Synthesis of Oxygen- and Nitrogen-Containing Heterocycles by Ring-Closing Metathesis

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1. Introduction

The olefin metathesis reaction has been known since the 1960s, but it was not until the early 1990s that this transformation became an important tool in synthetic organic chemistry. It was thus in 1992 that Grubbs and Fu published two seminal papers describing the application of ring-closing metathesis (RCM) to the synthesis of simple five-, six-, and seven-membered monocyclic systems containing oxygen and nitrogen atoms using a molybdenum catalyst that had been first prepared by Schrock.[1] After this exciting report, we and many others became interested in using RCM to form the functionalized rings present in natural products and other biologically active compounds, and a number of elegant applications of RCM in total synthesis have been recorded.

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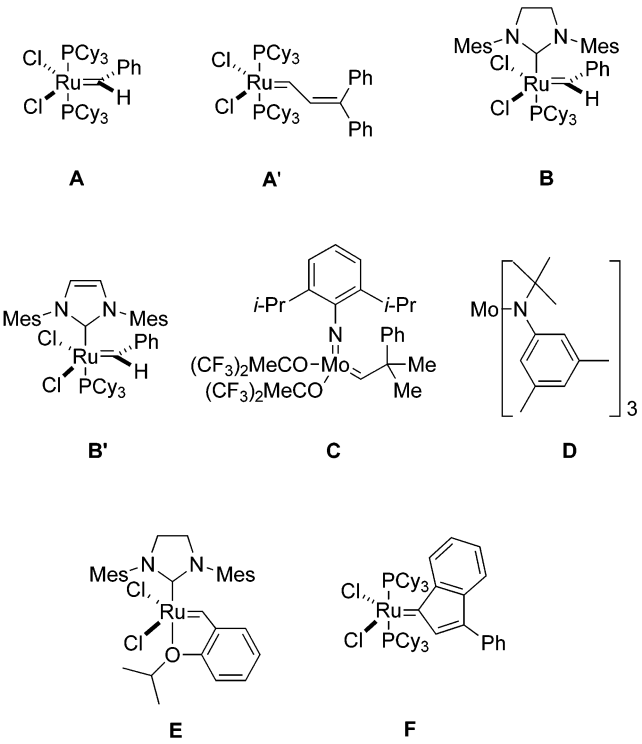
Progress in the development of the metathesis reaction has been directly correlated to improvements in the functional group compatibility and the reactivity of the catalysts. There are two main types of catalysts in use today. The first group contains ruthenium-complexes such as **A**, **A'**, **B**, and **B'** and



related catalysts such as **E** and **F**, whereas the second group is comprised of molybdenum complexes such as **C** and **D**. The catalysts **A**, **B**, and **C** are most commonly used for the RCM reactions described in this review. Those designated with a prime are closely related in structure to their parent complexes and show a similar reactivity pattern. Chiral variants of these catalysts are also available (see section 2.9). The functional group tolerance of the ruthenium and the molybdenum catalysts can vary somewhat, but the Mo-based complexes suffer the potential disadvantage of being more air and moisture sensitive. The high selectivity and reactivity of **A**−**F** for carbon−carbon π-bonds minimizes protecting group manipulations while enabling the use of RCM as an excellent alternative to other ring-forming reactions for the efficient construction of complex cyclic targets having a variety of ring sizes.

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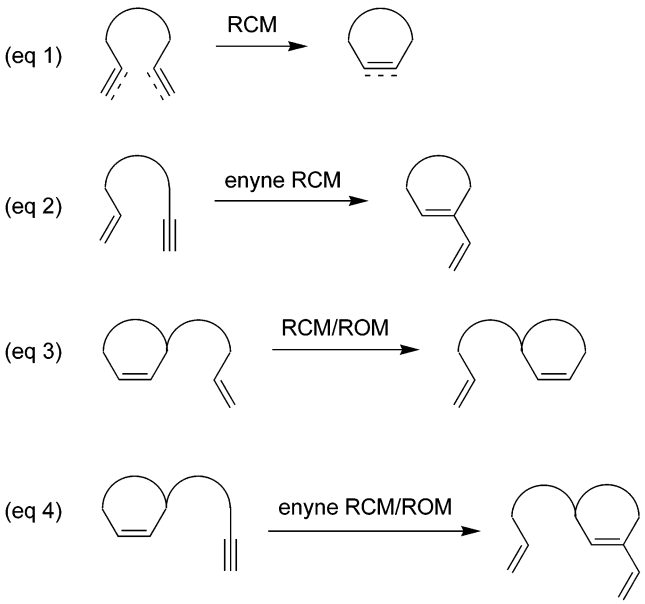
Alexander Deiters, born in Telgte, Germany, began his studies in chemistry in 1993 at the University of Münster, where he received his diploma degree in 1998. He then received his doctoral degree in 2000 for work in Professor Dieter Hoppe's group on novel cyclization reactions with enantioenriched allyllithium compounds. In 2001 he joined Professor Stephen Martin's laboratory at the University of Texas at Austin, where he worked as a postdoctoral fellow on the total synthesis of indole alkaloids. In 2002, he joined Professor Peter Schultz's group at The Scripps Research Institute in La Jolla as a postdoctoral fellow, where he was engaged in the in vivo incorporation of unnatural amino acids into proteins. In 2004, he joined the faculty at North Carolina State University as an Assistant Professor. His research interests range from organometallic and natural product to biological chemistry. He has received several awards in recognition of his accomplishments, perhaps most importantly for the best dissertation at the Departments for Natural Sciences, Mathematics, and Computer Science at the University of Münster in 2001. He was awarded fellowships from the German National Academic Foundation, the Fund of the Chemical Industry, the Alexander von Humboldt-Foundation, and the German Research Foundation in support of his research.

Stephen Martin, a native of New Mexico, received his B.S. degree in chemistry in 1968 from the University of New Mexico and his Ph.D. degree in 1972 from Princeton University, where he worked with Professor Edward C. Taylor. After postdoctoral years at the University of Munich with Professor Rudolf Gompper and Massachusetts Institute of Technology with Professor George Büchi, he joined the faculty at The University of Texas at Austin in 1974, where he currently holds the M. June and J. Virgil Waggoner Regents Chair in Chemistry. His current research interests lie generally in the areas of organic and bioorganic chemistry. In the former, his focus has been to develop and apply new tactics and strategies to concise syntheses of complex natural products that exhibit useful biological activity. In the arena of bioorganic chemistry, he has been involved in the design and synthesis of novel peptide mimics that may be used as tools to study protein–ligand interactions, and he is studying the mechanism, structure, and function of several phosphoryl transfer enzymes. He has received a number of awards honoring his outstanding accomplishments, and these include a NIH Career Development Award, an American Cyanamid Academic Award, an Alexander von Humboldt Award, an Arthur C. Cope Scholar Award, a Japanese Society for the Promotion of Science Award, and a Wyeth Research Award. He serves as a consultant for Elan Pharmaceuticals, Abbott Laboratories, and ICOS Corp., and he is the regional editor of *Tetrahedron* for the Americas. He has delivered numerous invited lectures at national and international meetings, academic institutions, and industrial companies, and he has published over 220 scientific papers in primary journals together with several reviews and articles in books. He is also coauthor of the popular undergraduate laboratory book *Experimental Organic Chemistry: A Miniscale and Microscale Approach*.

A number of reviews of RCM have been published to date,[2−6] but none of these focuses solely on the formation of heterocyclic structures.[7] In this review, applications of olefin and alkyne RCM (eq 1), enyne



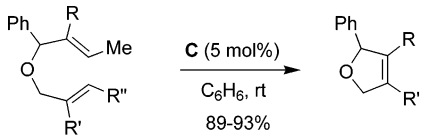
RCM (eq 2), and tandem processes in which these reactions are combined with ring-opening metathesis (ROM) (eqs 3 and 4) to construct *O*- and *N*-heterocycles will be presented with a particular emphasis on natural product synthesis. This review, which covers the literature until August 2003,[8] is not intended to be comprehensive. Rather it is designed to illustrate typical examples and situations where RCM was and can be used to construct complex heterocycles. The examples in each chapter are roughly organized by the size of the ring formed by the RCM reaction.

2. Oxygen Heterocycles

2.1. Five- and Six-Membered Cyclic Ethers

That RCM had considerable potential as a useful reaction in organic synthesis was clearly revealed in 1992 when Grubbs and co-workers reported that allylic ethers having a variety of substitution patterns could be cyclized in the presence of Schrock's molybdenum catalyst **C** to give dihydrofurans and dihydropyrans in excellent yields (Schemes 1 and 2).[1] It was noteworthy that even tetrasubstituted double bonds could be formed in high yields, although it was necessary to run the reaction for longer periods. Initial fears that the allyloxy group might interfere with the catalyst by acting as a Lewis base or that elimination pathways might occur from an alkylidene intermediate were found to be groundless.

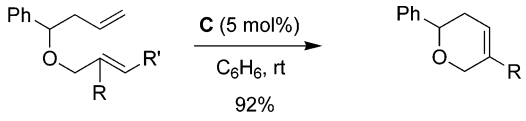
Scheme 1



1a: R = H, R' = H, R" = CH_3
1b: R = CH_3, R' = H, R" = CH_3
1c: R = CH_3, R' = CH_3, R" = H

2a: R = H, R' = H
2b: R = CH_3, R' = H
2c: R = CH_3, R' = CH_3

Scheme 2

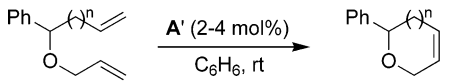


3a: R = H, R = CH_3
3b: R = CH_3, R = H

4a: R = H
4b: R = CH_3

The Schrock catalyst **C** is highly active, but its general suitability as a catalyst for RCM reactions is somewhat limited, because it is not compatible with a wide range of functionalities. It is also very moisture and air sensitive, so special precautions, rather than routine organic laboratory practices, must be employed. It was thus significant that Grubbs reported in 1993 that the ruthenium alkylidene **A**' was an active metathesis catalyst that could be employed to form cyclic ethers such as **6** from **5** in excellent yields (Scheme 3).[1b] Although **A**' could

Scheme 3

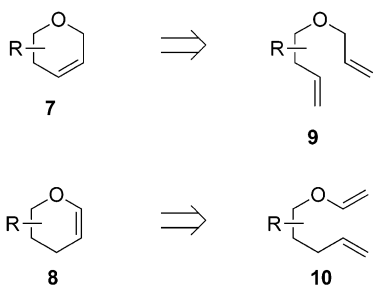


5 **6**

not be used to form tri- or tetrasubstituted double bonds, this new catalyst tolerated a wide range of functional groups, and it could be used in reagent grade solvents without an inert atmosphere. These seminal reports were the spark that initiated a wide range of studies that expanded the scope of RCM reactions in organic synthesis. There have subsequently been many reports of applications of RCM to the syntheses of a diverse array of heterocyclic compounds, some in enantiomerically pure form.

