resulting methylidene. Successful cyclization has been achieved through simple substrate modification; incorporation of an olefin substituent allows cyclization to proceed in good yield. A methyl-substituted substrate was cyclized in 60% conversion in methanol, and the incorporation of a phenyl substituent resulted in nearly quantitative cyclization. Phenyl-substituted substrates are best suited for the reaction, as a stable, active catalyst is regenerated upon each catalyst turnover. Using this methodology, 90% conversion of a water-soluble substrate to a substituted cyclopentene has been achieved in aqueous solution. This methodology has also been successfully applied to increase RCM yields in organic solvents.

Introduction:

Several techniques have been developed for the olefin metathesis of water-soluble substrates. Aqueous emulsions have allowed the Ring-Opening Metathesis Polymerization (ROMP) of water-soluble monomers with alkylidene **1**, which is insoluble in both methanol and water.[1,2] The use of $MeOH/CH_2Cl_2$ mixtures has also allowed the ROMP of monomers which are insoluble in CH_2Cl_2.[1a] In order to perform olefin metathesis in pure water, however, water-soluble alkylidenes are required. The synthesis of alkylidenes **2** and **3** has been reported recently,[3] and these alkylidenes are active for ROMP in both methanol and water.[4]



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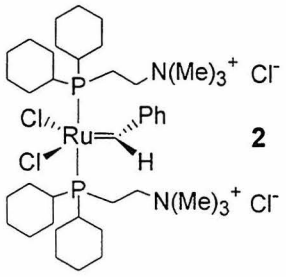

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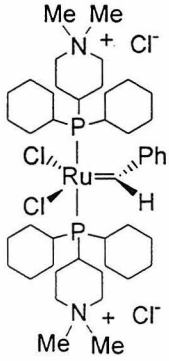
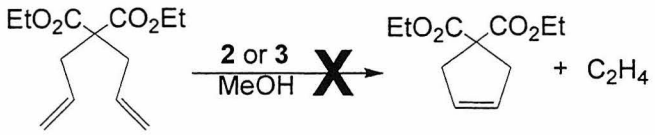


3

However, RCM under aqueous conditions has not been reported. For this reason, the current methods of applying RCM to biologically-relevant substrates focus on rendering the substrate soluble in organic solvents, either by extensive substrate protection[5] or binding of the substrate to solid support.[5b,6] However, the use of organic solvents can alter or destroy important higher-order structures which these substrates typically display in water.[7] The development of a methodology which enables efficient carbon-carbon bond formation in aqueous media would allow the synthesis of a variety of interesting compounds with biological applications. To this end, the RCM of unprotected substrates in water has remained an important goal.[8]

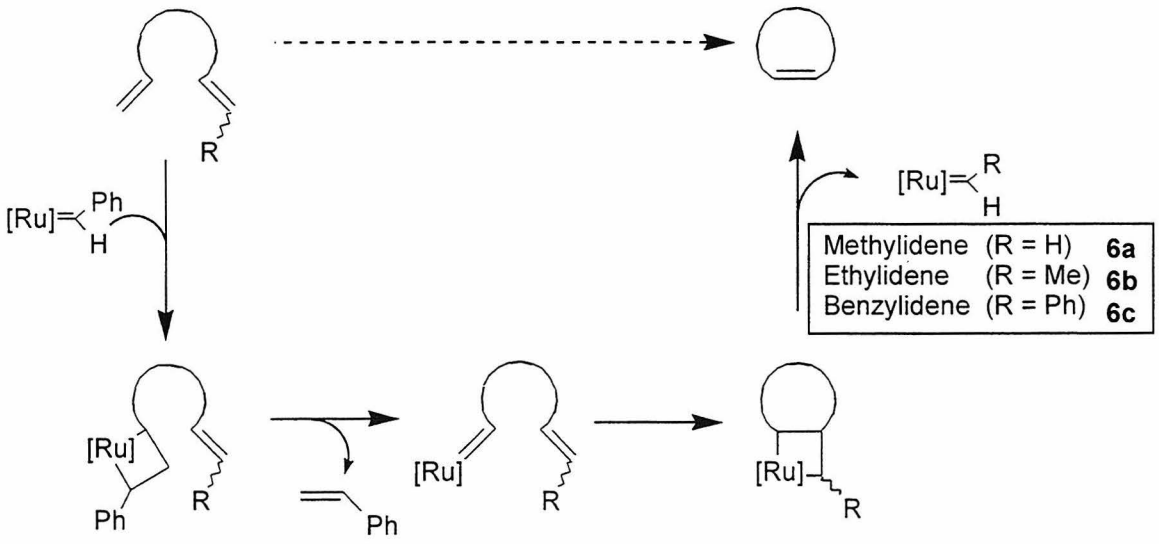
Initial attempts to probe the activities of **2** and **3** for RCM centered upon the cyclization of α,ω-dienes such as diethyl diallylmalonate (**4**). Alkylidene **1** cyclizes **4** rapidly and quantitatively to cyclopentene diester **5** in organic solvents.[9] However, the treatment of diene **4** with a catalytic amount of alkylidenes **2** or **3** in methanol gives no product (Eq. 1).[10]



4 **5** (1)

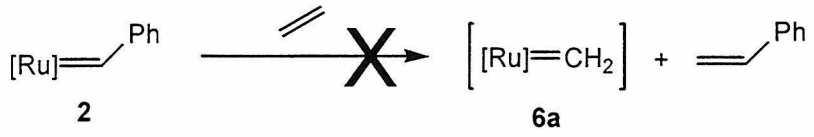
During the first turnover in the successful RCM of α,ω-dienes, a benzylidene (Scheme 1, **6c**) reacts with the diene to generate an equivalent of cyclized product, styrene and a methylidene (Scheme 1, **6a**). This methylidene is the true catalytic species. Although the methylidene derived from **1** is stable under a variety of conditions,[1b] the instability of other transition metal methylidenes is often a limiting factor in RCM.[11]

Scheme 1:



When alkylidene **2** or **3** is reacted with an α,ω-diene, styrene is observed by ^{1}H NMR spectroscopy but the methylidene is not.[12] This indicates that **2** and **3** react with the substrate but the methylidene which is formed decomposes before reentering the catalytic cycle.

Further evidence that methylidene instability was preventing RCM was obtained through reaction of alkylidenes **2** and **3** with simple acyclic olefins.[12] While reaction of **1** with ethylene proceeded quantitatively to the expected methylidene,[1b] the reaction of **2** with ethylene resulted in rapid decomposition (Eq. 2). Alkylidene **2** does react with either propene or *trans*-2-butene to yield a compound displaying a new resonance at 19.3 ppm in the ^{1}H NMR, which was assigned as an ethylidene (Eq. 3).



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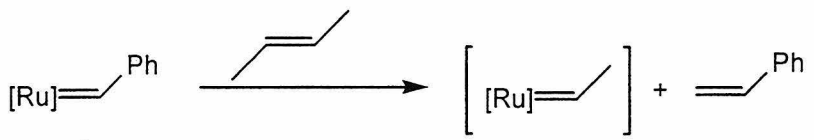


(3)

The increased stability of the ethylidene prompted the examination of RCM substrates containing substituted olefins. In the RCM of dienes containing one terminal olefin and one internal olefin (Scheme 1, R ≠ H), metathesis occurs initially at the terminal olefin[13] and the olefin substituent is transferred to the alkylidene upon cyclization. Therefore, it was reasoned that the incorporation of a substituent into a model diene would result in the generation of a more stable catalytic species, which

proved to be the case. The application of this technique to RCM in both aqueous and organic media is described below.

Results and Discussion:

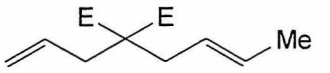
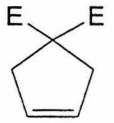
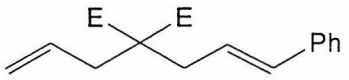
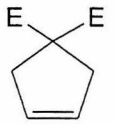
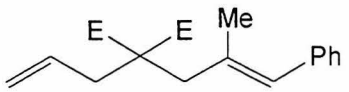
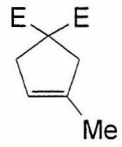
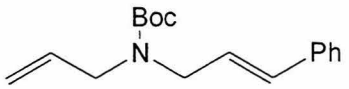
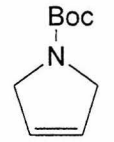
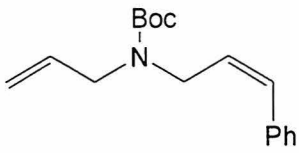
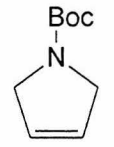
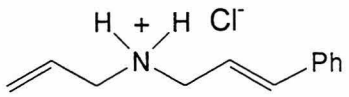
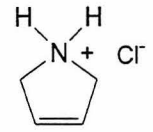
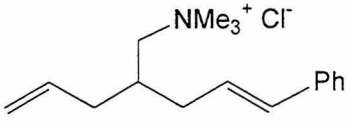
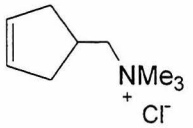
RCM of Substituted Olefins in Methanol:

Initial studies focused on the diethyl diallylmalonate system as a scaffold, because cyclization to the cyclopentene diester is kinetically favored by the Thorpe-Ingold effect,[14] analogs are easily synthesized, and the conversion of these substrates to cyclized product is easily monitored by ^{1}H NMR. The stability of the ethylidene prompted the synthesis of substrate **7**, a methyl-substituted diene.[15]

Treatment of **7** with 5 mol% alkylidene **2** or **3** in methanol gives 60% conversion to cyclic diester **5** (Table 1). The catalytic ethylidene was clearly observed by ^{1}H NMR spectroscopy during these reactions. The reactions were clean, consisting primarily of cyclic product and unreacted starting material. It should be noted that while replacement of a terminal olefin with an internal olefin in a RCM substrate alters the structure of the catalytically-active alkylidene, the structure of the desired cyclized products remains unaffected.

While the increased stability of the generated ethylidenes allows for RCM with alkylidenes **2** and **3**, catalyst stability is still a limiting factor because the ethylidene is observed to completely decompose before the starting material is consumed. This problem is further amplified by the decreased rate of olefin metathesis that accompanies increasing steric bulk around the olefin, allowing the rate of catalyst decomposition to be more competitive with the rate of RCM. After considering the greater reactivity and

Table 1:[a]

Substrate[b]		Product		Solvent	Conversion[c,d]
	**7**		**5**	MeOH	30% (**2**)[e] 60% (**3**)[e]
	**8**		**5**	MeOH	80% (**2**) 95% (**3**)
	**10**		**16**	MeOH	45% (**2**)[f] 55% (**3**)[f]
	**11**		**17**	MeOH	>95% (**3**)
	**12**		**18**	MeOH	40% (**2**) 90% (**3**)
	**13**		**18**	MeOH	30% (**2**) >95% (**3**)
	**14**		**19**	MeOH H_2O H_2O	75% (**2**) 10% (**2**) 5% (**3**)
	**15**		**20**	MeOH H_2O H_2O	90% (**3**) 60% (**3**) 90% (**3**)[g]

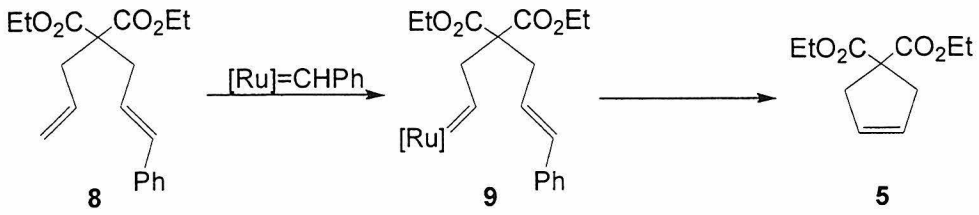
[a]The following conditions were used unless otherwise noted: 5 mol% catalyst (**2** or **3**), 0.37M substrate, 45°C. [b]E = CO_2Et. [c]Conversions were determined by ^1H NMR. [d]Numbers in parentheses indicate the alkylidene used. [e]Substrate conc. = 0.24M. [f]Substrate conc. = 0.1M. [g]10 mol% **3** used.

stability of benzylidene **1** compared to analogous methylidenes and ethylidenes,[1b] we examined a phenyl-substituted substrate.

Phenyl-substituted diene **8** was synthesized in an analogous manner to **7** using cinnamyl bromide. Incorporation of a phenyl substituent proved to be highly effective, as treatment of **8** with alkylidene **2** resulted in 80% conversion to cyclopentene **5**. Furthermore, cyclization proceeded nearly quantitatively in the presence of alkylidene **3**. While some alkylidene decomposition is evident, alkylidene **3** is still observed after all of diene **8** is converted to cyclic product. Alkylidenes **2** and **3** are regenerated in the RCM of phenyl-substituted substrates, and are therefore true catalysts.

The reason for the decomposition of benzylidenes **2** and **3** in the RCM of **8** is unclear, as these alkylidenes are stable for days in either methanol or water at 45°C. Styrene generated in the RCM of a phenyl substituted diene could react with a benzylidene to generate an unstable methylidene, although control reactions of alkylidenes **2** and **3** with styrene indicate that this is not a significant decomposition pathway. Another consideration is the decomposition of transitional alkylidene **9**, which is generated upon initial reaction of the catalyst with substrate **8** (Scheme 2). The stability of such an alkylidene is unknown but is expected to be similar to the analogous ethylidene.

Scheme 2:

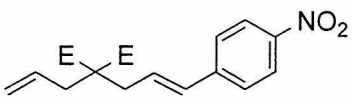


Alkylidene **3** is a significantly more active catalyst than alkylidene **2** in these cyclizations. This difference in reactivity can be explained through an analysis of phosphine electronic parameters.[9] For alkylidenes of the type $(PR_3)_2Cl_2Ru=CHR$, metathesis activities generally increase as the phosphine ligands become larger and more electron-rich.[9] Although the phosphines coordinated to **2** and **3** are sterically similar, the phosphines in **3** are more electron-rich.[4] While differences in the activities of these alkylidenes have not been noted for ROMP, the RCM of substrate **7** allows for a qualitative assessment of their relative activities. The treatment of **7** with alkylidene **2** results in 30% conversion after 1.5 h, while the use of alkylidene **3** results in 85% conversion over the same time period. This result is in accord with theoretical predictions.[4] A quantitative assessment of catalyst activities was not attempted due to alkylidene decomposition over the course of the reaction.

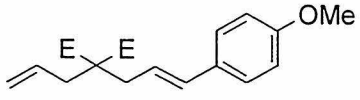
In order to try to increase the activity of the propagating alkylidene further, variations on the phenyl substituent were examined. Ruthenium alkylidenes with a range of electronic properties have previously been synthesized.[1a] Unfortunately, no clear relationship between the electronic nature of the alkylidene and activity could be established. In addition, varying the electronics of the substituent affects the electron density of the olefin, which can also affect the overall rate of the cyclization. Because of this ambiguity, it was unclear how changing the electronic nature would affect the rate of cyclization.

In order to examine an electron poor substituent, substrate **21** was synthesized and reacted with alkylidene **3** under standard conditions. A new alkylidene was observed as the propagating species; however, the reaction was much slower than the reaction with substrate **8**, and did not go to completion. Having determined that electron deficient

substrates were detrimental to the overall rate of RCM, substrate **22** was synthesized. Upon reaction with alkylidene **3**, a new alkylidene was observed and the rate was approximately the same as with substrate **8**. Unfortunately, the rate was not increased at all, and the difficulty in preparing *p*-methoxy substituted substrates makes this substituent inferior to the phenyl group.



21



22

In order to expand the scope of this methodology, the synthesis of cyclohexenes was investigated. The formation of diester **16** was achieved *via* cyclization of phenyl-substituted diene **10** with **2** and **3** in methanol (Table 1). The slower formation of a six-membered ring relative to a five-membered ring allows decomposition of the intermediate alkylidene to be more competitive with the rate of RCM (Scheme 2).[16,17] Surprisingly, the cyclization of methyl substituted diene **11** does not suffer from this rate decrease. Although ruthenium alkylidenes typically react sluggishly with trisubstituted olefins, the cyclization of **11** to cyclopentene **17** proceeds quickly and quantitatively.[18]

Olefin geometry also has a significant impact on cyclization rates. For example, the cyclization of *trans*-substituted substrate **12** with alkylidene **3** requires 30 h to reach 90% conversion, while cyclization of the *cis*-substituted derivative **13** proceeds quantitatively in 2 h (Table 1). This effect is not surprising, as *cis*-substituted olefins are able to coordinate to the metal center better than *trans*-olefins.[3a] The dramatic rate increase provided by the inclusion of *cis*-olefins can be an effective method for improving

the overall conversion by increasing the rate of cyclization relative to the rate of alkylidene decomposition.

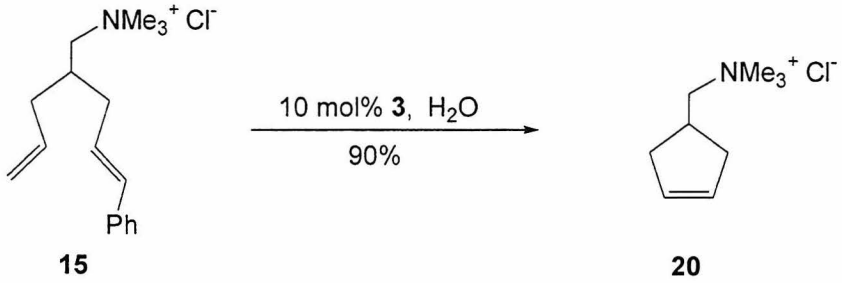
RCM in Water:

Having demonstrated the RCM of several substrates in methanol, we turned our attention to homogeneous RCM in water. Model substrates examined initially were based on a diallylamine hydrochloride framework[19] because analogs are easily synthesized and conversions are easily monitored by ^{1}H NMR spectroscopy. Phenyl-substituted diene **14** was cyclized with alkylidene **3** in methanol to give pyrroline hydrochloride **19** in 75% conversion (Table 1). While the RCM of this substrate in water only proceeds to 5-10% conversion with both alkylidenes **2** and **3**, these reactions represent the first observation of RCM in water. The cyclization of a *cis*-substituted analog yielded similar results, giving 15% conversion in the presence of catalyst **3**.

Catalysts **2** and **3** are active in the presence of acid[4] and have been shown to polymerize monomers containing amine hydrochlorides without loss of activity,[20] suggesting that the ammonium functionality was not degrading the alkylidene. Failure of the N,N-dimethyl analog of **14** to cyclize under the same conditions further suggested that other factors were responsible for these low conversions. Because alkylidene **1** reacts slowly with electron deficient olefins,[21] we considered that the strongly electron-withdrawing nature of the ammonium group was deactivating these dienes for RCM.

In order to circumvent this possibility, a water-soluble substrate was designed with the quaternary ammonium functionality further removed from the olefins. Diene **15** was synthesized through functional group manipulation of malonate **8**. This new substrate showed a dramatic increase in conversion in both water and methanol.

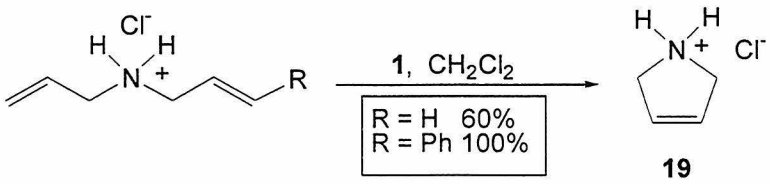
Treatment of ammonium salt **15** with alkylidene **3** gives cyclopentene **20** in 60% conversion in water and 90% in methanol (Table 1). Although conversions in water are lower than in methanol, excellent conversions in either solvent can be achieved through an increase of the catalyst loading. The increase in conversion observed with this increase in catalyst loading indicates that catalyst decomposition is still a limiting factor in these reactions. For example, in the presence of 10 mol% **3**, cyclization of **15** *proceeds to 90% conversion in aqueous solution* (Eq. 4).



15 **20** (4)

Applications to Organic Systems:

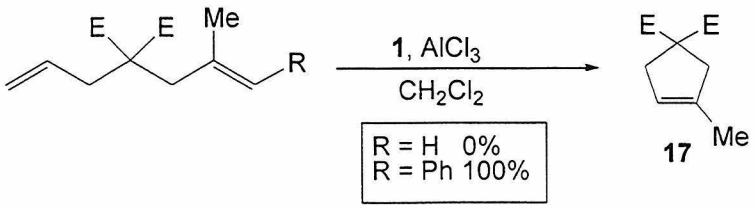
The beneficial effects of diene substitution are not limited to RCM with alkylidenes **2** and **3**. Even though the methylidene derived from **1** is quite robust, under certain reaction conditions its instability can limit conversion. For example, RCM of diallylamine hydrochloride with 5 mol% alkylidene **1** only proceeds to 60% conversion in methylene chloride (Eq. 5). RCM of the readily synthesized phenyl-substituted analog **14**, however, gives pyrroline hydrochloride (**19**) *quantitatively* under the same conditions with minimal decomposition of the catalytic benzylidene. This simple modification of the starting material greatly improved the yield of the desired product, and could be applied generally to increase RCM yields with **1** in organic solvents.



19 (5)

Olefin substitution has also proved to be quite useful in $AlCl_3$ accelerated RCM in organic solvents. Addition of $AlCl_3$ to a RCM reaction catalyzed by alkylidene **1** causes an enormous acceleration, with the RCM of diethyl diallylmalonate proceeding quantitatively in less than fifteen minutes.[23] The mechanism of this acceleration is not fully known, but it is believed that the aluminum acts as a phosphine scavenger in the same way that CuCl does.[22] However, alkylidene **1** appears to be significantly more active in the presence of $AlCl_3$ than CuCl, making aluminum activated reactions quite attractive for difficult cyclizations.

Unfortunately, the methylidene derived from benzylidene **1** is extremely unstable in the presence of $AlCl_3$.[23] Reaction of substrate **23** with alkylidene **1** in the presence of $AlCl_3$ gave only decomposition of the substrate, presumably through reaction with the products of the decomposition of the ruthenium methylidene (Eq. 6). On the other hand, the use of substrate **11** gave quantitative conversion to **17** in less than fifteen minutes, and the benzylidene could still be observed after the reaction had finished. The combination



17 (6)

of the acceleration of $AlCl_3$ and the stability imparted by a phenyl substituent should significantly increase the activity of alkylidene **1** for virtually any RCM reaction.

Conclusions:

The first examples of ring-closing metathesis in water and methanol have been demonstrated. Although alkylidenes **2** and **3** do not perform RCM on α,ω-dienes, simple olefin substitution allows for successful RCM to afford the desired product. Several factors have been described which influence the success of these reactions. In particular, the choice of olefin substituent is important because it directly impacts the stability and reactivity of the resultant catalytic alkylidenes. Phenyl substituents have proven to be the most effective, allowing for quantitative conversions to cyclized product in methanol. Additionally, dienes containing *cis*-olefins cyclize considerably faster than those containing *trans*-olefins. This methodology describes an efficient, metal-catalyzed, carbon-carbon bond forming process which proceeds to high conversion *in aqueous media.* It has also been extended to increase conversions in RCM catalyzed by **1** in organic solvents, including reactions involving $AlCl_3$. The incorporation of substituted olefins in complex, water-soluble dienes should allow for the construction of biologically-interesting architectures in aqueous media.

Acknowledgements:

First and foremost, Dr. David Lynn is gratefully acknowledged for performing the RCM reactions detailed, as well as for his intellectual contributions throughout the research detailed in this chapter. Melanie Sanford is also gratefully acknowledged for

performing the RCM reactions detailed in the $AlCl_3$ portion of the chapter and for significant intellectual contributions as well. This research was generously funded through grants from the NIH and NSF.

Experimental Section:

General Considerations. All manipulations and reactions involving ruthenium alkylidenes were performed in a nitrogen-filled drybox or by use of standard Schlenk techniques under an atmosphere of argon. Distilled deionized water and reagent grade methanol were used for these reactions, and were rigorously degassed by purging with argon and stirring under high vacuum prior to use. All other reagents were used without further purification unless otherwise noted. Alkylidenes **1**,[1b] **2**,[3] **3**,[3] substrates **7**,[24] **8**,[25] **14**,[26] **23**,[27] and products **5**,[28] **16**,[29] **17**,[30] **18**,[13c] **19**,[31] and **20**[32] have been previously prepared and reported. Substrate **4** is commercially available and was degassed prior to its use. Argon was purified by passage through columns of BASF R3-11 catalyst (Chemalog) and 4 Å molecular sieves (Linde). Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness). Flash column chromatography was performed using silica gel 60 (230-400 mesh) from EM Science.[33]

General RCM Procedure. In a typical reaction, substrate **8** (35 mg, 0.11 mmol) was placed in a vial and dissolved in CD_3OD (0.15 mL). In a separate vial, **2** (5.0 mg, 5.54 μmol) was placed in a vial and dissolved in CD_3OD (0.15 mL). The catalyst and substrate solutions were combined, placed in an NMR tube, and the tube was sealed with

a rubber septum. The reaction was heated to 45°C, and monitored by ^{1}H NMR. Conversion to product (80%) was determined *via* integration of the methylene protons α to the olefin in the cyclized product (2.95 ppm, s) relative to the methylene protons of the uncyclized substrate (2.68 ppm, dd).

RCM in the Presence of $AlCl_3$ (General Procedure). Alkylidene **1** (3.4 mg, 4.1 μmol) and $AlCl_3$ (0.55 mg, 4.1 μmol) were added to a solution of diene **11** (26 mg, 0.082 mmol) in CD_2Cl_2 (0.75 mL). A ^{1}H NMR spectrum of the reaction was taken immediately, and it showed that the substrate had been completely converted to cyclopentene **17**.

4,4-Dicarboethoxy-1-phenyl-1,7-octadiene (10). Diester **10** was synthesized from 1,1-dicarboethoxy-4-pentene and cinnamyl bromide according to a previously published procedure.[34] 1,1-Dicarboethoxy-4-pentene was synthesized according to the same method. Diester **10** was isolated as a clear, colorless oil (33%, two steps): ^{1}H NMR δ ($CDCl_3$) 7.32-7.17 (m, 5H), 6.44 (d, J = 7.8 Hz, 1H), 6.11-6.00 (m, 1H), 5.84-5.73 (m, 1H), 5.04 (d, J = 8.6 Hz, 1H), 4.96 (d, J = 5.1 Hz, 1H), 4.19 (q, J = 5.3 Hz, 4H), 2.06-2.03 (m, 4H), 1.24 (t, J = 4.8 Hz, 6H); ^{13}C NMR δ ($CDCl_3$) 170.8, 137.3, 136.8, 133.5, 128.2, 127.1, 125.9, 123.8, 114.8, 61.0, 57.3, 36.2, 31.6, 28.2, 13.9; HRMS calcd for $C_{20}H_{26}O_4$ (M^+) 330.1831, found 330.1825.

4,4-Dicarboethoxy-1-phenyl-2-methyl-1,6-heptadiene (11). Diester **11** was synthesized from diethyl allylmalonate and 3-bromo-1-phenyl-2-methyl-2-propene in an analogous manner to substrate **10**. 3-bromo-1-phenyl-2-methyl-2-propene was

synthesized from the commercially available alcohol in an analogous manner to *cis*-cinnamyl bromide. Diester **11** was isolated as a clear, colorless oil (12%, two steps): ^{1}H NMR δ ($CDCl_3$) 7.32-7.27 (m, 3H), 7.19 (d, J = 4.0 Hz, 2H), 6.35 (s, 1H), 5.79-5.68 (m, 1H), 5.13 (d, J = 5.0 Hz, 1H), 5.09 (s, 1H), 4.22-4.14 (m, 4H), 2.86 (s, 2H), 2.73 (d, J = 3.4 Hz, 2H), 1.79 (s, 3H), 1.24 (t, J = 7.0 Hz, 6H); ^{13}C NMR δ ($CDCl_3$) 171.2, 137.9, 133.7, 132.8, 130.4, 129.0, 128.1, 126.4, 119.1, 61.3, 57.7, 43.4, 37.2, 18.7, 14.2.