Six-membered cyclic ethers such as the 3,6-dihydropyrans **7** are common structural motifs in natural products, whereas the 3,4-dihydropyrans **8** are versatile intermediates in organic synthesis (Scheme 4).[9] The formation of 3,6-dihydropyrans via the RCM of allylic−homoallylic ethers **9** is a fast and straight-

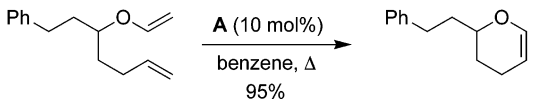
Scheme 4



forward reaction (Schemes 1−3). On the other hand, direct preparation of 3,4-dihydropyrans by the RCM of **10** is somewhat more restricted.

Schrock's catalyst **C** was used to prepare the first 3,4-dihydropyrans by RCM.[10] Early reports suggested that enol ethers were poor substrates for Grubbs' catalyst **A**, because the carbene resulting from the initial metathesis of the vinyl ether and **A** seemed to be inert to further reaction.[11] However, Sturino was able to use **A** to catalyze the cyclizations of a variety of vinyl ethers, including the highly efficient conversion of **11** to **12** (Scheme 5).[12]

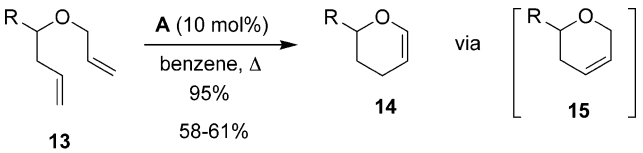
Scheme 5



11 **12**

A clever and perhaps more general approach to 3,4-dihydropyrans was recently reported by Snapper,[13a] who developed a tandem process that commenced with the RCM of readily available allyl homoallylic ethers **13** using the ruthenium alkylidene **A**. Subsequent ruthenium hydride-catalyzed isomerization of the initially formed RCM product **15** gave **14** (Scheme 6). The reaction was run under an atmosphere of

Scheme 6



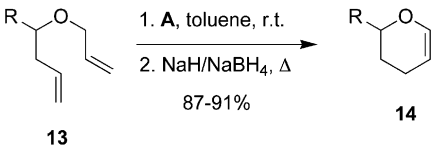
13 **14** **15**

R = Ph, *p*-MeOPh, *p*-ClPh, $PhCH_2CH_2$

dilute hydrogen gas (N_2/H_2 = 95:5) to allow formation of the isomerization-active catalyst while the competing double bond hydrogenation was kept to a minimum (<10%).[13a,14] The reaction is applicable to the synthesis of other cyclic enol ethers and enamides. Although the yields were modest, the process still represents a significant improvement over the RCM of vinyl ethers with **A**.

Schmidt recently reported a similar approach for preparing 3,4-dihydropyrans and other five- and seven-membered cyclic enol ethers from allyl homoallylic ethers (Scheme 7).[13b] In this case, the ruthenium−

Scheme 7



13 **14**

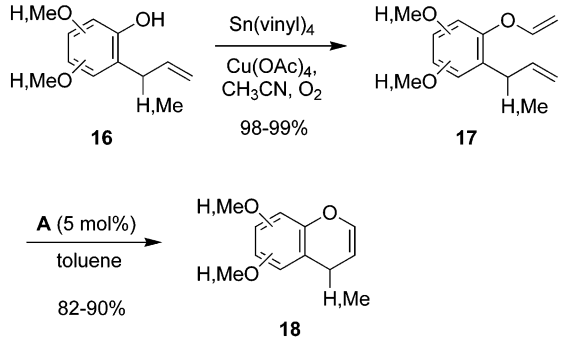
R = Ph, $PhCH_2CH_2$, PhCH=CH, Ph 

alkylidene catalyst was activated in a second step using NaH or $NaBH_4$, thereby making the method a two-step, one-pot procedure. The dienes **13** first underwent RCM with 5 mol% of **A** in 20−60 min at room temperature in toluene; NaH or $NaBH_4$ was then added and the reaction mixture heated to 110 °C to form **14**. This procedure appears to give

products in higher yields than the Snapper protocol, although the harsher conditions for the second step might be a disadvantage for sensitive substrates.

The synthesis of 4*H*-chromenes by RCM is also difficult because such constructions involve the metathesis of vinyl ethers. Nonetheless, Van Otterlo recently reported the first route to 4*H*-chromenes that features the RCM of a series of five phenolic vinyl ethers **17** using 5 mol% of **A** to deliver **18** in good to excellent yields (Scheme 8).[15] The RCM

Scheme 8

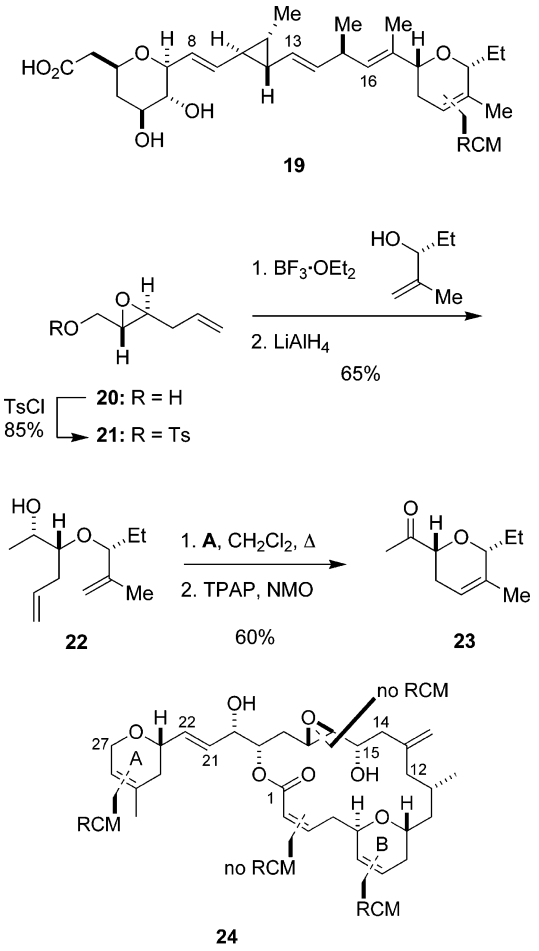


substrates **17** were readily prepared in three steps by *O*-allylation of a phenol followed by a Claisen rearrangement to give **16**, which was allowed to react with tetravinyltin to provide **17**.

3,6-Dihydropyrans occur widely as structural subunits in biologically active natural products, so there have been a number of interesting examples of constructing these heterocycles by RCM reactions. Precursors for these RCM reactions may be formed in a variety of ways, including glycolate Claisen rearrangements[16a] or Pd(II)-mediated couplings of secondary alcohols with 1-methoxy-1,2-propadiene.[16b] Another tactic for forming a 3,6-dihydropyran by a RCM may be found in Martin's total synthesis of the complex, antifungal natural product (+)-ambruticin S (**19**).[17] The diene **22** was constructed in three steps from a known enantiomerically pure epoxide **20** via the tosylate **21** (Scheme 9). Treatment of **22**, which bears an unprotected hydroxyl group, with Grubbs catalyst **A** in refluxing CH_2Cl_2 resulted in a smooth RCM to give an intermediate that was oxidized to furnish the ketone **23** in 60% overall yield. In a series of subsequent steps, the natural product **19** was assembled in a highly convergent fashion using two Julia couplings to form the C8−C9 and the C13−C14 double bonds. In another synthesis of (+)-ambruticin S reported almost simultaneously, Jacobsen employed an asymmetric hetero-Diels−Alder (HDA) reaction as an alternate strategy for constructing a dihydropyran subunit similar to **23**.[18]

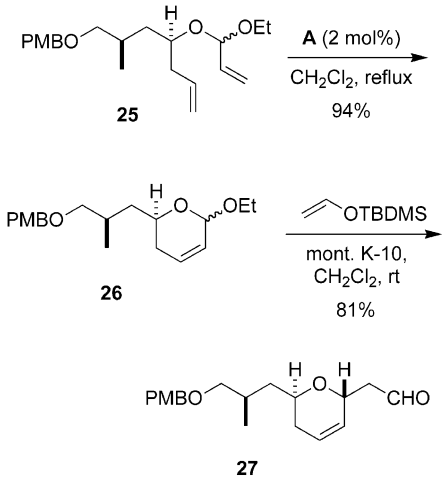
RCM has been employed as a key construct in syntheses directed toward laulimalide (**24**),[19] which stabilizes microtubules and is a potent inhibitor of cellular proliferation in several tumor cell lines.[20] Laulimalide bears two 3,6-dihydropyran units and a macrolactone that harbors a double-bond and an oxirane ring, a precursor of which would be another double bond. Interestingly, whereas the dihydropyran rings in **24** have been generated by RCM, the unsaturated lactone has not.[21]