N-Boc-N-allyl-*trans*-cinnamylamine (12). Allylamine (10.9 g, 0.191 mol) and di-*tert*-butyl dicarbonate (13.9 g, 63.6 mmol) were dissolved in CH_2Cl_2 (250 mL) at 0°C and allowed to stir for 8 h. The solution was then washed with water (100 mL), dried with $MgSO_4$ and concentrated to give N-Boc-allylamine as a pale yellow solid (9.7g, 97%) which was used without further purification.

N-Boc-allylamine (2.88 g, 18.29 mmol) was allowed to react with NaH (0.48 g, 20.12 mmol) in DMF (50 mL) for 15 min. Then *trans*-cinnamyl bromide (3.97 g, 20.12 mmol) was added and the solution was heated to 60°C. After stirring for 16 h, the reaction was quenched with water (50 mL) and extracted with ether (3 × 50 mL). The combined extracts were dried over $MgSO_4$, concentrated and purified on silica gel (5% EtOAc in hexanes) to yield **12** as a clear, colorless oil (3.98 g, 80%): ^{1}H NMR δ ($CDCl_3$) 7.42-7.21 (m, 5H), 6.46 (d, J = 7.9 Hz, 1H), 6.20-6.11 (m, 1H), 5.85-5.76 (m, 1H), 5.18-5.12 (m, 2H), 3.96 (br s, 2H), 3.87 (br s, 2H), 1.49 (s, 9H). ^{13}C NMR δ ($CDCl_3$) 155.5, 136.9, 134.1, 131.8, 128.7, 127.7, 126.5, 125.7, 116.8, 79.8, 48.8, 48.4, 28.6; HRMS calcd for $C_{17}H_{23}NO_2$ (M^+) 273.1729, found 273.1730.

N-Boc-N-allyl-*cis*-cinnamylamine (13). *Cis*-cinnamyl alcohol (2.07g, 15.4 mmol), which was prepared as previously reported,[35] was dissolved in CH_2Cl_2 (50 mL) and cooled to 0°C. To this solution was added PPh_3 (6.07 g, 23.1 mmol) and CBr_4 (7.66 g, 23.1 mmol). After 1 h the solvent was removed *in vacuo*, the solid residue was taken up in hexanes and filtered through a plug of silica. This afforded *cis*-cinnamyl bromide (1.8 g, 60%), which was used without further purification.[36]

Substrate **13** was then synthesized in a similar manner to **12** using *cis*-cinnamyl bromide. It was isolated as a clear, colorless oil (74%): ^{1}H NMR δ ($CDCl_3$) 7.38-7.19 (m, 5H), 6.57 (d, J = 5.9 Hz, 1H), 5.74-5.61 (m, 2H), 5.01 (d, J = 4.9 Hz, 1H), 4.91 (d, J = 8.6 Hz, 1H), 4.12 (br s, 2H), 3.75 (br s, 2H), 1.44 (s, 9H). ^{13}C NMR δ ($CDCl_3$) 155.5, 136.8, 133.9, 131.2, 129.4, 128.9, 128.3, 126.5, 116.7, 79.8, 49.1, 44.3, 28.6; HRMS calcd for $C_{17}H_{23}NO_2$ (M^+) 273.1729, found 273.1729.

2-Allyl-5-phenyl-4-penten-1-ol. To a solution of diester **8** (3.14 g, 9.92 mmol) in DMSO (20 mL) was added H_2O (0.67 g, 37.22 mmol) and NaCl (0.70g, 12.41 mmol). This was heated at reflux for 90 h, quenched with H_2O (75 mL), extracted with ether (3 × 40 mL) and dried over $MgSO_4$. After removal of solvent and elution of the resulting black oil through a pad of SiO_2 (10% EtOAc in hexanes), a yellow, clear oil was obtained (1.31g) which was used without further purification.

Dropwise addition of a solution of this oil in THF (10 mL) to a suspension of $LiAlH_4$ (0.41g, 10.7 mmol) in THF (20 mL) at 0°C was completed over 30 min. After this solution had stirred for 2 h it was quenched with H_2O (1 mL) followed by 15% NaOH (5 mL). Removal of the resulting solids by filtration, removal of solvent *in vacuo*

and purification of the resultant oil on silica gel gave the known alcohol in good accordance with literature values (0.93 g, 49%, two steps).[37]

1-(N,N,N-Trimethyl ammonium chloride)-2-allyl-5-phenyl-4-pentene (15). A solution of tosyl chloride (0.55 g, 2.89 mmol) in CH_2Cl_2 (25 mL) was cooled to 0°C. 2-allyl-5-phenyl-4-penten-1-ol (0.50 g, 2.63 mmol) and NEt_3 (0.40 g, 3.94 mmol) were added and the solution was allowed to warm to room temperature. After stirring for 12 h, the reaction mixture was quenched with water (25 mL), extracted with CH_2Cl_2 (25 mL) and dried over $MgSO_4$. The resulting oil was carried on without further purification.

This tosylate (1.26 g, 3.66 mmol) was added to a solution of LiBr (0.95 g, 10.97 mmol) in acetone (20 mL) and the reaction mixture was refluxed. After 12 h, the reaction was quenched with water (25 mL), extracted with pentane (3 × 25 mL) and dried over $MgSO_4$. The resulting oil was added to a flask containing MeOH (15 mL) which had been purged with NMe_3 for 5 min. This reaction mixture was heated to 50°C for 24 h, and then all of the solvent was removed to give a brown solid. This solid was eluted through a column packed with Amberlite IRA-400 Cl^- ion exchange resin with MeOH, then triturated with Et_2O to yield **15** as a white crystalline solid (53%, three steps): ^1H NMR δ ($CDCl_3$) 7.38-7.18 (m, 5H), 6.48 (d, J = 7.9 Hz, 1H), 6.27-6.17 (m, 1H), 5.86-5.77 (m, 1H), 5.17 (d, J = 4.4 Hz, 1H), 5.13 (d, J = 5 Hz, 1H), 4.14 (s, 2H), 3.45 (s, 9H), 2.44-2.16 (m, 5H); ^{13}C NMR δ ($CDCl_3$) 136.8, 134.6, 134.2, 128.9, 127.8, 126.4, 125.9, 119.5, 69.8, 53.9, 38.5, 37.7, 33.5; HRMS calcd for $C_{17}H_{26}ClN$ ($M\text{-}Cl^+$) 244.2065, found 244.2060.

4,4-Dicarboethoxy-1-*p*-nitrophenyl-1,6-heptadiene (21): Diester **21** was synthesized from diethyl allylmalonate and *p*-nitrocinnamylbromide[38] in a manner analogous to substrate **10**. Substrate **21** was isolated as a yellow solid (54%): ^{1}H NMR δ ($CDCl_3$) 8.14 (d, J = 8.7 Hz, 2H), 7.43 (d, J = 8.8 Hz, 2H), 6.52-6.46 (m, 1H), 6.33-6.25 (m, 1H), 5.73-5.64 (m, 1H), 5.14 (d, J = 8.4 Hz, 2H), 4.19 (q, J = 7.2 Hz, 4H), 2.81 (d, J = 7.5 Hz, 2H), 2.68 (d, J = 7.4 Hz, 2H), 1.24 (t, J = 7.1 Hz, 6H); ^{13}C NMR δ ($CDCl_3$) 170.7, 147.1, 143.7, 132.3, 132.1, 130.0, 126.9, 124.2, 119.7, 61.6, 57.7, 37.7, 36.7, 14.3; IR (CH_2Cl_2, cm^{-1}) 2983, 2360, 1728, 1598, 1520, 1344, 1215, 1192, 738, 702.

4,4-Dicarboethoxy-1-*p*-methoxyphenyl-1,6-heptadiene (22): Ruthenium alkylidene **1** (134 mg, 0.163 mmol) was dissolved in CH_2Cl_2 (30 mL), followed by addition of diethyl allylmalonate and *p*-methoxystyrene. The reaction was heated at reflux overnight, and then the solvent was stripped. Purification on silica gel (15% EtOAc in hexanes) gave 4,4-dicarboethoxy-1-*p*-methoxyphenyl-1-butene, which was immediately carried on.

4,4-dicarboethoxy-1-*p*-methoxyphenyl-1-butene (500 mg, 1.63 mmol) was added to a suspension of NaH (47 mg, 1.959 mmol) in dimethylformamide (20 mL). After the solution became homogeneous, allyl bromide (395 mg, 3.264 mmol) was added and the reaction was heated to 60°C for 24 h. The reaction was then quenched with water (50 mL) and extracted with Et_2O (3 × 30 mL). Purification over silica gel (7.5 % EtOAc in hexanes) gave **22** as a pale yellow oil (42%, two steps): ^{1}H NMR δ ($CDCl_3$) 7.24 (d, J = 8.8 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 6.38 (d, J = 15.6 Hz, 1H), 5.95-5.84 (m, 1H), 5.75-5.66 (m, 1H), 5.14 (d, J = 8.4 Hz, 1H), 5.10 (s, 1H), 4.18 (q, J = 7.1 Hz, 4H), 3.76 (s, 3H), 2.76 (d, J = 7.6 Hz, 2H), 2.68 (d, J = 7.4 Hz, 2H), 1.23 (t, J = 7.1 Hz, 6H); ^{13}C NMR δ

($CDCl_3$) 170.8, 159.1, 133.4, 132.5, 130.0, 127.4, 121.6, 119.2, 113.9, 61.3, 57.7, 55.3, 37.1, 36.2, 14.2; IR (neat, cm^{-1}) 3464, 3078, 2982, 2837, 2359, 2058, 1732, 1642, 1608, 1577, 1513, 1445, 1367, 923, 857, 841, 522.

References:

† Portions of this chapter have been published as: Kirkland, T. A.; Lynn, D. M.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 9904-9909.

[1] a) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.*, **1996**, *118*, 100-110. b) Schwab, P.; France, M. B.; Grubbs, R. H.; Ziller, J.W. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2039-2041.

[2] a) Kanai, M.; Mortell, K. H.; Kiessling, L. L. *J. Am. Chem. Soc.* **1997**, *119*, 9931-9932, and references therein. b) Lynn, D. M.; Kanaoka, S.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 784-790. c) Fraser, C.; Grubbs, R. H. *Macromolecules* **1995**, *28*, 7248-7255.

[3] Mohr, B.; Lynn, D. M.; Grubbs, R. H. *Organometallics* **1996**, *15*, 4317-4325.

[4] Lynn, D. M.; Mohr, B.; Grubbs, R. H. *J. Am. Chem. Soc.* **1998**, *120*, 1627-1628.

[5] a) Blackwell, H. E.; Grubbs, R. H., **1998**, manuscript in preparation. b) Xu, Z.; Johannes, C. W.; Salman, S. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 10926-10927. c) Overkleeft, H. S.; Pandit, U. K. *Tetrahedron Lett.*, **1996**, *37*, 547-550. d) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606-9614. e) Clark, T. D.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1995**, *117*, 12364-12365.

[6] For general references on solid supported RCM, see : a) Peters, J-U.; Blechert, S. *Synlett.*, **1997**, 348-350. b) Pernerstorfer, J.; Schuster, M.; Blechert, S. *J. Chem. Soc.*

Chem. Commun., **1997**, 1949-1950 c) Piscopio, A. D.; Miller, J. F.; Koch, K. *Tetrahedron Lett.*, **1997**, *38*, 7143-7146. d) van Maarseveen, J. H.; den Hartog, J. A. J.; Engelen, V., Finner, E.; Visser, G.; Kruse, C. G. *Tetrahedron Lett.*, **1996**, *37*, 8249-8252. e) Schuster, M.; Pernerstorfer, J.; Blechert, S. *Angew. Chem. Int. Ed. Engl.*, **1996**, *35*, 1979-1980.

[7] Blackwell, H. E.; Grubbs, R. H. Unpublished results.

[8] For general reviews of other carbon-carbon bond forming processes in water, see: a) Li, C. J. *Tetrahedron* **1996**, *52*, 5643-5668. b) Breslow, R. A. *Acc. Chem. Res.* **1991**, *24*, 159-164.

[9] Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887-3897.

[10] In certain cases, the use of 5 mol% **2** in the RCM of **4** gives up to 5% product. The use of alkylidene **3** or increased loading of alkylidene **2** affords no increase in conversion.

[11] Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426-5427, and references therein.

[12] Lynn, D. M. Ph. D. Thesis, California Institute of Technology, **1999**.

[13] a) Kirkland, T. A.; Grubbs R. H. *J. Org. Chem.* **1997**, *62*, 7310-7318. b) Kim, S. H.; Zuercher, W. J.; Bowden, N. B.; Grubbs, R. H. *J. Org. Chem.* **1996**, *61*, 1073-1081. c) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H.; *J. Am. Chem. Soc.* **1993**, *115*, 9856-9857.

[14] Forbes, M. D. E.; Patton, J. T.; Myers, T. L.; Maynard, H. D.; Smith, D. W.; Schulz, G. R.; Wagener, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 10978-10980 and references therein.

[15] For a general procedure for malonate alkylation, see: Gilman, H.; Blatt, A. H. *Organic Syntheses*, Coll. Vol. I, John Wiley and Sons: New York, 2nd ed., 250-251.

[16] For a discussion of the effects of substrate homologation on intramolecular cyclizations, see: Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113,* 224-232 and references therein.

[17] Another factor which should be considered is substrate dimerization, but this does not appear to be significant in the RCM of **10** as conversion is not dependent on substrate concentration.

[18] In the synthesis of unsymmetrical olefins with this methodology, it is critical that the phenyl substituent be placed on the more substituted olefin as in substrate **11**. If the phenyl substituent is placed on the less substituted olefin, the ruthenium carbene will preferentially react with the 1,2-disubstituted olefin, then react with the *gem*-disubstituted olefin intramolecularly, giving one equivalent of cyclized product and the unstable methylidene.

[19] Chlorides were used exclusively as exposure of ruthenium alkylidenes of the type $(PR_3)Cl_2Ru{=}CHR$ to other coordinating anions such as Br^- results in fast anion exchange, typically yielding a significantly less active catalyst. This effect is not observed for very weakly coordinating anions such as SO_3^-. See Ref 9.

[20] Lynn, D. M.; Grubbs, R. H. Unpublished results.

[21] Ulman, M.; Grubbs, R. H. *Organometallics* **1998**, *17*, 2484-2489.

[22] Dias, E. L.; Grubbs, R. H. *Organometallics* **1998**, *17*, 2758-2767.

[23] Sanford, M. S.; Grubbs, R. H.; Unpublished results.

[24] Grigg, R.; Malone, J. F.; Mitchell, T. R. B.; Ramasubbu, A.; Scott, R.M. *J. Chem. Soc., Perkin Trans.* **1984**, 1745-1754.

[25] Hanessian, S.; Leger, R. *J. Am. Chem. Soc.* **1992**, *114*, 3115-3117.

[26] Crozet, M. P.; Kaafaran, M.; Surzur, J. M. *Bull. Soc. Chim. Fr.* **1984**, 390-398.

[27] Doran, W. J.; Shonle, H. A. *J. Am. Chem. Soc.* **1937**, *59*, 1625-1626.

[28] Nugent, W. A.; Feldman, J.; Calabrese, J. C. *J. Am. Chem. Soc.* **1995**, *117*, 8992-8998.

[29] Bachman, G. B.; Tanner, H. A. *J. Org. Chem.* **1939**, *4*, 493-501.

[30] Schweizer, E. E.; O'Neill, G. J. *J. Org. Chem.* **1965**, *30*, 2082-2083.

[31] Gajda, T.; Zwierzak, A. *Liebigs Ann. Chem.* **1986**, 992-1002.

[32] Tropsha, A. E.; Nizhinni, S. V.; Yaguzhinskii, L. S. *Bioorg. Khim.* **1985**, *11*, 1931-1941.

[33] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

[34] Gilman, H.; Blatt, A. H. *Org. Synth.* **1935**, *Collect. Vol. 1*, 250-251.

[35] Davis, F. A.; Reddy, R. T. *J. Org. Chem.* **1992**, *57*, 2599-2606.

[36] The quick isomerization of this compound resulted in the presence of <10% **11** in **10**, as determined by ^{1}H NMR. This did not affect the behavior of the **11** and was discounted.

[37] Atkinson, R. S.; Grimshire, M. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1135-1145.

[38] Elpern, B.; Gardner, L. N.; Grubach, L. *J. Am. Chem. Soc.* **1957**, *79*, 1951-1954.

Chapter 4:

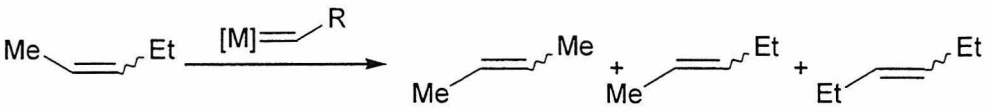
Investigation of the Relative Rates and *Cis/Trans* Selectivity of Olefin Metathesis Catalysts

Abstract:

The stereoselectivity of metathesis of acyclic olefins was investigated for several ruthenium alkylidenes. This was primarily done using *cis*-2-pentene metathesis. Data from *cis*-2-pentene metathesis was also used to determine relative metathesis rates for various alkylidenes and reaction conditions. An alkylidene bearing tricyclopentyl phosphines (**13**) was significantly more *cis* selective than one with tricyclohexyl phosphines (**8**). Alkylidene **8** was moderately *cis* selective for *cis*-2-pentene metathesis and slightly *cis* selective for *trans*-2-pentene metathesis.

Introduction:

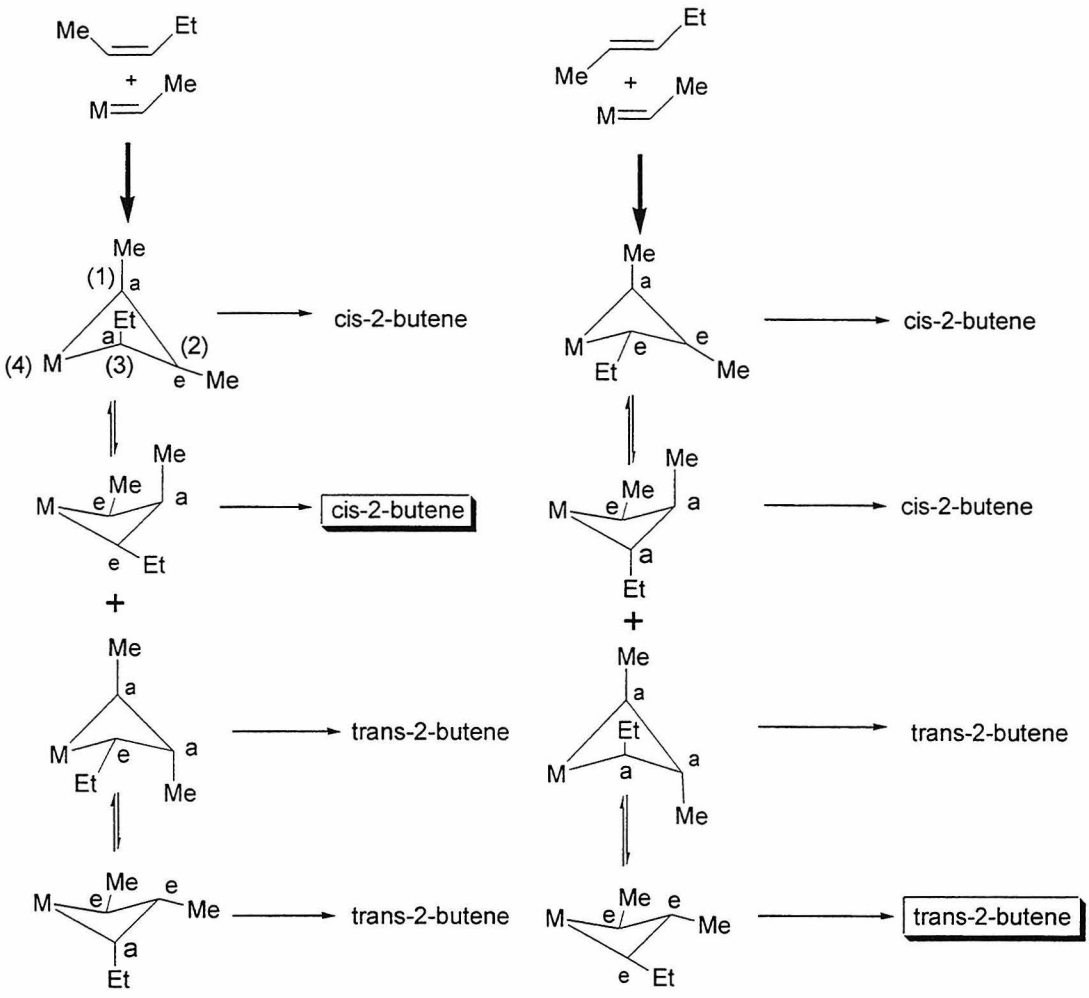
Olefin metathesis was first discovered through the metathesis of acyclic, aliphatic olefins.[1] During the investigation of this new process, it was observed that metathesis of disubstituted olefins tended to occur with retention of configuration.[2] In 1975, Basset *et al.* developed a system for systematically analyzing the stereoselectivity of catalysts through the examination of 2-pentene metathesis.[3] 2-Pentene is used for this purpose because it is the simplest internal olefin which yields new products that are not isomers of the original olefin. Metathesis of either isomer of 2-pentene yields the *cis* and *trans* isomers of 2-butene, 2-pentene and 3-hexene (Eq. 1).



(1)

The proposed model which explains the selectivity of the catalysts stemming from the geometry of the reacting olefin[4] is based on the proposed idea that a slightly puckered conformation is the lowest energy arrangement for substituted metallacyclobutanes (Figure 1).[5] The lowest energy pathways are determined by minimizing the 1,3-interactions. If *a* represents axial and *e* represents equatorial, the magnitude of the 1,3-interaction decreases in the order *aa*>*ae*>*ee*. Using this model, one can see how *cis*-2-pentene tends to produce *cis*-2-butene and *trans*-2-pentene tends to produce *trans*-2-butene. Other interactions between substituents on the metallacyclobutane will be considered throughout this chapter.

Figure 1:

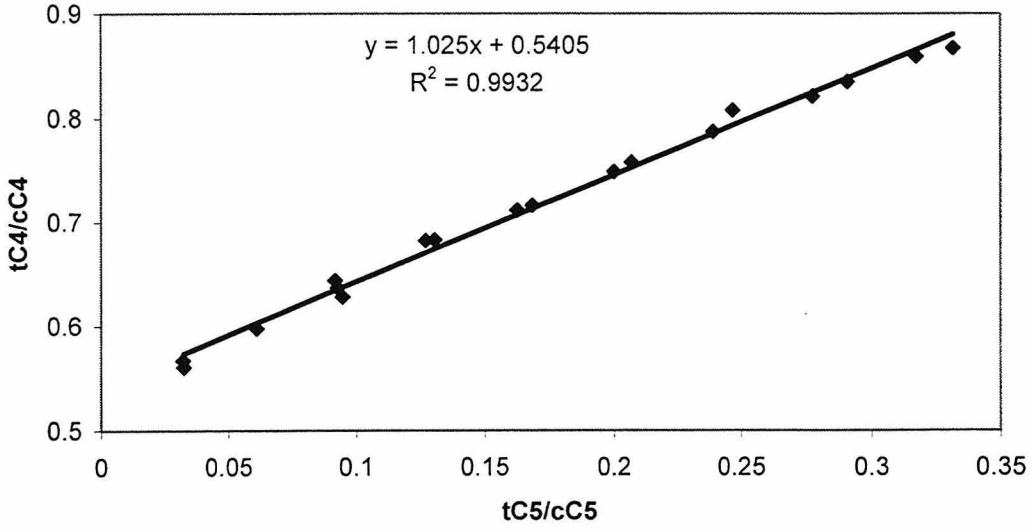


One difficulty in quantifying the stereoselectivity of these catalysts is that the products of 2-pentene metathesis are also metathesis active. All 2-pentene systems will eventually equilibrate to form a ratio of 1:2:1 for 2-butene:2-pentene:3-hexene, with a thermodynamic mixture of isomers.[3] The stereoselectivity of 2-butene formation by a particular metathesis catalyst is illustrated by the ratio of *trans*-2-butene to *cis*-2-butene (tC4/cC4)[6] formed by the metathesis of *cis*-2-pentene. Therefore, it is only at the beginning of the reaction when *cis*-2-pentene is the sole species present that the numbers obtained for stereoselectivity are meaningful. Of

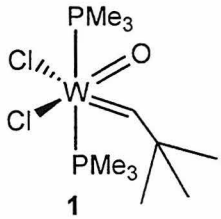
course, there is no 2-butene at time zero, so the ratios acquired are simply numbers which give an indication of the selectivity for 2-butene formation.

In order to determine the ratio of *cis*-2-butene to *trans*-2-butene at time zero, the reaction is sampled at several time points and tC4/cC4 is graphed versus tC5/cC5. A sample determination of stereoselectivity is shown in Figure 2. The isomerization of *cis*-2-pentene to *trans*-2-pentene is used as an internal standard to measure the progress of the reaction.[4] Extrapolating the tC5/cC5 term back to zero approximates time zero of the reaction, and thus the y-intercept denotes the stereoselectivity for *cis*-2-pentene metathesis of the catalyst being studied. A value of zero indicates a completely *cis* selective catalyst. In this example, the observed stereoselectivity for 2-butene formation is 0.54 (Figure 2). The selectivity of 3-hexene formation from *cis*-2-pentene can be found analogously by graphing tC6/cC6 *vs* tC5/cC5. This method has also been adapted to determination of the

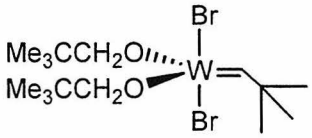
Figure 2:



stereoselectivity of the formation of other olefins through metathesis. The stereoselectivities of several ill-defined metathesis catalysts for *cis*-2-pentene metathesis have been reported using this method.[7]



1



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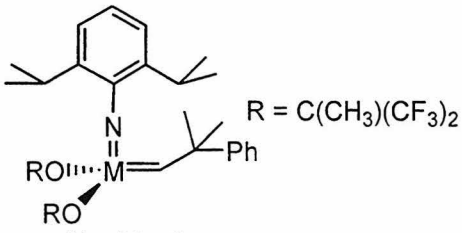
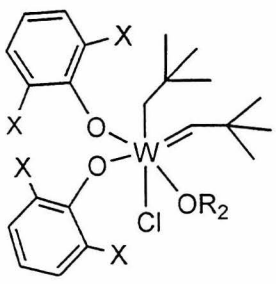


M = Mo **3**

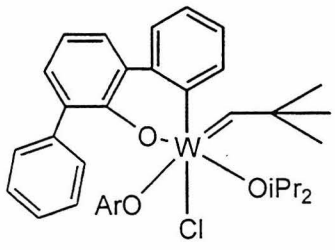
M = W **4**

Alkylidenes **1-4** are representative examples of well-defined Group VI alkylidenes which are active for the metathesis of acyclic olefins.[8] In fact, the metathesis of *cis*-2-pentene to equilibrium is a standard measure of activity for metathesis catalysts. Alkylidenes **3** and **4** are quite active, **3** converting >1000 eq/min of *cis*-2-pentene to equilibrium[8c] and **4** converting >250 eq/min.[8d] Although several studies have reported the stereoselectivity of ill-defined catalysts for acyclic



R = Et; X = Ph, Me, Cl, F
5a, 5b, 5c, 5d

R = ^{i}Pr; X = Ph, Cl, F
5e, 5f, 5g



Ar = 2,6-$C_6H_3Ph_2$

6

metathesis, the only well-defined catalysts for which stereoselectivities have been rigorously determined with acyclic olefins are alkylidenes **5a-g** and **6**.[9]

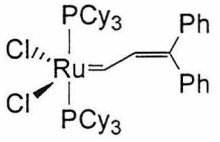
The stereoselectivity ratios for the metathesis of *cis*-2-pentene using alkylidenes **5a-g** are shown in Table 1.[9a] The nature of the substituents on the phenoxide ligand affects the stereoselectivity (F ≈ Cl << Me < Ph). However, in this case the major effect of the ligands seems to be electronic rather than steric, judging by the large difference between hydrocarbon and the halide substituents and by the small difference between the methyl and phenyl substituents. In a subsequent report, the orthometallation of alkylidene **5e** to form alkylidene **6** was detailed.[9b] Alkylidene **6** shows very high stereoselectivity for retention of configuration of *cis* and *trans*-2-pentene, presumably due to its more rigid structure. Its stereoselectivity was estimated at 0.01 (tC4/cC4) for *cis*-2-pentene metathesis, although this value was imprecise due to the high activity of this alkylidene.