Scheme 9



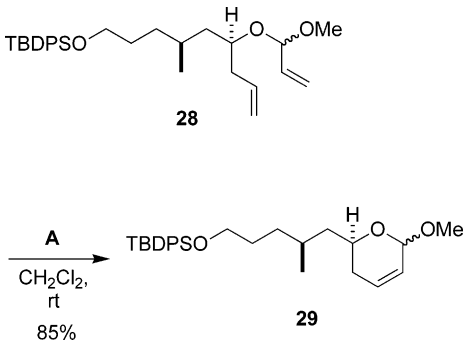
Several closely related entries to the C1−C12 fragment of laulimalide, which contains one of the two dihydropyran rings, have been reported.[22−24] For example, Mulzer cyclized **25**, which was prepared in six steps from commercially available (*S*)-2-methyl-3-hydroxybutyrate, in the presence of Grubbs catalyst **A** to give **26** (Scheme 10).[22] Subsequent selective displacement of the allylic ethoxy group with vinyloxy-*tert*-butyldimethylsilane in the presence of montmorillonite K-10 gave **27**. Similarly, Davidson used **A** to catalyze the cyclization of the diene **28**, which was prepared from (−)-citronellal in six steps, to give

Scheme 10



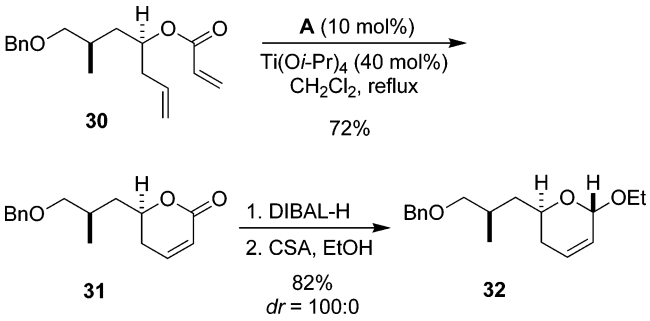
29 as a key step in their synthesis of the C1−C14 fragment of laulimalide (**24**) (Scheme 11).[23] They also

Scheme 11



reported the generation of the dihydropyran ring by a diastereoselective HDA reaction. In his total synthesis of laulimalide, Ghosh employed a very similar approach for the construction of the benzyl protected analogue of **29**.[24] He also described the RCM of the α,β-unsaturated ester **30** to provide the lactone **31** (Scheme 12). Use of a relatively large amount of **A**

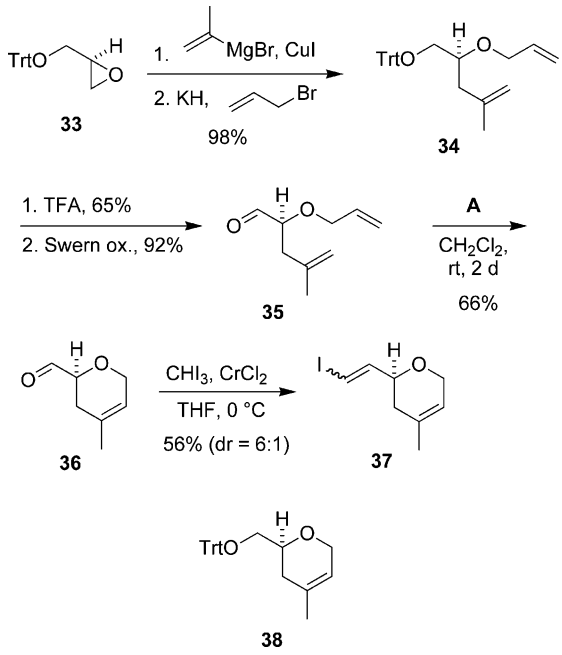
Scheme 12



(10 mol%) in the presence of Ti(O*i*Pr)$_4$, a tactic developed by Fürstner,[25] was found to be crucial for this cyclization. The subsequent reduction of **31** followed by acetal formation to give **32** proceeded with complete diastereoselectivity.

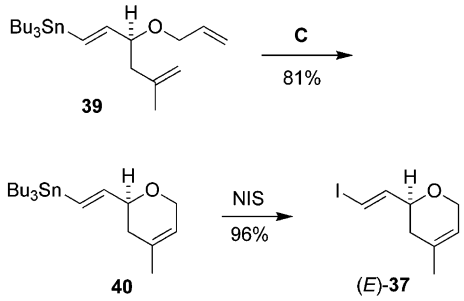
Key steps in Davidson's route to the C15−C28 fragment of laulimalide are shown in Scheme 13.[26a] The enantiomerically pure oxirane **33** was opened by nucleophilic attack of a cuprate at the less substituted carbon atom. Subsequent *O*-allylation of the resultant hydroxy group yielded **34**, which was converted into the diene **35**. Cyclization of **35** by RCM using Grubbs catalyst **A** delivered the dihydropyran **36**, which was subjected to a Takai iodo olefination reaction to form the C21−C22 double bond, albeit as a mixture of *E*- and *Z*-isomers. More efficient ways of forming this double bond starting from **36** include a Corey−Fuchs reaction followed by a Lindlar reduction,[24] a Kocienski-modified Julia coupling,[26b] a Horner−Wadsworth−Emmons reaction,[27] and an aldol condensation.[28] Alternatively, the RCM of the diene **34** gave the protected alcohol **38** in 95% yield, as shown by Mulzer[27] and Ghosh.[24b] While most of the synthetic approaches to (−)-laulimalide exploit RCM reactions to form the dihydropyrans, Paterson has employed an asymmetric Jacobsen−HDA reaction to prepare the dihydropyran **36**.[28]

Scheme 13



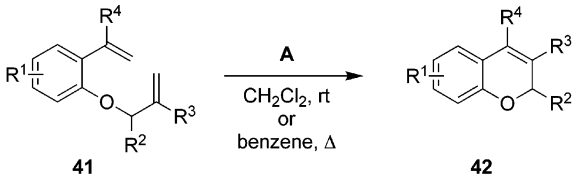
A more selective route to the vinyl iodide **37** was reported by Nelson in his synthesis of laulimalide (**24**).[29] Namely, cyclization of the geometrically and enantiomerically pure **39** provided **40** via a metathesis reaction that involved only the mono- and 1,1-disubstituted double bonds in **39**; the sterically more encumbered vinylstannane was not affected (Scheme 14). The vinyl iodide (*E*)-**37** was then effectively generated by reaction of **40** with NIS.

Scheme 14



Benzo-fused oxabicyclic compounds are found in a variety of important natural products and hence are interesting scaffolds for drug design. Of these, one prominent class of oxygen heterocycles are the chromenes.[30] Grubbs reported a facile route to 2*H*-chromenes that features a RCM reaction as the key transformation.[31] The requisite dienes **41** were prepared in either one step by a Mitsunobu coupling of an *o*-hydroxystyrene with a secondary alcohol ($R^2 \neq$ H, R^3 = H) or in two steps by an allylation of an *o*-hydroxybenzaldehyde followed by a Wittig olefination (R^2 = H, R^3 = H, CH_3) (Scheme 15). The RCM reactions of **41** generally proceeded smoothly with catalyst **A** (2 mol%) to furnish the chromenes **42** in high yields. The electronic properties of the ring substituents R^1 had little influence on the cyclization, and the catalyst **A** was tolerant of a variety of functional groups. However, when R^3 was a methyl group, the reaction required elevated temperatures,

Scheme 15



R^1 = H, 6-Br, 7-Et_2N, 6-NO_2, 7-MeO, 7-OAllyl, 7-$(CH)_4$-8;
R^2 = H, CH_3, *p*-MeOPhe; R^3 = H, CH_3; R^4 = H, CH_3

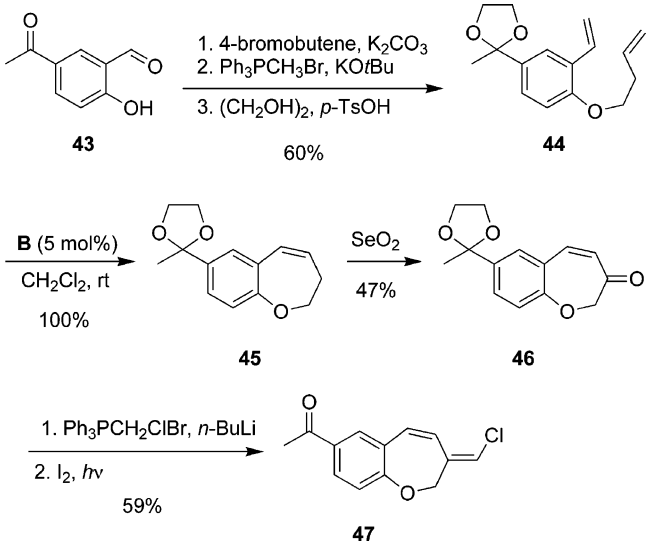
and when R^2 was either Ar or CH_3, the reaction times were longer and 5 mol% of **A** was required.

2.2. Seven-, Eight-, and Nine-Membered Cyclic Ethers

The synthesis of medium-sized rings from acyclic precursors may be difficult owing to entropic factors and transannular repulsions that develop as the ring is formed.[32] Like other cyclizations that produce such rings, RCM tends to work best when there are conformational constraints that favor ring formation. Such structural features include the presence of another ring, a *gem*-dimethyl group, or a *N*-tosyl group in the chain linking the reacting double bonds.[33,34]

That a benzene ring constitutes an excellent conformational constraint is illustrated by the use of RCM in recent syntheses of two natural products containing medium-sized oxacycles fused to a benzene ring. For example, pterulone (**47**) is a chlorinated fungal metabolite with interesting antifungal activities that was prepared by Grubbs.[35] The salicylaldehyde **43** was converted in three steps into **44**, which underwent a RCM reaction with the second-generation Grubbs catalyst **B** (Scheme 16). Although

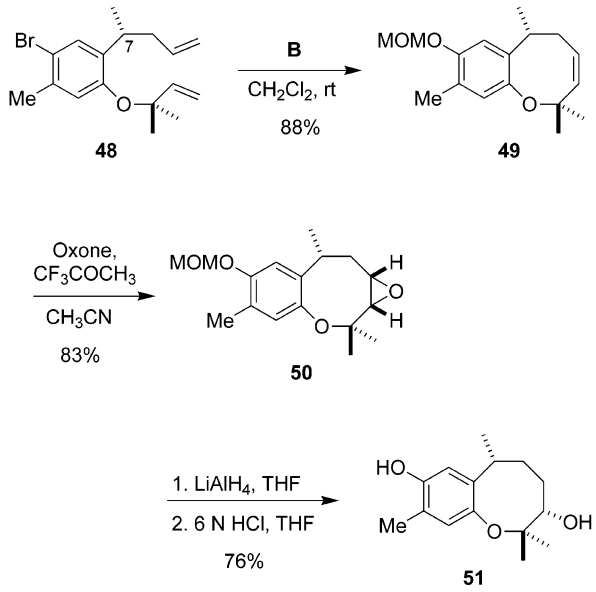
Scheme 16



the allylic oxidation of **45** was more difficult than anticipated, SeO_2 furnished the α,β-unsaturated alkene **46** in 47% yield. The synthesis of **47** was completed by another Wittig reaction followed by double-bond isomerization.