Table 1:

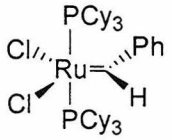
Catalyst	tC4/cC4	tC6/cC6	Catalyst	tC4/cC4	tC6/cC6
5a	0.20	0.35	**5e**	0.06	0.11
5b	0.18	0.40	**5f**	0.80	1.10
5c	0.80	1.40	**5g**	0.80	1.10
5d	0.90	1.50			

A family of ruthenium alkylidenes has also been developed which are active for the metathesis of acyclic olefins.[10] Alkylidene **7** reacts with *cis*-2-pentene at a rate of 103 eq/hr in CD_2Cl_2,[10b] compared to hundreds of equivalents per minute for

some early metal catalysts.[8c,8d,9b] Alkylidene **8** initiates faster than **7**, and therefore performs the metathesis of *cis*-2-pentene somewhat faster.

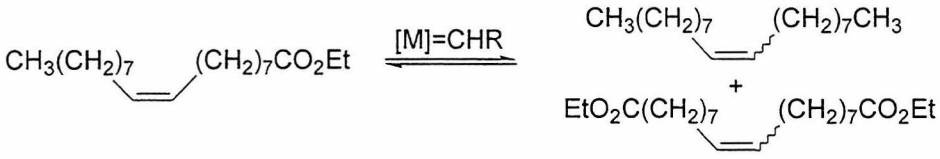


7



8

The advantage these alkylidenes have over early transition metal alkylidenes is their functional group tolerance. This advantage is seen in the cross-metathesis of functionalized olefins.[11] For example, in the cross metathesis of ethyl oleate, alkylidene **7** is nearly as active as alkylidene **3** and performs many more turnovers before decomposing (Eq. 2).[12] In addition, alkylidene **7** catalyzes the metathesis of oleic acid, which is not tolerated by any of these Group VI alkylidenes. This functional group tolerance has led to the extensive use of alkylidenes **7** and **8** in cross-metathesis applications.[11,13]



(2)

Although many issues of regioselectivity have been worked out for cross-metathesis using alkylidene **8**, stereoselectivity is still a major problem for this process.[11b] The tendency of metathesis catalysts to react with acyclic internal olefins with retention of configuration can be used to synthesize products enriched in one isomer. Although cross-metathesis reactions will eventually give a thermodynamic

mixture of isomers, stopping the reaction at low conversion can potentially give a product which is enriched in the desired isomer. Therefore, the stereoselectivity of several ruthenium alkylidenes was measured through *cis*-2-pentene metathesis. Several conditions were examined in order to maximize the stereoselectivity of the reaction. In an attempt to relate this data to functionalized systems, a preliminary investigation of the stereoselectivity of the cross-metathesis of fatty esters with aliphatic olefins will also be described.

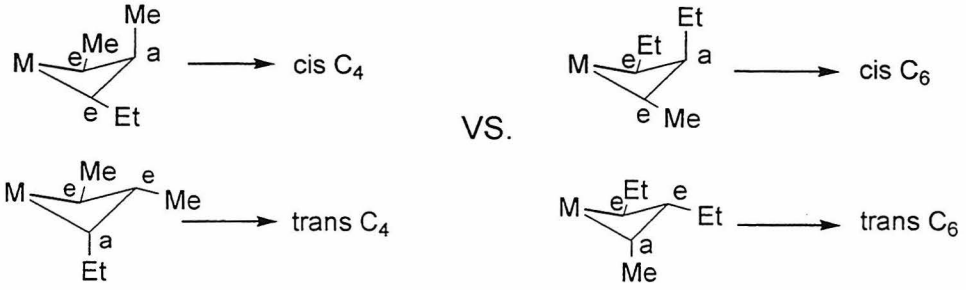
Results and Discussion:

Analysis of Factors Affecting Stereoselectivity:

Alkylidene **8** was used as the model catalyst for analyzing the effect of various reaction conditions on the rate and stereoselectivity for *cis*-2-pentene metathesis. The stereoselectivity for butene formation (tC4/cC4) with **8** is 0.543±0.007. The stereoselectivity for hexene formation (tC6/cC6) is approximately 5.[14] The rate of cis-2-pentene metathesis by **8** under standard conditions is 1.23±0.04 min^{-1}.[15]

The *trans* selectivity of alkylidene **8** seen for 3-hexene formation is in contrast with the *cis* selectivity for 2-butene formation. This change in selectivity is due to a larger 1,2 interaction (two ethyl groups instead of two methyl groups) in the metallacyclobutane, while the 1,3 interaction remains the same (Figure 3). As substituents in the 1 and 2 positions increase in size, the amount of *trans* olefin formed increases regardless of the configuration of the starting olefin.[18] This effect has been observed in the cross-metathesis of other functionalized olefins as well.[11b]

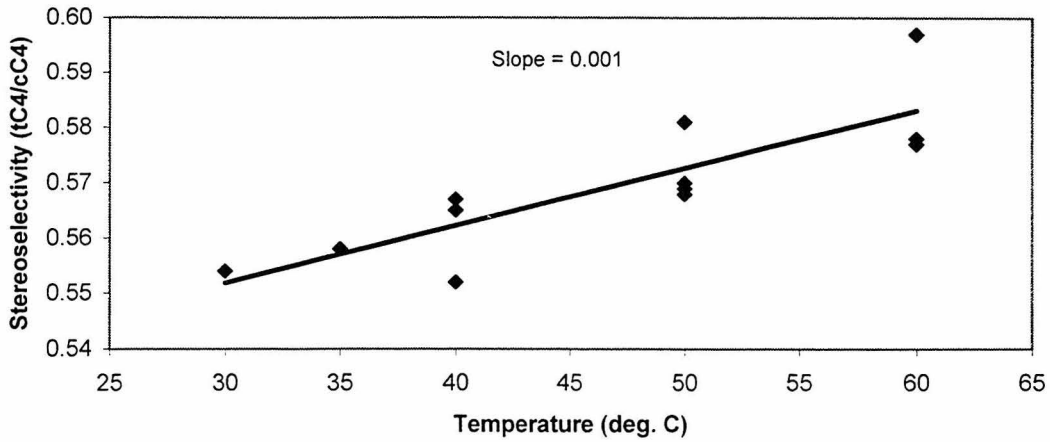
Figure 3:



Following the initial determination of the stereoselectivity and rate of benzylidene **8** for *cis*-2-pentene metathesis, the effect of conditions was investigated. As expected, variation of the molar ratio of catalyst to *cis*-2-pentene gave no significant variation of stereoselectivity,[16] although the rate increased as expected. Variation of the solvent also had no effect on the stereoselectivity, although the rates are substantially affected by the choice of solvent. Reactions in toluene and chlorobenzene have similar rates, and both are slightly slower than reactions in benzene. Surprisingly, reactions in dichloroethane are substantially slower than all three. This trend is different from that observed in ester metathesis, where benzene, toluene and dichloroethane all have similar rates.

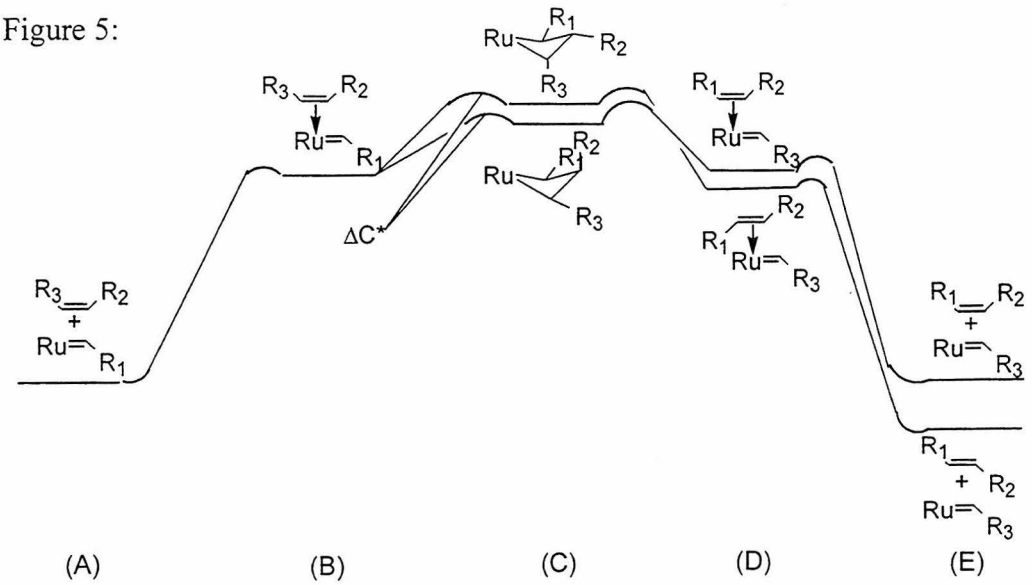
Temperature was the final parameter studied, and it has a significant effect on the stereoselectivity (Figure 4). Although this effect is small, it is reproducible and significant. The slope given is only intended as an indication of the magnitude of the change in stereoselectivity. This decrease in selectivity with an increase in temperature can be understood through an examination of the thermodynamics of metathesis.[17] A representation of the relative energy levels in acyclic olefin metathesis with a ruthenium catalyst is given in Figure 5.[18] The transition from state B to one of the two possible states of C sets the stereochemistry of the final product

Figure 4:



(state E). Therefore, the stereoselectivity is a result of the difference in activation energy leading to the two states (ΔC*), which is equivalent to the thermodynamic difference $\Delta\Delta G^{\ddagger}$ between the two reaction paths. The selectivity will change according to the expression $e^{-\Delta C^*/kT}$, where k is Boltzmann's constant and T is the temperature. Therefore, at higher temperatures the selectivity is expected to decrease

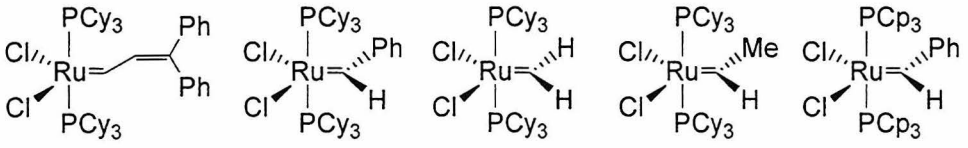
Figure 5:



for any ruthenium catalyzed metathesis. This argument was also used to explain the correlation between the activity and stereoselectivity for a series of ill-defined tungsten catalysts.[17]

Analysis of Different Catalyst Species:

Initially, alkylidenes **7**, **8**, **11**, and **12** were compared in order to determine if the nature of the alkylidene substituent affected the stereoselectivity. It was expected that a difference could be observed due to initiation effects, but the stereoselectivities are not significantly different from benzylidene **8** (Table 2). The slower rate seen with vinyl alkylidene **7** is due to the poor initiation, and the rates for the methylidene (**11**) and ethylidene (**12**) were not determined due to difficulty in removing the catalyst.



7 **8** **11** **12** **13**

A change in the coordinated phosphine did have a pronounced effect on the stereoselectivity. The tricyclopentyl phosphine benzylidene (**13**) was found to have a stereoselectivity for 2-butene formation of 0.31 (Table 2). In more descriptive terms, **13** produces over three *cis*-2-butenes for every *trans*-2-butene produced while **8** produces less than two *cis*-2-butenes for every *trans*-2-butene produced. The rate of metathesis using alkylidene **13** is 0.18, significantly slower than the tricyclohexyl phosphine derivative.

Table 2:

Alkylidene[a]	Stereoselectivity[b]	Rate (min^{-1})
$(PCy_3)_2Cl_2RuCHPh$ (**8**)	0.54	1.2
$(PCy_3)_2Cl_2RuCHCHCPh_2$ (**7**)	0.53	0.64
$(PCy_3)_2Cl_2RuCH_2$ (**11**)	0.53	Not Determined
$(PCy_3)_2Cl_2RuCHCH_3$ (**12**)	0.55	Not Determined
$(PCp_3)_2Cl_2RuCHPh$ (**13**)	0.32	0.18
$(RO)_2(NAr)MoCHCMe_3$ (**3**)	0.70	1.9

[a]Cy = cyclohexyl, and Cp = cyclopentyl. [b]Stereoselectivity refers to tC4/cC4.

The large difference in the stereoselectivity between **8** and **13** is presumably due to a combination of steric and kinetic effects. Clearly, tricyclopentyl phosphine is less bulky than tricyclohexyl phosphine. The smaller ligand interacts less with the substituents on the metallacyclobutane, allowing the predisposition for cis olefins to become more dominant. Therefore, the substitution of a less bulky phosphine increases ΔC^* (Figure 5). Additionally, a less active catalyst is likely to be more stereoselective, as discussed by Basset.[17] Both of these effects point towards an increase in selectivity for alkylidene **13**.

For the sake of comparison with the ruthenium alkylidenes, molybdenum alkylidene **3** was also analyzed using this methodology. This molybdenum alkylidene **3** has a stereoselectivity of 0.70 (tC4/cC4), which means that it is much less selective than alkylidene **8** (Table 2). This may be due to the extremely high activity of alkylidene **3**. The average rate measured for *cis*-2-pentene metathesis with **3** is 1.9±0.2.[15] This rate is orders of magnitude slower than the rate reported by

Schrock *et al.* for this catalyst,[8d] although those reactions were done in neat *cis*-2-pentene and the reaction conditions reported here are 0.38 M *cis*-2-pentene in C_6H_6. In addition, throughout the reaction with *cis*-2-pentene, the rate increases. Presumably, this is because alkylidene **3** initiates slowly with internal olefins, but the molybdenum ethylidene and propylidene are very reactive.[8d] Therefore, as the reaction goes on, more and more highly reactive species are formed, causing the observed rate increase.

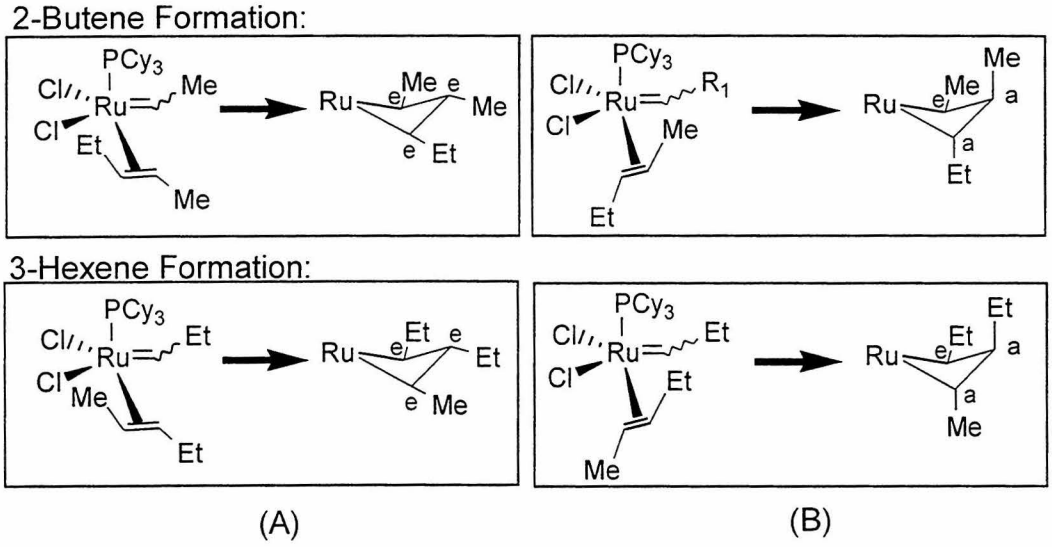
Metathesis of trans-2-Pentene:

The metathesis of *trans*-2-pentene by **8** gives a stereoselectivity of 1.15 (cC4/tC4), which is modestly *cis* selective. The less bulky tricyclopentyl phosphine catalyst **13** is less *cis* selective for *trans*-2-pentene, having a stereoselectivity (cC4/tC4) of 1.04. This *cis* selectivity for the metathesis of *trans* olefins is unusual. All of the molybdenum and tungsten catalysts studied have higher *trans* selectivity for *trans* olefins than *cis* selectivity for *cis* olefins,[7] which is predicted by the 1,3 interactions in the metallacyclobutanes (Figure 1).[19] This *cis* selectivity for *trans*-2-pentene metathesis with alkylidene **8** is not general, however, as the selectivity for 3-hexene formation using benzylidene **8** is 0.30 (cC6/tC6), which is quite *trans* selective.

These results can be reconciled if the favored isomer is formed through the transition state in which the larger substituent on the bound olefin is oriented away from the coordinated phosphine (Figure 6). According to this hypothesis the favored transition state for 2-butene formation is B which leads to the *cis* isomer, while the favored transition state for 3-hexene is A, leading to the *trans* isomer. In addition,

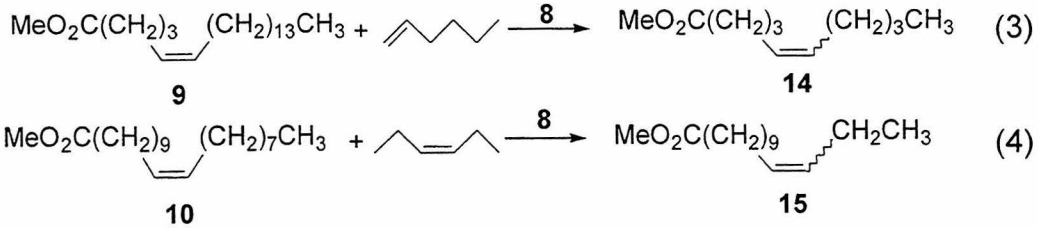
the smaller phosphine on alkylidene **13** reduces these binding effects, which leads to the reduced *cis* selectivity observed for 2-butene formation with this catalyst.

Figure 6:



Metathesis of Eicosenoates with Olefins:

In order to examine the stereoselectivity of **8** for metathesis of functionalized olefins, two model studies were performed. The reactions of fatty esters with both terminal and internal olefins were studied (Eqs. 3 and 4). The cross metathesis of fatty esters is particularly interesting because it is a convenient way to synthesize valuable insect pheromones.[20] A majority of these compounds have only one active



stereoisomer,[20] however, and the thermodynamic mixture arising from the metathesis of internally saturated esters and terminal olefins can be difficult to separate.[20c]

Formation of **14** proceeds with good conversion to give the desired ester and its isomer.[21] The percentage of **14** (both isomers) produced is approximately 48% of the total products isolated. The metathesis of **9** to produce **14** is *cis* selective, as expected from the *cis* starting material.[22] Early termination of the reaction gives a *cis/trans* ratio of 6.7, and late termination of the reaction gives a *cis/trans* ratio of 2.0. No significant effect on the stereoselectivity was seen with changes of solvent or the concentration of any of the reactants. However, the rate increased when there was an increase in the concentration of the catalyst or an increase in the concentration of 1-hexene relative to ester **9**. The reaction was slower in ethereal solvents than in aromatic and chlorinated solvents.

The cross-metathesis of **10** with *cis*-3-hexene to produce **15** is *trans* selective using alkylidene **8**. Early termination of the reaction gives a *cis/trans* ratio of 0.3-0.4, and late termination gives a ratio of 0.2. This reaction is much slower than the preceding reaction, which is expected when comparing the reaction of two internal olefins to the reaction of a terminal and an internal olefin. Although the *trans* selectivity of benzylidene **8** for this reaction is contrary to the results for 2-butene formation, it is comparable to that observed for 3-hexene formation, which is presumably a better model for this reaction.

Conclusions:

The general system for evaluating the stereoselectivities and rates of metathesis catalysts with either isomer of 2-pentene developed by Basset[3] has been

applied to molybdenum and ruthenium alkylidenes. In addition, a study of the effect of reaction conditions on stereoselectivity and rate has been carried out. It was determined that ruthenium alkylidene **13** was a significantly more *cis* selective alkylidene than the benzylidene **8**. Finally, the stereoselectivity of **8** was examined for two model fatty ester systems.

Acknowledgements:

Dr. Eric Dias, Dr. Bobby Maughon and Mike Ulman are acknowledged for intellectual contributions to this work. The author would also like to thank Bend Research for providing the fatty ester substrates, the GC column and the appropriate temperature programs. This research was generously supported by the NIH.

Experimental Section:

Instrumentation: Analysis of the samples was performed on a Hewlett-Packard 5890 Series II gas chromatograph. All of the pentene metathesis measurements were performed with a Hewlett-Packard 19091Z-205 capillary column. The metathesis of the methyl eicosenoates was analyzed with a J&W Scientific DB-225 capillary column.

Materials: *cis*-2-Pentene, *trans*-2-pentene, 1-hexene and *cis*-3-hexene were dried over CaH_2 and degassed before use. CuCl and decane were used as received. *Z*-Methyl-5-eicosenoate and *Z*-methyl-11-eicosenoate were degassed before use. All solvents were dried and degassed before use. The molybdenum alkylidene **4**[8d] and

ruthenium alkylidenes **7**,[10b] **8**,[10a] **11**,[10a] **12**,[10a] and **13**[10a] were prepared according to published procedures.

2-Pentene Metathesis (General Procedure). In a dry box, two aliquots of *cis*-2-pentene (52.5 mg, 0.75 mmol) were weighed out into vials. Alkylidene **8** (6.2 mg, 7.5 μmol) was weighed into a separate vial and dissolved in benzene (4 mL). Both vials were closed with caps containing septa. Outside of the box, half of the catalyst solution was distributed into each vial. Aliquots (0.2 mL) were removed by syringe at measured intervals. The septa were sealed with paraffin after each injection. Samples were eluted through silica gel with decane to remove the catalyst.

Metathesis of a Fatty Ester with an Olefin (General Procedure). In a dry box, *Z*-methyl-5-eicosenoate (10.0 mg, 0.031 mmol) and *cis*-3-hexene (13.0 mg, 0.154 mmol) were weighed into a vial. Alkylidene **8** (1.3 mg, 1.54 μmol) was weighed into a second vial. The catalyst was dissolved in benzene and the contents of the vials were combined. Outside of the dry box, aliquots were taken and eluted through silica gel with Et_2O. Unfortunately, the catalyst could not be removed from the esters quickly enough to obtain good rate data.

Data Analysis. Ratios of the various alkenes are taken directly from the peak integration off the GC. Stereoselectivities were determined by graphing tC4/cC4 *vs* tC5/cC5 (cC4/tC4 *vs* cC5/tC5 for trans-2-pentene)[14] and extrapolating back to zero as described by Basset.[3] Rates of metathesis are also reported by graphing the percentage of *cis*-2-pentene remaining while it is being consumed in a pseudo first

order manner (>65% cC5) *vs* the time of reaction in minutes. The slope of this line yields k_{obs} in min^{-1}, where $k_{obs} = k_p+k_i+k_r$. Here k_p is defined as productive metathesis, or metathesis of cC5 to give C4 or C6; k_i is isomerization, or metathesis of cC5 to give tC5, and k_r is regenerative metathesis, or the sum of the rate constants which produce cC5 from other olefins in the solution. The reaction displays pseudo first order kinetics as long as k_r is negligible.

Metathesis of the eicosenoates was analyzed by reporting the ratio of *cis* to *trans* for the formation of the ester of interest (see results section). An internal measure of the progress of the reaction was provided by the fraction of eicosenoate remaining. Because the *cis* and *trans* isomers of the starting eicosenoates were not fully separable by GC, it was not possible to use a ratio of the concentration of starting diastereomer over concentration of the isomerization product as an internal standard as was done with *cis*-2-pentene.[3]

References:

[1] Calderon, N.; Chen, H. Y.; Scott, K. W. *Tetrahedron Lett.* **1967**, 3327-3329.

[2] Calderon, N.; Ofstead, E. A.; Ward, J. P.; Judy, W. A.; Scott, K. W. *J. Am. Chem. Soc.* **1968**, *90*, 4133-4140.

[3] Basset, J. M.; Bilhou, J. L.; Mutin, R.; Theolier, A. *J. Am. Chem. Soc.* **1975**, *97*, 7376-7377.

[4] Bilhou, J. L.; Basset, J. M.; Mutin, R.; Graydon, W. F. *J Am. Chem. Soc.* **1977**, *99*, 4083-4090.

[5] Tinland, B.; Quignard, F.; Leconte, M.; Basset, J.M. *J. Am. Chem. Soc.* **1983**, *105*, 2924-2925.

[6] The abbreviations used for the internal olefins encountered in *cis*-2-pentene metathesis are structured as follows: The first letter indicates *cis* with c or *trans* with t, and the second letter and number indicate the olefin by carbon number. Therefore, cC4 represents *cis*-2-butene, tC6 represents *trans*-3-hexene, etc.

[7] Taghizadeh, N.; Quignard, F.; Leconte, M.; Basset, J. M.; Larroche, C.; Laval, J. P.; Lattes, A. *J. Mol. Cat.* **1982**, *15*, 219-244.

[8] a) Schrock, R.; Rocklage, S.; Wengrovius, J.; Rupprecht, G.; Fellmann, J. *J. Mol. Cat.* **1980**, *8*, 73-83. b) Kress, J.; Wesolek, M.; Osborn, J. A.; *J. Chem. Soc., Chem. Commun.* **1982**, 514-516. c) Schrock, R.R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875-3886. d) 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.

[9] a) Quignard, F.; Leconte, M.; Basset, J. M. *J. Chem. Soc., Chem. Commun.* **1985**, 1816-1817. b) Couturier, J-L.; Paillet, C.; Leconte, M.; Basset, J-M.; Weiss, K. *Angew. Chem. Int. Ed. Eng.* **1992**, *31*, 628-631.

[10] a) Schwab, P. E.; Grubbs, R. H.; Ziller, Z. W. *J. Am. Chem. Soc.* **1996**, *118*, 100-110. b) Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 9858-9859.