Shishido completed the enantioselective total synthesis of (−)-heliannuol A (**51**), a naturally occurring

Scheme 17

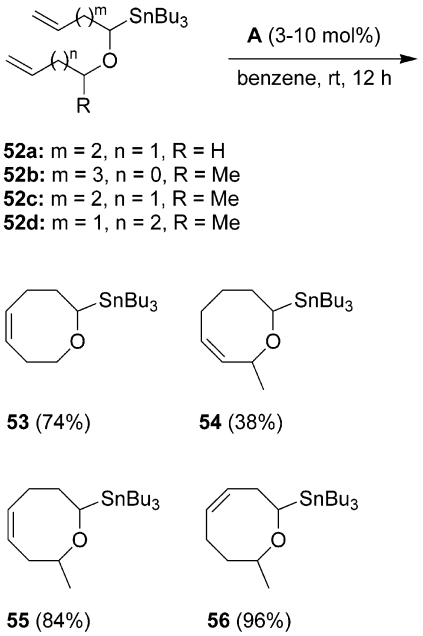


sesquiterpenoid that possesses an eight-membered benzo-fused oxacycle and exhibits strong allelopathic activity.[36] The diene **48** was constructed in 10 steps in a sequence in which the stereogenic center at C7 was set by the enzymatic resolution of a prochiral diol. Catalyst **B** induced RCM of the diene **48** in 88% yield (Scheme 17). The high yield for this cyclization might be a consequence of conformational constraints induced by both the benzene ring and the geminal dimethyl group.[37] Epoxidation of **49** with methyl(trifluoromethyl)dioxirane proceeded with complete diastereoselectivity to give **50**. Regioselective opening of the oxirane ring in **50** from the less hindered side and removal of the MOM protecting group completed the synthesis of **51**.

Medium-ring ethers are a common structural motif found in many toxins that are isolated from marine organisms and in metabolites found in the *Laurencia* species. Because these compounds often lack a fused ring, other tactics to introduce conformational constraints that will enable cyclizations via RCM have been devised.[38] In this context, Linderman discovered that introducing a removable tributylstannyl substituent α to the oxygen atom in α,ω-unsaturated acyclic ethers gave substrates that cyclized readily by RCM to provide eight-membered oxacycles (Scheme 18).[39] The precursors **52a**−**d** were easily formed by adding lithiotributylstannane to an aldehyde, followed by displacement of a derived mesylate with a terminal alkenol, and the cyclizations of **52a**−**d** in the presence of **A** (3−10 mol%) proceeded smoothly to give **53**−**56**. When the tributylstannyl group was replaced with a *tert*-butyl group, the RCM still occurred albeit in lower yield, presumably owing to the smaller size of a carbon atom relative to a tin atom. The stannyl group was transmetalated by lithio destannylation, and the intermediate carbanion could be trapped with electrophiles to provide substituted oxocines.

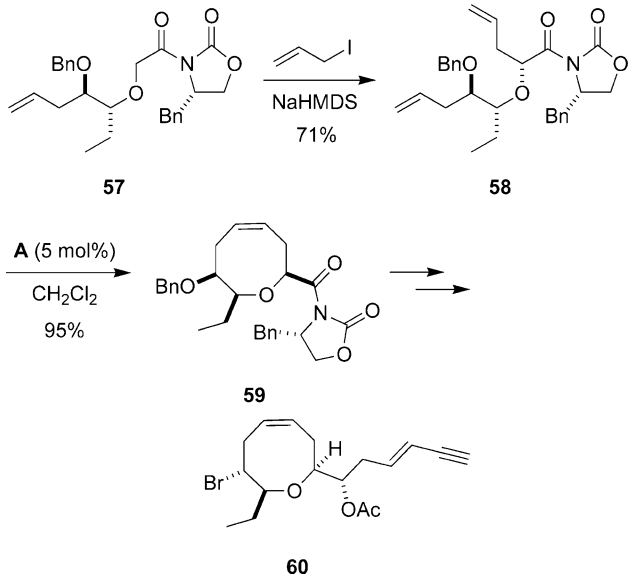
Crimmins has discovered that α,ω-dienes having vicinal stereogenic centers bearing oxygen atoms may undergo facile cyclization via RCM to produce α,α'-*cis*- and α,α'-*trans*-disubstituted eight- and nine-

Scheme 18



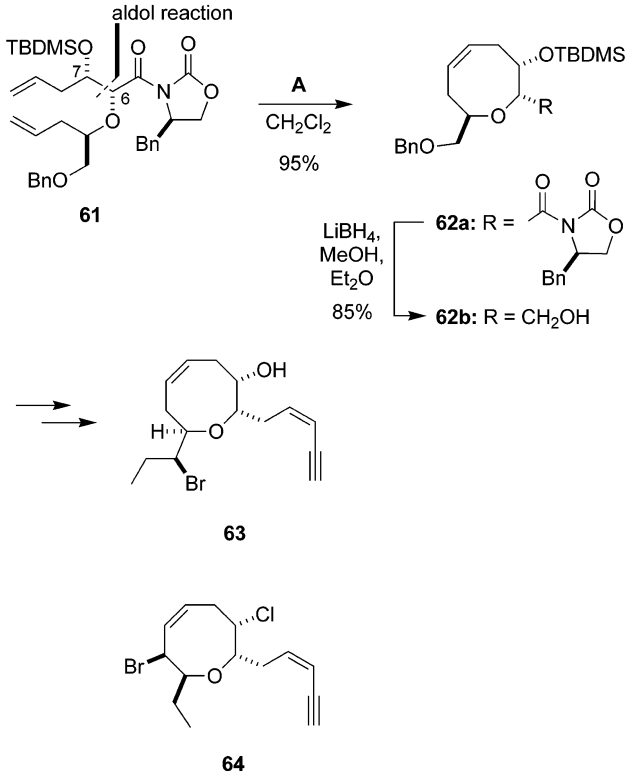
membered ring ethers. It was proposed that the gauche effect of 1,2-dioxygen substitution stabilizes a conformation in which the pendant olefinic side chains are gauche and hence predisposed in orientations necessary for cyclization. The requisite 1,2-dioxy intermediates may be readily prepared by enantioselective aldol and alkylation reactions. For example, a key step in a synthesis of (+)-laurencin (**60**) involved the RCM of **58**, which was formed by stereoselective (dr >95:5) alkylation of the enolate of **57**, using catalyst **A** to furnish the α,α'-*cis*-oxocene **59** (Scheme 19).[40] The conversion of **59** into (+)-laurencin (**60**) required 10 steps.

Scheme 19



Crimmins also exploited the gauche effect in his synthesis of (+)-prelauretin (**64**) (Scheme 20).[40c] Thus, treatment of **61**, which was prepared via a diastereoselective aldol reaction, with Grubbs catalyst **A** gave **62a** with no detectable dimerization. Reductive

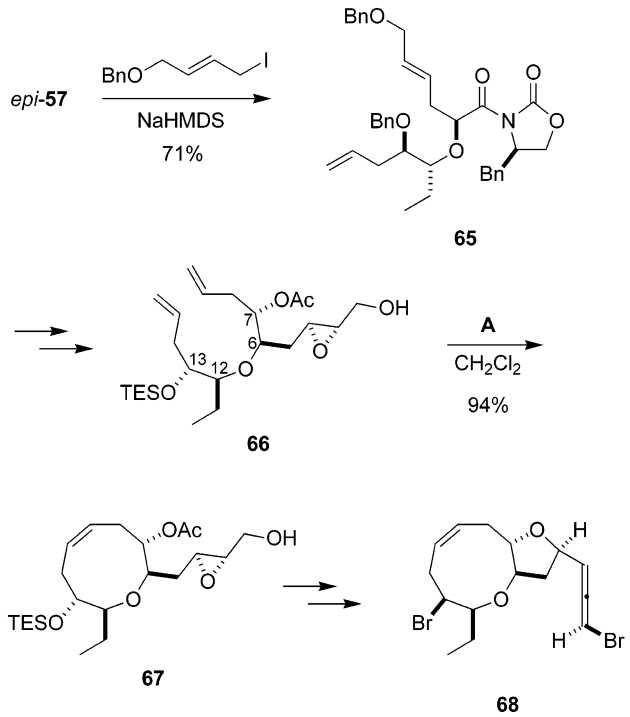
Scheme 20



removal of the chiral auxiliary furnished the primary alcohol **62b** that was converted into **63**. He has also applied a similar strategy to the synthesis of (+)-obtusenyne (**64**).[41]

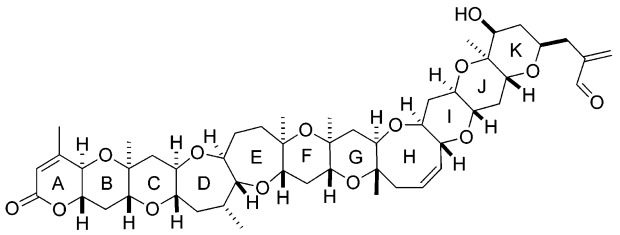
To address the question of whether the gauche effect induced by vicinal dihydroxy groups would enable generation of nine-membered cyclic ethers, Crimmins embarked on the synthesis of isolaurallene (**68**) (Scheme 21).[42] The key step in the synthesis of

Scheme 21

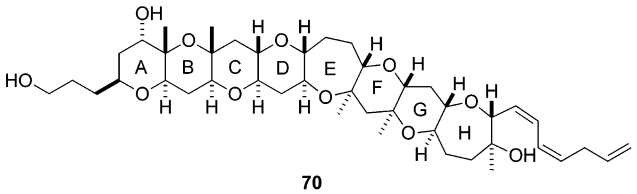


the diene **66** was the asymmetric alkylation of *epi*-**57** that proceeded with excellent diastereoselectivity (97:3). Cyclization of **66** with Grubbs catalyst **A** occurred efficiently to furnish the nine-membered oxacycle **67**. It was argued that the diene **66** underwent such facile closure because of a gearing effect that was created by two synergistic gauche effects at C6−C7 and C12−C13. The substituents and side chains on **67** were then elaborated to deliver (−)-isolaurallene (**68**).

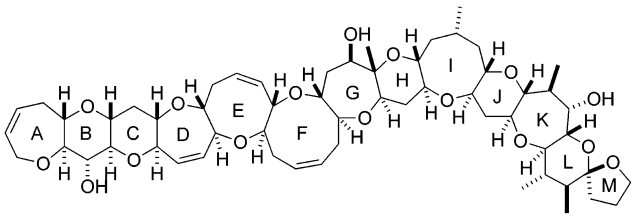
Since the discovery of brevetoxin B (**69**) in 1981, a number of ladder-like polycyclic ethers including gambierol (**70**) and ciguatoxin CTX3C (**71**) have been



69



70

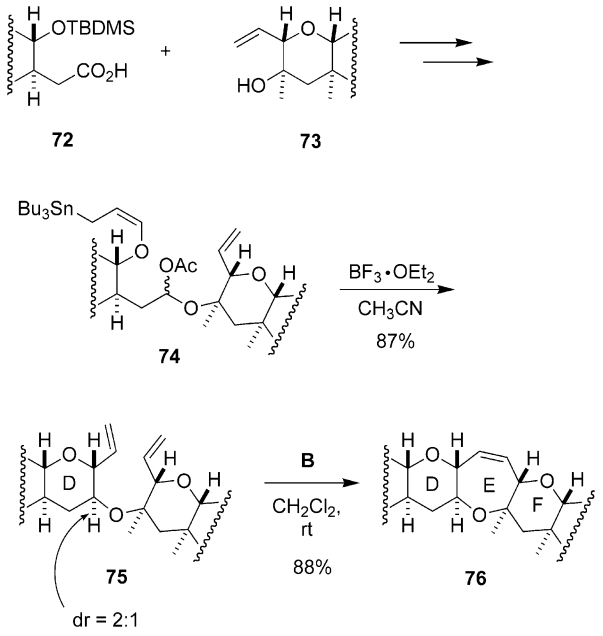


71

isolated from marine algae.[43,44] These algae proliferate during red tide incidents, which are the result of vast phytoplankton blooms that turn the sea red, brown, or green. Indeed, it is believed that compounds related to **69**−**71** are responsible for the massive fish kills resulting from red tides in several regions of the world. The ciguatoxins are even more toxic than the brevetoxins and are responsible for ciguatera, a severe disease caused by consuming poisoned seafood.

Owing to their structural complexity and the potent biological activities, polycyclic ethers as **69**−**71** have been attractive targets for synthesis and for the development and testing of new methods. In this context, Yamamoto recently completed the synthesis of gamberiol (**70**) by a convergent strategy featuring the intramolecular allylation of α-acetoxy ethers and a subsequent RCM reaction to generate the DE ring subunit, thereby connecting the ABC and FGH fragments (Scheme 22).[45] Thus, the carboxylic acid **72** and the alcohol **73** were coupled under Yamaguchi conditions to give an ester that was converted into the acetoxy ether **74** in four transformations. Com-

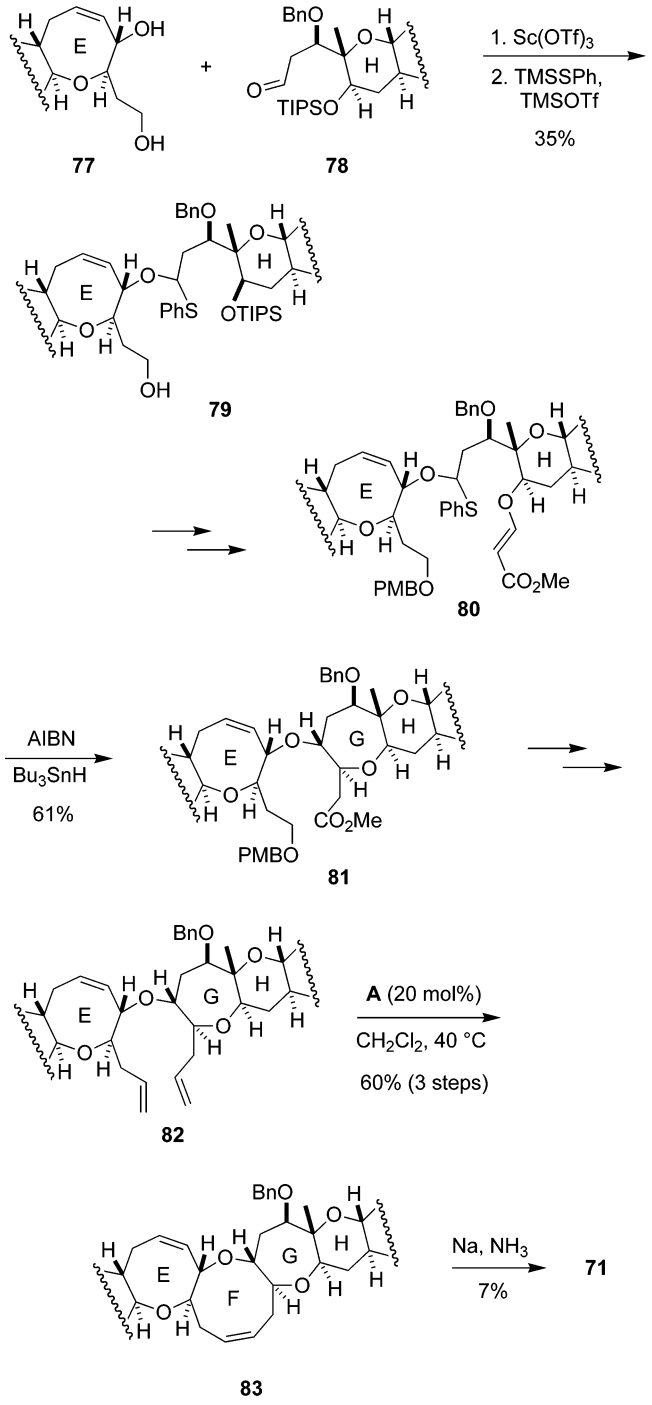
Scheme 22



pound **74** cyclized upon treatment with Lewis acid to form the tetrahydropyran D ring in **75** as a mixture (2:1) of epimers. This methodology has been shown to be generally applicable for constructing six-, seven-, and eight-membered cyclic ethers, usually with higher diastereoselectivities than 2:1.[45b] The E ring was then formed by RCM of **75** in the presence of the second-generation Grubbs catalyst **B**. It was found that similar substrates also underwent efficient RCM reactions using **A** as the catalyst.[45a] The synthesis of gamberiol (**70**) was then completed by hydrogenation of the E ring double bond and refunctionalization of the H ring.

Hirama recently completed an elegant total synthesis of CTX3C (**71**) that convincingly demonstrates the utility of RCM in the synthesis of complex molecules as every double bond found in **71** was formed by a RCM.[46] This strategy is exemplified in the final stage of the synthesis of **71** in which the FG rings are formed to unite the ABCDE and the HIJKLM fragments **77** and **78** that contain the other 11 ether rings (Scheme 23). In the event, the ABCDE fragment **77** was condensed with the HIJKLM aldehyde **78**, and the resultant cyclic *O*,*O*-acetal was subsequently transformed into the *O*,*S*-acetal **79**. Refunctionalization of **79** led to **80**, which underwent stereoselective radical cyclization onto the vinylogous carbonate to form the G ring and to give **81**. The side chains on **81** were then modified to gave the diene **82**, which underwent RCM upon treatment with Grubbs catalyst **A** to furnish fully protected CTX3C **83**. This step demonstrates the high chemoselectivity of the RCM reaction as the double bonds in the A, D, and E rings were untouched. The synthesis of **71** was completed by global deprotection of **83** under Birch conditions. Unfortunately, this deprotection proved much more difficult than anticipated, and after successfully elaborating the 3 nm long structure containing 13 rings and 30 stereogenic centers, **71** was obtained in only 7% yield.

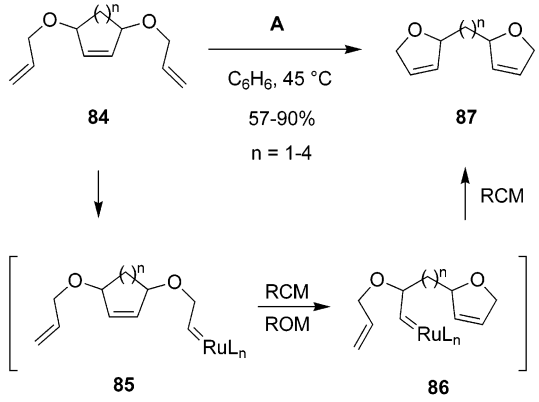
Scheme 23



2.3. Cyclic Ethers via Tandem Metathesis Reactions

The tactic of using tandem ring-opening−ring-closing metathesis (ROM−RCM) processes to prepare polycyclic ethers was introduced by Grubbs. This sequence is nicely illustrated by the transformations of the readily available bis-allyl ethers **84** with 3−6 mol% of the benzylidene carbene **A** to afford the bicyclic products **87** in good to excellent yields (Scheme 24).[47] In this sequence the endocyclic double bond served as the relay between the two allylic ether groups. Although cyclohexene is a poor substrate in ring-opening−polymerization metathesis, the reaction of **84** (n = 2) proceeded in good yield, suggesting

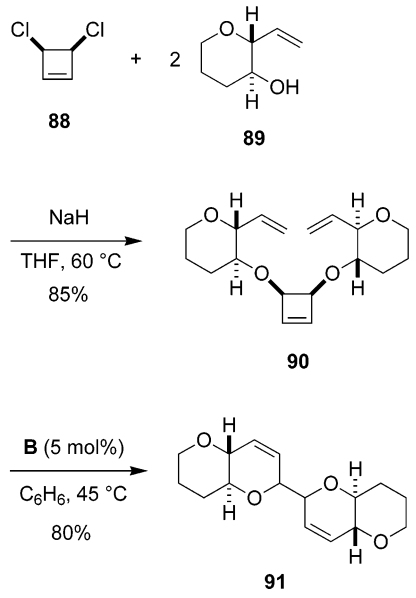
Scheme 24



there may be a substantial entropic driving force associated with ethylene production. Ancillary experiments in which substrates with increasing olefinic substitution were used at different concentrations support a mechanism in which the initial metathesis occurs on an olefinic side chain (i.e., **84** → **85** → **86** → **87**).