[11] a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413-4450. b) Randall, M. L.; Snapper, M. L. *J. Mol. Catal.* **1998**, *133*, 29-40.

[12] Nguyen, S.T.; Grubbs, R.H.; Feldman, J. Unpublished results.

[13] For some leading references, see: a) O'Leary, D. J.; Blackwell, H. E.; Washenfelder, R. A.; Grubbs, R. H. *Tetrahedron Lett.* **1998**, *39*, 7427-7430. b) Brümmer, O.; Rückert, A.; Blechert, S. *Chem. Eur. J.* **1997**, *3*, 441-446.

[14] In the GC analysis of the products of *cis*-2-pentene metathesis, baseline separation of the peaks was not achieved for the *cis* and *trans* isomers 3-hexene. Thus, a linear correlation for tC6/cC6 *vs* tC5/cC5 was never achieved, and the values reported for this value are partly approximated.

[15] All rates are reported as the slope of the line given by graphing [cC5] vs. time, and have units of min^{-1} (see the experimental section). This rate is purely relative, but is effective for comparing the rates of different metathesis catalysts.

[16] A deviation of more than 2σ from the reported mean will be considered significant.

[17] Quignard, F.; Leconte, M.; and Basset, J.M. *J. Mol. Cat.* **1985**, *28*, 27-32.

[18] Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Metathesis Polymerization*; Academic Press: London, **1997**.

[19] This type of *cis* selectivity has also been observed in ill-defined catalysts of the type $Cl_2W(OAr)_4$, where the OAr ligands are *ortho*-substituted phenoxides. Dodd, H. T.; Rutt, K. J. *J. Mol. Cat.* **1985**, *28*, 33-36.

[20] For some representative syntheses of insect pheremones through cross-metathesis, see: a) Crisp, G. T.; Collis, M. P. *Aust. J. Chem.* **1988**, *41*, 935-942. b) Banasiak, D. S. *J. Mol. Cat.* **1985**, *28*, 107-115. c) Levisalles, J.; Villemin, D. *Tetrahedron* **1980**, *36*, 3181-3185. d) Baker, R.; Crimmin, M. J.

Tetrahedron Lett. **1977**, 441-442 and references therein. e) Rossi, R. *Synthesis* **1977**, 817-836.

[21] Due to the difficulty in separating the esters from the catalyst, neither the stereoselectivity of the catalyst for formation of **14** or **15** nor the rate could be determined in the manner used for *cis*-2-pentene metathesis (see the experimental section). The stereoselectivities are reported as *cis/trans* ratios after quenching the reaction after 1 hr (early termination) and after 14 hr (late termination).

[22] Little research concerning the stereoselectivity of cross-metathesis with linear, terminal alkenes has been performed. However, a comprehensive study of the reactivity of alkylidene **8** with terminal olefins has been reported: Ulman, M.; Grubbs, R. H. *Organometallics* **1998**, *17*, 2484-2489.

Chapter 5:

The Conversion of Acid Chlorides to Substituted Acetylenes with Tungsten Alkylidynes

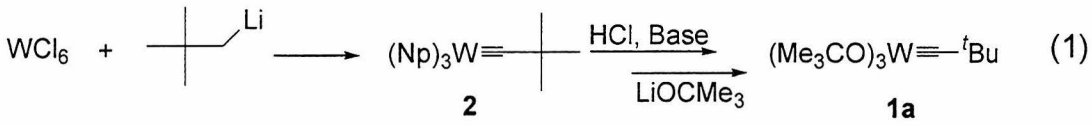
Abstract:

An investigation into the conversion of acid chlorides to substituted acetylenes using tungsten alkylidynes is discussed. A new route to DIPP tungsten alkylidynes is described. Several aromatic acid chlorides are converted into acetylenes using these alkylidynes in good yields. Finally, attempts at the synthesis of $W_2(DIPP)_6$ are described.

Introduction:

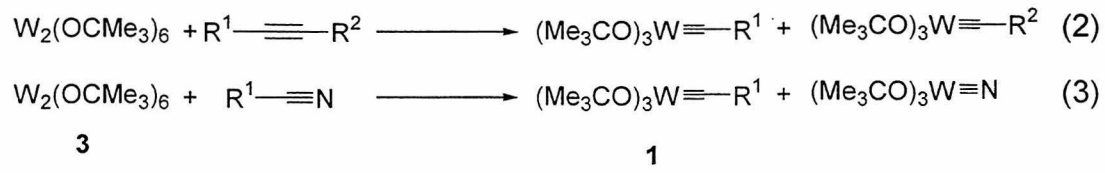
There are a limited number of methods for converting carbonyl compounds into substituted acetylenes, and nearly all of these methods require multi-step procedures.[1,2] A method which shows some promise as a one step synthesis of substituted acetylenes is the reaction of well-defined tungsten alkylidynes with acid chlorides.[3] This reaction has been reported, but no investigation of the scope or applicability to organic systems has been conducted. The ready availability of acid chlorides from carboxylic acids should allow the synthesis of a wide array of acetylenes using tungsten alkylidynes. For this reason, a study of the reaction between alkylidynes and acid chlorides was undertaken.

Well-defined tungsten alkylidynes have been shown to be active for acetylene metathesis,[4] and some applications of this methodology are described in the Introduction.[5] The first well-defined tungsten alkylidyne synthesized was the trialkylalkylidyne **2**, which was synthesized from NpLi and WCl_6 (Eq. 1).[6] Addition

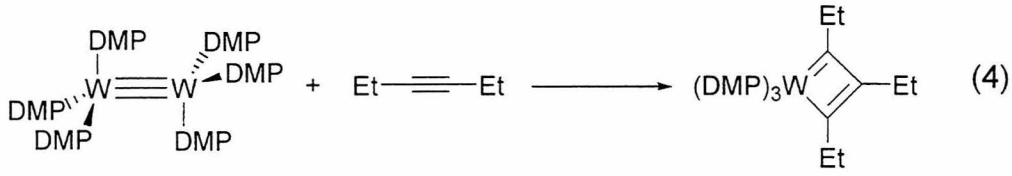


(1)

of HCl and a Lewis Base gave a compound which could then be converted to **1a** through the addition of $LiOCMe_3$.[7] A more general entry into the family of tungsten alkylidynes came from the discovery that $W_2(OCMe_3)_6$ (**3**)[8] reacts with acetylenes and nitriles to give tungsten alkylidynes (Eqs. 2 and 3).[9] This route enabled the synthesis of a variety of alkyl-substituted and functionalized alkylidynes.[9b]

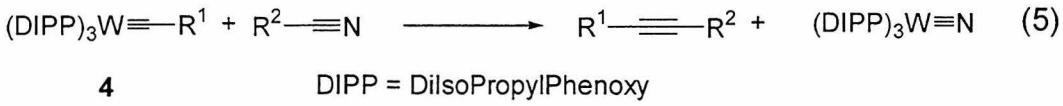


In addition to compound **3**, many other tungsten and molybdenum dimers containing metal-metal triple bonds have been reported[10] and this class of compounds has a rich and varied chemistry. However, only bulky alkoxy dimers have been reported to undergo a metathesis reaction with acetylenes and nitriles (Eqs. 3 and 4).[9,11] Bulky alkoxy substituents are essential for these dimers to retain a six-coordinate structure.[10] Less sterically demanding alkoxide substituents allow the tungsten (III) compounds to exist as trimeric and tetrameric structures, which do not perform the desired reaction with acetylenes.[10] In addition to compound **3**, several other tungsten dimers have been synthesized which possess the desired six coordinate structure.[11,12] One example is the *ortho*-DiMethylPhenoxy (DMP) complex $W_2(DMP)_6$.[11a] This dimer reacts with acetylenes to provide tungsten metallacyclobutadiene complexes (Eq. 4).

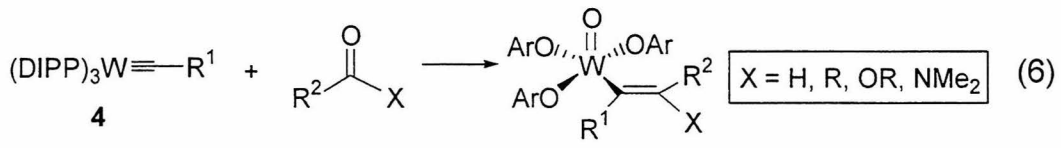


In addition to the reported aryloxy dimers, alkylidynes **4** bearing DiIsoPropylPhenoxy (DIPP) substituents have been synthesized.[13] These alkylidynes have been shown to metathesize acetylenes, but like the DMP compounds, the resting

state tends to be a metallacyclobutadiene complex instead of a free alkylidyne. Alkylidynes **4** also react with a variety of other functional groups metathetically.[3] Unlike the reaction with acetylenes, these reactions are stoichiometric, and the most electronegative element is transferred to the tungsten. For example, reactions of alkylidynes with nitriles generate a new acetylene and a terminal tungsten nitride (Eq. 5).

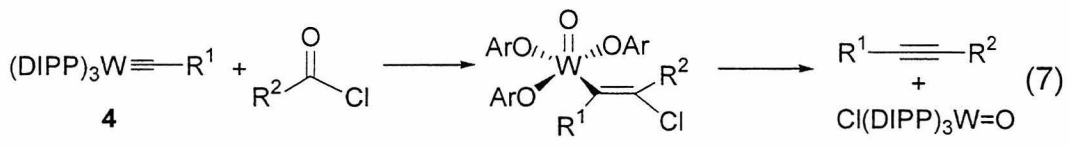


The reaction of alkylidynes **4** with carbonyl functionalities results in the formation of a vinyl-oxo species (Eq. 6).[3] The reaction is high yielding with aldehydes, ketones, and formate esters. However, tri-*tert*-butoxy tungsten alkylidynes (**1**) react with carbonyl compounds either sluggishly or not at all. In contrast, the DIPP complexes react with acetylenes slowly but react with carbonyl compounds quickly.



When the carbonyl compound is an acid chloride, a further reaction can take place.[3] Elimination of the chloride and tungsten species provides an acetylene composed of the substituent from the acid chloride and the substituent from the

alkylidyne. The tungsten species that is eliminated presumably ends up as a chlorotrialkoxy species (Eq. 7).



(7)

The research presented in this chapter represents an attempt to expand this methodology. The reaction of several tungsten alkylidynes with a variety of acid chlorides is discussed. In addition, preliminary attempts to simplify the synthesis of DIPP alkylidynes are described.

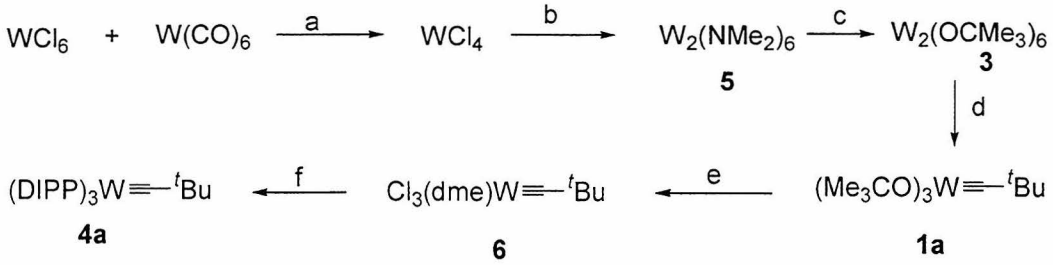
Results and Discussion:

Alkylidyne Synthesis:

The synthesis of DIPP tungsten alkylidynes was reported using the methodology developed in the first synthesis of tungsten alkylidynes.[6] However, the synthesis and purification of alkylidyne **2** is quite difficult, so another route to **4a** was developed (Scheme 1). Although WCl_4 is commercially available, this material is not sufficiently pure for the synthesis of $W_2(NMe_2)_6$ (**5**). Only freshly prepared WCl_4 can be used to obtain **5** in a synthetically useful yield.[14] Reaction of WCl_4 with one equivalent of sodium amalgam provides a tungsten (III) dimer with ligated THF and chlorides possessing an indeterminate structure. Although the isolation and characterization of this dimer has been reported,[14,15] our attempts at isolation gave only an unidentifiable black tar. Fortunately, synthesis of this dimer followed by the *in situ* addition of $LiNMe_2$ gave the hexaamido dimer **5** in moderate yield.[15a]

Addition of compound **5** to an excess of *tert*-butanol in benzene gave compound **3** in high yield.[8]

Scheme 1:



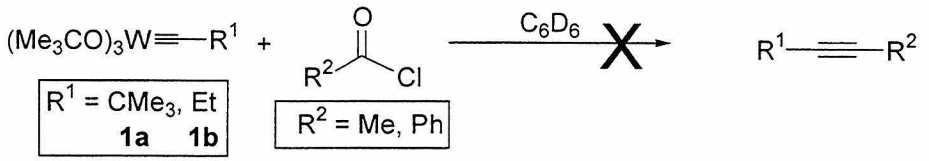
a) PhCl, reflux. b) 0.5% Na/Hg, then $LiNMe_2$, THF. c) Me_3COH, C_6H_6.
d) $Me_3C{-}{\equiv}{-}Me$, pentane. e) BCl_3, dme, pentane, -78°C. f) LiDIPP, Et_2O.

Once dimer **3** was prepared, subsequent synthesis of the desired alkylidyne was relatively straightforward. The reaction of 4,4-dimethyl-2-pentyne with **3** under a partial vacuum to remove the 2-butyne provided **1a**.[6] This alkylidyne was reacted with BCl_3 in the presence of dimethoxyethane to provide **6**.[16] Reaction of alkylidyne **6** with lithium diisopropylphenoxide provided **4a**, in 37% overall yield from **3**.[13]

Reaction with Acid Chlorides:

In order to determine if tungsten alkylidynes other than **4a** can perform this reaction, acid chlorides were reacted with alkylidynes **1a**, **1b** and **6**. Ethyl substituted alkylidyne **1b** was synthesized analogously to **1a** using 3-hexyne.[9a] Alkylidyne **1a** did not react with acetyl chloride (**7a**) at room temperature and decomposed upon heating (Eq. 8). Alkylidyne **1b** also did not react with acetyl and benzoyl chloride. The poor reactivity of **1a** and **1b** with acid chlorides was expected, as the reported reaction of *tert*-butoxy alkylidyne **1a** with aldehydes and carbonitriles is extremely

sluggish and ketones and esters do not react with this substrate.[3] Addition of acetyl chloride to alkylidyne **6** also gave no reaction.