Nicolaou has applied tandem ring-opening−ring-closing metathesis to form complex cyclic polyethers using *cis*-3,4-dichlorocyclobutane (**88**) as a tethering building block. Thus, **88** was treated with 2 equiv of the alkoxide derived from enantiopure tetrahydropyran **89** to give **90** via two stereoselective *syn* S_N2' displacements (Scheme 25).[48] Although **90** did not

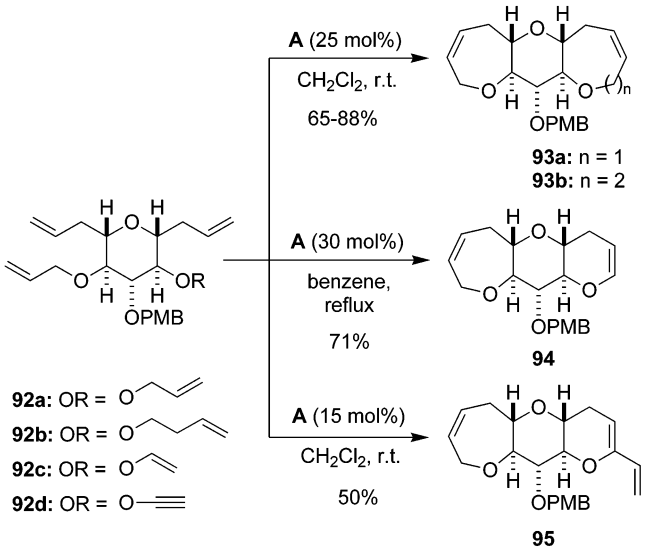
Scheme 25



undergo olefin metathesis in the presence of catalyst **A**, use of the second-generation catalyst **B** led to the tetracycle **91**, which was modified by stereospecific epoxidation and subsequent opening of the oxirane. Synthetic studies toward maitotoxin and construction of polycyclic compounds similar to **91** via the RCM of olefinic esters using Tebbe-type reagents have also been reported.[49]

Another approach to the synthesis of *trans*-fused polyoxacyclic frameworks involving double RCM reactions of allylic ethers, enol ethers, and alkynyl

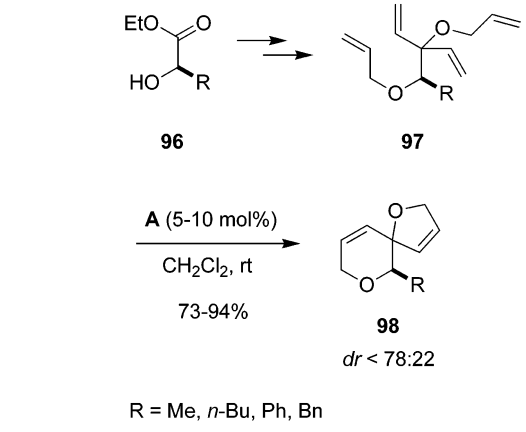
Scheme 26



ethers has been developed by Clark (Scheme 26).[50] The unsaturated substrates **92a**−**d**, which were prepared in 12−14 steps starting from commercially available tri-*O*-acetyl-D-glucal, were treated with 15−30 mol% of the first-generation Grubbs catalyst **A** to give the tricyclic ethers **93a**,**b** in very good yields; no bridged bicyclic ethers were isolated. The efficient formation of **94** via RCM of an enol ether was somewhat surprising, as enol ethers are normally not very good substrates for **A**.[50b] In another example, the tricyclic system **95**, which corresponds to the ABC fragment of CTX3C (**71**), was produced via an enyne metathesis reaction.[50c,d] All of these cyclizations required relatively high catalyst loadings and extended reaction times; however, when the more reactive Schrock catalyst **C** was used, lower yields of products were obtained.

There are a number of other reports of syntheses of bicyclic ethers by double RCM reaction.[51] One of these features the diastereoselective cyclization of a substrate bearing diastereotopic vinyl groups (Scheme 27).[51e] The enantiomerically pure tetraenes **97** were

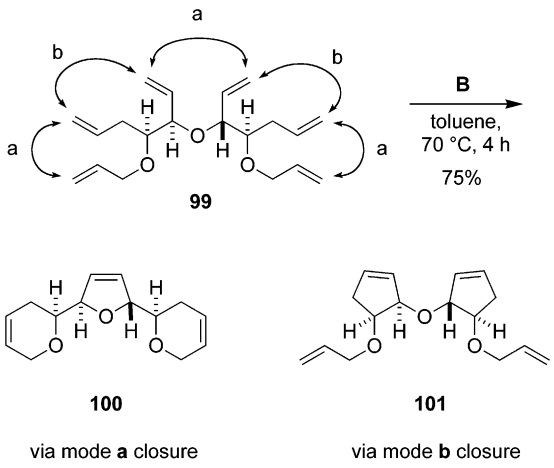
Scheme 27



prepared by reaction of the α-hydroxy esters **96** with 2 equiv of vinyl Grignard reagent followed by allylation of the hydroxy groups. Although the RCM reactions of **97** gave the spiro compounds **98** in good yields, the diastereoselectivity was rather low.

Triple RCM reactions have also been recorded, as exemplified by the cyclization of the hexaene **99**, which was prepared in enantiomerically pure form by a nine-step sequence in which a Sharpless epoxidation was used to introduce the absolute stereochemistry (Scheme 28).[52] Although cyclization of **99**

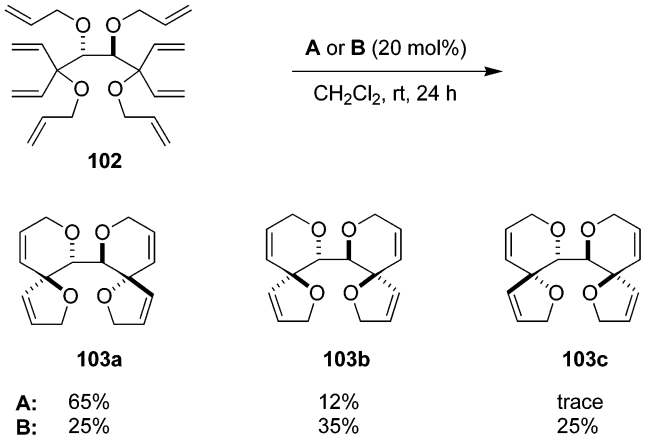
Scheme 28



could occur by two manifolds to give **100** and/or **101**, reaction of **99** with the second-generation Grubbs catalyst **B**, which was more effective than **A**, led to the exclusive formation of the tricyclic ether **100**. Like an earlier report,[51a] this experiment shows that the formation of cyclic ethers is favored over the formation of carbocycles of the same ring size.

As many as four RCM cyclizations have been conducted with a single substrate, although it is unlikely that this record will endure. The octaene **102** was synthesized from L-tartrate and cyclized in the presence of **A** to give a mixture of the C_2 symmetric bis-spirocyclic ether **103a** and the unsymmetric diastereomer **103b** (Scheme 29).[53] When the more

Scheme 29

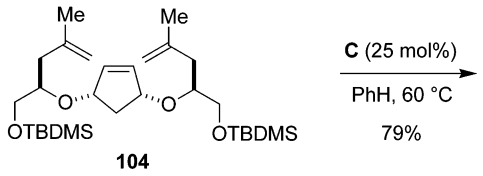


reactive catalyst **B** was used, the combined yield increased, but the selectivity decreased, with the three diastereomeric bis-spirocyclic ethers **103a**−**c** being formed in similar amounts. On the basis of experiments that were allowed to proceed to partial completion, it seems likely that a dihydrofuran ring

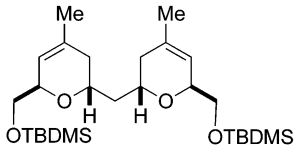
is formed as the first step, but it has not yet been possible to elucidate additional features of the reaction pathway.

It is thus apparent that multi-RCM reactions constitute a powerful tool for the rapid assembly of complex polycyclic ethers. Indeed, such strategies have been used to develop approaches to natural products. For example, **105**, which is a symmetric precursor of the C(20)−C(36) subunit of halichondrin B, has been prepared in a one-pot operation involving a ring opening and a double ring closing metathesis reaction of **104** employing Schrock's catalyst **C** (Scheme 30).[54] Another interesting application is

Scheme 30



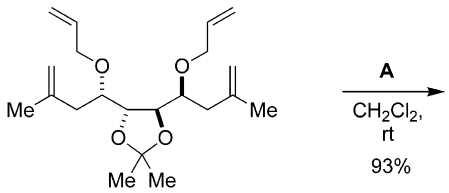
104



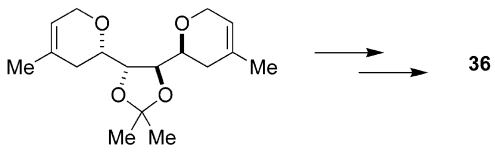
105

illustrated by the two-directional approach toward the C15−C27 fragment of (−)-laulimalide (**24**) that is outlined in Scheme 31.[55] The metathesis precursor

Scheme 31



106



107

106 was synthesized from D-mannitol and cyclized in excellent yield to give the bis-dihydropyran **107** that was transformed into **36** in two more steps. Owing to the diverse substitution patterns of hydropyran rings in natural products, care must be exercised in applying a multi-RCM strategy, as it may not be superior to using sequential RCM reactions.