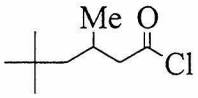
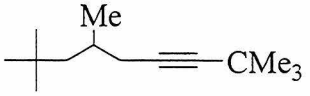
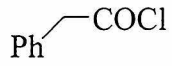
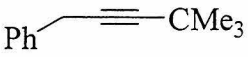
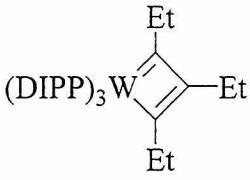
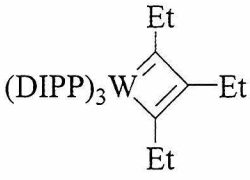


(8)

However, the conversion of acetyl chloride to 4,4-dimethyl-2-pentyne through reaction with alkylidyne **4a** was successful as reported (Table 1).[3] The reaction of aromatic acid chlorides with alkylidyne **4a** also proceeded to give the desired acetylenes. The reaction of benzoyl chloride and *p-tert*-butylbenzoyl chloride with **4a** proceeded in 50-70% yield under dilute conditions, but the reaction of substrate **9a** under more concentrated conditions proceeded in 80% yield. Substrate **10a** with a nitro substituent reacted with **5a** much more sluggishly, giving only 35% conversion after five days. Aliphatic acid chlorides **11a** and **12a** reacted with alkylidyne **4a**, but the ^{1}H NMR spectra of these reaction mixtures were complex, and they did not correspond with the expected spectra of the desired products in either case. The alkylidyne and the acid chloride were both consumed, however.

In order to further broaden the scope of this synthesis of acetylenes, the synthesis of ethyl substituted acetylenes was attempted. Complicating this process is the fact that, while **4a** exists as the alkylidyne, reaction with 3-hexyne gives the metallacyclobutadiene **4b** (Table 1). Reaction of **4b** with **7a** and **8a** gave a new set of products which did not correspond to the desired product in either case.

Table 1:

Acid Chloride	Alkylidyne	Desired Product	Yield[a]
CH_3COCl **7a**	$(DIPP)_3W{\equiv}CCMe_3$ **4a**	Me—≡—CMe_3 **7b**	60%
PhCOCl **8a**	$(DIPP)_3W{\equiv}CCMe_3$ **4a**	Ph—≡—CMe_3 **8b**	50%
Me_3C—C$_6$H$_4$—COCl **9a**	$(DIPP)_3W{\equiv}CCMe_3$ **4a**	Me_3C—C$_6$H$_4$—≡—CMe_3 **9b**	80%[b]
O_2N—C$_6$H$_4$—COCl **10a**	$(DIPP)_3W{\equiv}CCMe_3$ **4a**	O_2N—C$_6$H$_4$—≡—CMe_3 **10b**	35%
 **11a**	$(DIPP)_3W{\equiv}CCMe_3$ **4a**	 **11b**	No Product
 **12a**	$(DIPP)_3W{\equiv}CCMe_3$ **4a**	 **12b**	No Product
CH_3COCl **7a**	 **4b**	Me—≡—Et **7c**	No Product
PhCOCl **8a**	 **4b**	Ph—≡—Et **8c**	No Product

[a]Unless otherwise noted, these reactions were run in C_6D_6, at RT and at 0.01M in both reactants. [b]Reaction was run at 0.1M.

Attempted Synthesis of $W_2(DIPP)_6$:

Once it had been determined that these alkylidynes could successfully convert several acid chlorides to acetylenes, a simpler route to the active alkylidyne **4a** was investigated. The dimer $W_2(DMP)_6$ (DMP = 2,6-dimethylphenoxide) can be synthesized in two or three steps from WCl_6.[11a] If the analogous $W_2(DIPP)_6$ could be synthesized, a much shorter route to DIPP alkylidynes could potentially be developed.

Two syntheses of $W_2(DIPP)_6$ were attempted, the reduction of WCl_4 in the presence of LiDIPP and the alcoholysis of $W_2(NMe_2)_6$ with diisopropylphenol. Each of these techniques resulted in a red, crystalline solid following crystallization from hexanes. Unfortunately, the ^1H and ^{13}C NMR spectra were inconsistent with the desired product, and no reaction of this material with 3-hexyne was observed. It is possible that a reductive method from $W(DIPP)_3Cl_3$ would be successful based on the synthesis of $W_2(DMP)_6$.

Conclusions:

The use of tungsten alkylidynes to convert acid chlorides into substituted acetylenes has been demonstrated. This transformation, which has few parallels in organic chemistry, is effective using alkylidyne **4a**. It was demonstrated that aromatic acid chlorides react with this alkylidyne in the desired manner, while many aliphatic acid chlorides do not. In addition, the synthesis of the tungsten dimer $W_2(DIPP)_6$ was attempted. If the synthesis of these DIPP alkylidynes can be synthesized, this methodology could be readily applied to organic synthesis.

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Experimental Section:

General Considerations. All manipulations and reactions involving tungsten compounds were performed in a nitrogen-filled drybox or by use of standard Schlenk techniques under an atmosphere of argon. Pentane, benzene and C_6D_6 were purified by passing them through alumina columns. Diethyl ether, THF and hexanes were purified by distillation from a sodium benzophenone ketyl pot. All other solvents and commercially available reagents were distilled off of CaH_2. All solvents and reagents were rigorously degassed by purging with argon prior to use. WCl_4,[14] $W_2(NMe_2)_6$,[15a] **1a**,[9a] **1b**,[9a] **3**,[8] **4a**,[13] **4b**,[13] and **6**[16] were synthesized as previously reported. Lithium dimethyl amide and lithium diisopropylphenoxide were synthesized by reacting an excess of dimethyl amine and diisopropylphenol respectively with butyl lithium, and then removing solvent and washing with pentane. NMR spectra were recorded on either a General Electric QE-300 (300.1 MHz ^1H; 75.49 MHz ^{13}C) or a Jeol GX-400 (399.65 MHz ^1H; 100 MHz ^{13}C) spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane with reference to internal solvent. Infrared spectra were obtained on a Perkin-Elmer Paragon 1000 FT-IR.

1-*p-tert*-butylphenyl-3,3-dimethyl-1-butyne (9b). This procedure is general for all of the reactions of alkylidynes with acid chlorides. Alkylidyne **4a** (73.2 mg, 0.093 mmol) was dissolved in C_6D_6 (1 mL) in a J-Young tube. Acid chloride **9a** (18.3 mg, 0.093 mmol) was added, and the solution quickly turned from orange to deep red. After 24 h, the ^1H NMR showed no alkylidyne remaining and the product had grown in. The reaction was opened to air, and filtered over a plug of silica gel with hexanes. Removing solvent provided acetylene **9b** (80%): ^1H NMR (C_6D_6, 300 MHz) δ 7.50 (d, J = 8.7 Hz, 2H), 7.09 (d, J = 8.7 Hz, 2H), 1.28 (s, 9H), 1.10 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.5, 131.2, 125.0, 121.0, 97.8. 79.0, 34.6, 31.2, 31.1, 27.9.

W_2(DIPP)$_6$. First attempted synthesis: Sodium amalgam (64 mg Na/12.9 g Hg) was added dropwise to a suspension of WCl_4 (0.91 g, 2.80 mmol) in THF (30 mL). The reaction turned dark green, and a white precipitate formed over 5 h. Lithium diisopropylphenoxide (1.50 g, 8.38 mmol) was added and the reaction turned brown quickly. After stirring overnight, the suspension was filtered over Celite and the solvent was stripped. The resultant solid was dissolved in hexanes, insoluble material was filtered off, and the brown solution was cooled. After 3 days, red crystals were observed, but NMR analysis of this material showed it to be inconsistent with the desired product, and it was not identified.

Second attempted synthesis: Diisopropylphenol (1.75 g, 9.81 mmol) was added to a solution of $W_2(NMe_2)_6$ (0.62 g, 0.98 mmol) in C_6H_6 (20 mL). The reaction instantly changed color from orange to red. After 12 h, the C_6H_6 was

vacuum transferred off, and then the resultant red oil was heated at 70°C for 4 h under full vacuum to remove the excess phenol, leaving behind a tar. Recrystallization from hexanes provided red crystals. This material was not consistent with the desired material and did not correspond to the material made through the first synthesis. In addition, this material did not react with 3-hexyne to provide metallacyclobutadiene **4b**.

References:

[1] All of the common techniques require more than one step for this conversion. For some examples, see: a) Logan, R. T.; Roy, R. G.; Woods, G. F. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1079-1084. b) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1979**, *44*, 4997-4998. c) Lythgoe, B.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2429-2436. d) Kano, S.; Yokomatsu, T.; Shibuya, S. *J. Org. Chem.* **1978**, *43*, 4366-4367. e) Bartlett, P. A.; Green, F. R.; Rose, E. H. *J. Am. Chem. Soc.* **1978**, *100*, 4852-4858.

[2] There are a number of reports of the synthesis of unsubstituted acetylenes from aldehydes, but again multiple steps are required to obtain substituted acetylenes. For some representative examples, see: a) Matsumoto, M.; Kuroda, K. *Tetrahedron Lett.* **1980**, *21*, 4021-4024. b) Miyano, S.; Izumi, Y.; Hashimoto, H. *J. Chem. Soc., Chem. Commun.* **1978**, 446-447. c) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769-3772.

[3] Freudenberger, J. H.; Schrock, R. R. *Organometallics* **1986**, *5*, 398-400.

[4] For some reviews of this process, see: a) Schrock, R. R. *Polyhedron* **1995**, *14*, 3177-3195. b) Engel, P. F.; Pfeffer, M. *Chem. Rev.* **1995**, *95*, 2281-2309. c) Mayr, A.; Hoffmeister, H. *Adv. Organomet. Chem.* **1991**, *32*, 227-324. d) Schrock, R. R. *Acc. Chem. Res.* **1986**, *19*, 342-348.

[5] a) Kloppenburg, L.; Song, D.; Bunz, U. H. F. *J. Am. Chem. Soc.* **1998**, *120*, 7973-7974. b) Fürstner, A.; Siedel, G. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1734-1736. c) Kaneta, N.; Hikichi, K.; Asaka, S.; Uemura, M.; Mori, M. *Chem. Lett.* **1995**, 1055-1056. d) Krouse, S. A.; Schrock, R. R. *Macromolecules* **1989**, *22*, 2569-2576. e) Krouse, S. A.; Schrock, R. R.; Cohen, R. E. *Macromolecules* **1987**, *20*, 904-906. f) Villemin, D.; Cadiot, P. *Tetrahedron Lett.* **1982**, *23*, 5139-5140.

[6] Schrock, R. R.; Clarck, D. N.; Sancho, J.; Wengrovius, J. H.; Rocklage, S. M.; Pedersen, S. F. *Organometallics* **1982**, *1*, 1645-1651 and references therein.

[7] Wengrovius, J. H.; Sancho, J.; Schrock, R. R. *J. Am. Chem. Soc.* **1981**, *103*, 3932-3934.

[8] Akiyama, M.; Chisolm, M. H.; Cotton, F. A.; Extine, M. W.; Haitko, D. A.; Little, D.; Fanwick, P. E. *Inorg. Chem.* **1979**, *18*, 2266-2270.

[9] a) Listemann, M. L.; Schrock, R. R. *Organometallics* **1985**, *4*, 74-83. b) Schrock, R. R.; Listemann, M. L.; Sturgeoff, L. G. *J. Am. Chem. Soc.* **1982**, *104*, 4291-4293.

[10] For some reviews, see: a) Buhro, W. E.; Chisholm, M. H. *Adv. Organomet. Chem.* **1987**, *27*, 311-369. b) Chisholm, M. H.; Conroy, B. K.; Eichhorn, B.

W.; Folting, K.; Hoffman, D. M.; Huffman, J. C.; Marchant, N. S. *Polyhedron* **1987**, *6*, 783-792. c) Chisholm, M. H. *Polyhedron* **1983**, *2*, 681-721.

[11] For some other examples, see: a) Latham, I. A.; Sitan, L. R.; Schrock, R. R. *Organometallics* **1986**, *5*, 1508-1510. b) Freudenberger, J. H.; Pedersen, S. F.; Schrock, R. R. *Bull. Soc. Chim. Fr.* **1985**, 349-352. c) Strutz, H.; Schrock, R. R. *Organometallics* **1984**, *3*, 1600-1601.

[12] Dietz, S. D.; Eilerts, N. W.; Heppert, J. A. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 66-68 and references therein.

[13] Churchill, M. R.; Ziller, J. W.; Freudenberger, J. H.; Schrock, R. R. *Organometallics* **1984**, *3*, 1554-1562.

[14] Schrock, R. R.; Sturgeoff, L. G.; Sharp, P. R. *Inorg. Chem.* **1983**, *22*, 2801-2806.

[15] a) Chisholm, M. H.; Eichhorn, B. W.; Folting, K.; Huffman, J. C.; Ontiveros, C. D.; Streib, W. E.; Van Der Sluys, W. G. *Inorg. Chem.* **1987**, *26*, 3182-3186. b) Sharp, P. R.; Schrock, R. R. *J. Am. Chem. Soc.* **1980**, *102*, 1430-1431.

[16] Stevenson, M. A.; Hopkins, M. D. *Organometallics* **1997**, *16*, 3572-3573.