2.4. Macrocyclic Ethers

There are numerous reports of the synthesis of small- and medium-ring ethers by RCM, but the application of such constructions to forming large cyclic ethers is relatively rare. Nicolaou's use of RCM to generate a strained 11-membered macrocyclic ether in the total syntheses of coleophomones B [(16*E*)-**111**] and C [(16*Z*)-**111**] is thus noteworthy.[56] The triketone **108** was first assembled in a highly convergent fashion. When **108** was treated with catalyst **B**, cyclized products were obtained in <20% yield (Scheme 32). However, independent cyclizations of each of the derived enol ethers **109a** and **109b** in the presence of catalyst **B** proceeded with high regio- and stereoselectivity to give the macrocycles **110a** and **110b**, each corresponding to a different coleophomone framework. No spiro cyclopentene product was isolated. The stereochemistry of the $\Delta^{16,17}$ double bond formed by the RCM reaction depended upon the structure of the starting enol ether. Because only the prenyl group *cis* to the adjacent C12 methyl group underwent ring closure, the remaining prenyl side chain and the C12 methyl group are *trans* to one another. The total syntheses of (16*E*)-**111** and (16*Z*)-**111** were then completed in three steps from **110a** and **110b**.

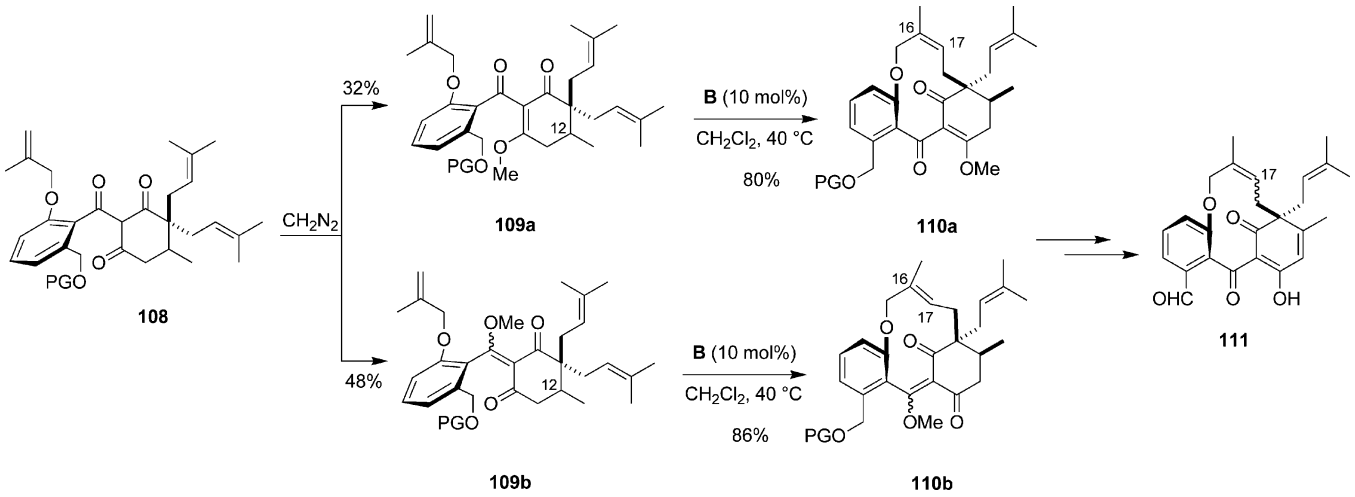
An extremely efficient, albeit somewhat exotic, application of RCM to the preparation of macrocyclic ethylene glycols involves preorganizing the reaction partners with transition metals as templates to synthesize catenanes and knots.[57] For example, Sauvage synthesized a molecular trefoil knot using a RCM approach. When the iron bis(terpyridine) complex **112** was treated with catalyst **A** the knot **113** was isolated in as a 55:45 mixture of *cis*- and *trans*-isomers (Scheme 33). This strategy for the synthesis of these topologically novel structures has the advantage that only four reaction centers participate in the cyclizations. In previous entries to these compounds, the phenolic functions were alkylated with a polyoxyethylenic diiodide, thereby involving eight reaction centers and providing the products in diminished yields.[57b]

2.5. Bridged Bicyclic Ethers

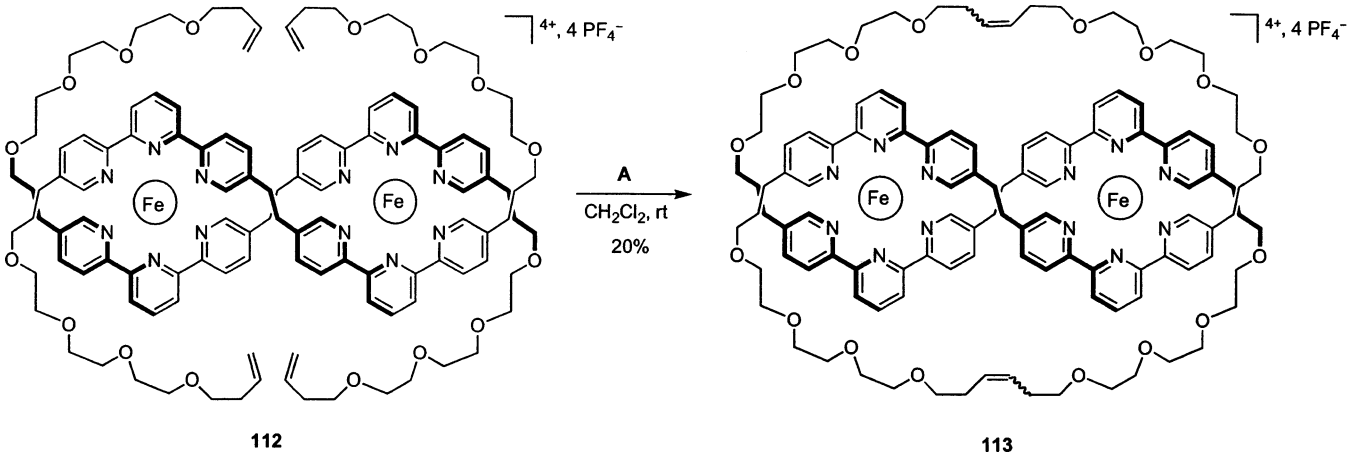
Applications of RCM to the syntheses of bridged bicyclic oxygen heterocycles are relatively rare, despite the fact that such structures are commonly found in natural products[58] and are useful templates in organic synthesis.[59] It is thus noteworthy that Grubbs recently reported a synthesis of the bicyclic ether (−)-frontalin (**116**) employing an approach that featured a RCM reaction.[60] The metathesis substrate **114** was prepared as a mixture of C5 epimers, (1*S*,5*S*)-**114** and (1*S*,5*R*)-**114**, in which the absolute stereochemistry at C1 was set by an asymmetric Mukaiyama allylation (Scheme 34). When this mixture was treated with **A**, (1*S*,5*S*)-**114** and the cyclized product **115** were obtained. The uncyclized (1*S*,5*S*)-**114** was equilibrated under acidic conditions to provide a mixture of (1*S*,5*S*)-**114** and (1*S*,5*R*)-**114** that was resubjected to the RCM conditions. The synthesis of (−)-**116** was completed by hydrogenation of the double bond in **115**.

Burke has also developed a concise strategy for the stereoselective synthesis of bridged bicyclic ethers that has been applied to preparing a number of

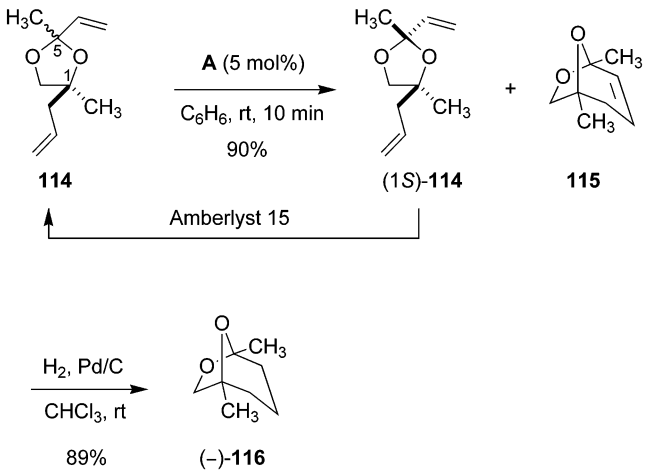
Scheme 32



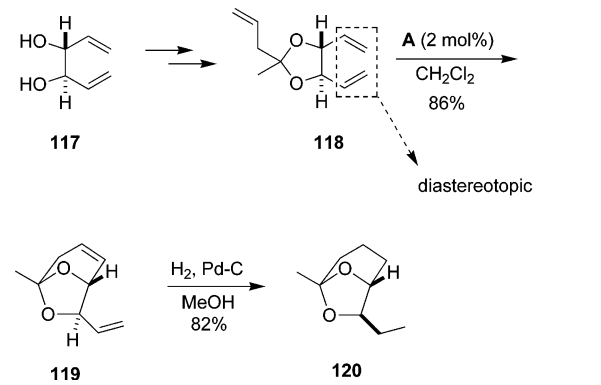
Scheme 33



Scheme 34



Scheme 35

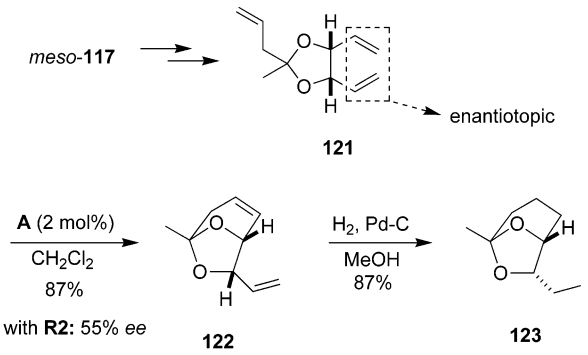


targets.[61] For example, the enantiomerically pure diol **117** was transformed in two steps into the ketal **118** wherein the two vinyl groups are diastereotopic (Scheme 35).[61a] The RCM reaction of **118** in the presence of Grubbs catalyst **A** furnished the bridged bicyclic acetal **119** with complete diastereoselectivity. Reduction of **118** by catalytic hydrogenation then gave (+)-*exo*-brevicomin (**120**).

When the achiral diol *meso*-**117** was used as the starting material, the derived acetal **121**, in which the two vinyl groups are enantiotopic, underwent RCM to give **122**; reduction of **122** then provided *endo*-brevicomin (**123**) (Scheme 36). In the first application of the chiral Schrock–Hoveyda catalyst **R2** (see section 2.9) to natural product synthesis, cyclization of **121** in the presence of **R2** furnished **122** in an enantiomeric excess of 55%. The low ee is likely a consequence of the high catalyst–substrate specificity of chiral Mo-alkylidenes, and improved enantioselectivity might be obtained using other chiral catalysts such as **R3**–**R7** (see section 2.9).

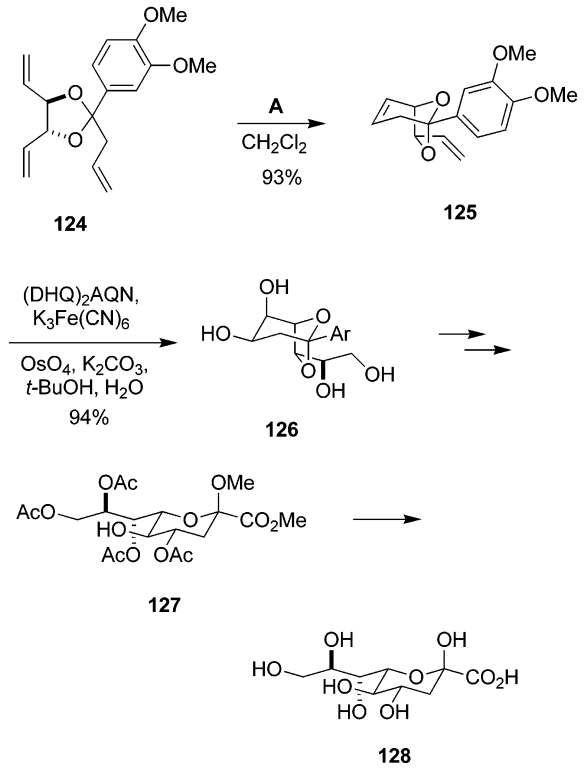
Hydrogenation of the carbon–carbon double bond formed by the RCM reaction of a diene might be

Scheme 36



regarded as an undesirable waste of functionality. It is thus noteworthy that Burke has exemplified a more expedient use of such a double bond in developing a synthesis of sialic acids, a family of biologically important compounds related to neuraminic acid, via a bicyclic acetal related to **119** and **122**.[61b] In the event, the RCM of **124** in the presence of **A** gave **125**, in which the dimethoxyphenyl ring served as a masked carboxyl group (Scheme 37).[61c] Bis-hydroxy-

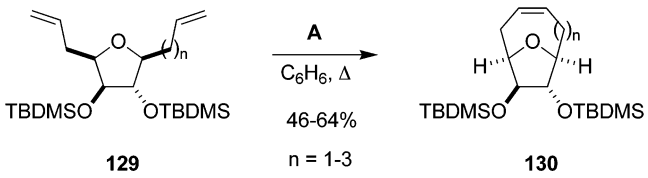
Scheme 37



lation of **125** under Sharpless conditions gave **126**. The tetraol **126** was then converted into the ester **127**, which had previously been transformed into the sialic acid KDN (**128**).[62]

A RCM approach toward medium-sized oxabicyclic systems in enantiomerically pure form is depicted in Scheme 38. The dienes **129** were easily synthesized in a stereospecific fashion from inexpensive, commercially available carbohydrates using straightforward procedures. Upon treatment with Grubbs catalyst **A** in refluxing benzene, they underwent meta-

Scheme 38

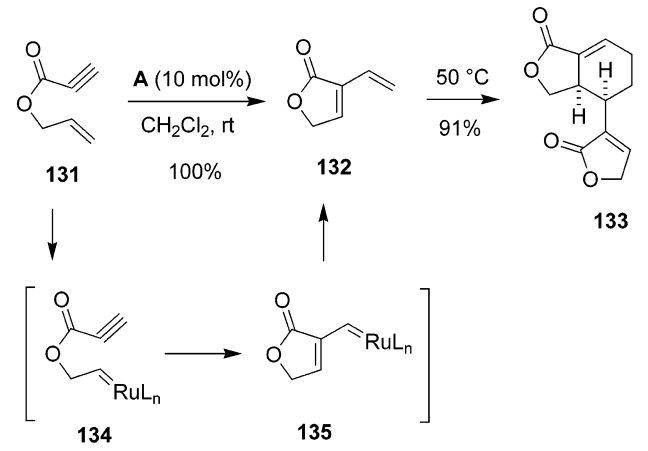


thesis to afford the bicyclic products **130** in good yields.[63]

2.6. Five- and Six-Membered Lactones

In contrast to the numerous applications of RCM to the synthesis of dihydrofurans and dihydropyrans, there are fewer reports of forming five- and six-membered lactones via RCM reactions. Hoye reported a nice example of a tandem enyne metathesis/Diels−Alder reaction as the key step in the synthesis of the butenolide natural product differolide (**133**).[64] When the Grubbs catalyst **A** was added slowly to allyl propynoate (**131**), enyne metathesis ensued to generate the diene **132**, which underwent spontaneous dimerization via a [4 + 2]-cycloaddition to give differolide (**133**) (Scheme 39). The Diels−Alder reaction

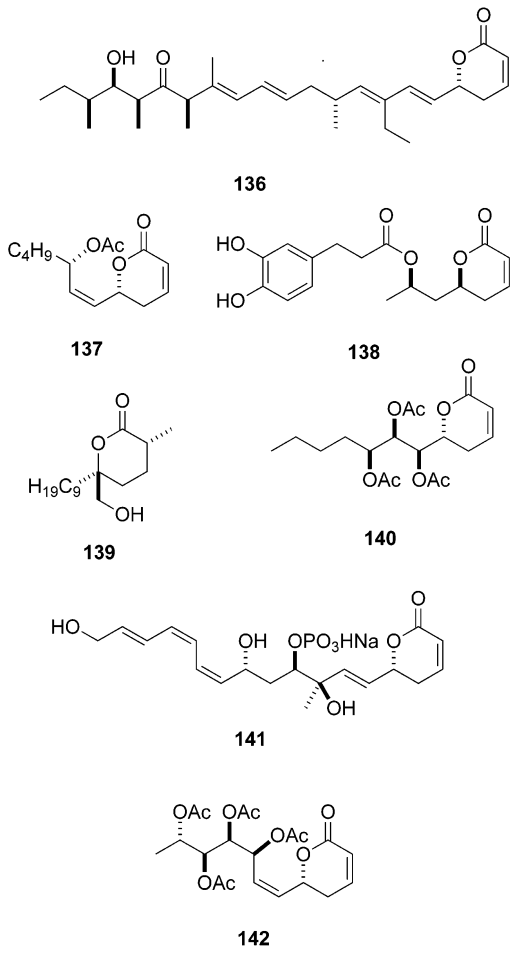
Scheme 39



proceeded with complete stereoselectivity and 9:1 regioselectivity. Investigation of the enyne RCM reaction by ^{1}H NMR suggested that the benzylidenecarbene **A** initially reacted with the double bond in **131** to give **134** that then underwent RCM to give **135**. This "ene−then−yne" mechanism was supported by the finding that a high substrate concentration was necessary to achieve high conversion rates.

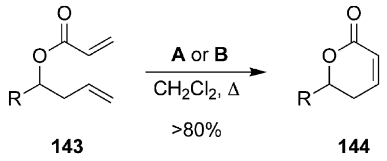
Six-membered lactone rings constitute a structural feature common to numerous biologically active natural products,[65] many of which exhibit antitumor properties. Members of this class of compounds that have been synthesized using RCM include laulimalide (**24**),[24] callystatin A (**136**),[67a] umuravumbolide (**137**),[67b] tarchonanthuslactone (**138**),[67c] malyngolide (**139**),[66] boronolide (**140**),[67e] fostriecin (**141**),[67d,f] and spicigerolide (**142**).[67g]

The strategies that were developed for preparing all of these natural products featured RCM reactions wherein allyl acrylates **143** were treated with either Grubbs catalyst **A** or **B**, sometimes in the presence



of a Lewis acid such as titanium tetraisopropoxide, to yield **144** (Scheme 40). Hydroxyl groups have typically been protected during the RCM step, although this tactic was more frequently a consequence of the synthetic pathway rather than because of problems with the ruthenium catalysts.

Scheme 40

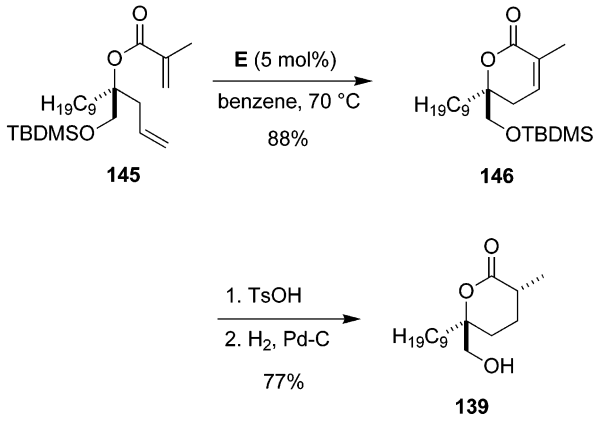


An illustrative example of using a RCM in the synthesis of valerolactone-derived natural products is found in Honda's synthesis of malyngolide (**139**) (Scheme 41).[66] The RCM substrate **145** was first prepared by a sequence that featured a Sharpless epoxidation to generate the first stereocenter. When **145** was treated with Grubbs catalyst **A**, the lactone **146** was obtained in low yield. However, use of 1 mol% of the more reactive and recyclable Hoveyda catalyst **E**[68] afforded **146** in very good yield, and the synthesis of **139** was then completed in two steps.

2.7. Nine- and Ten-Membered Lactones

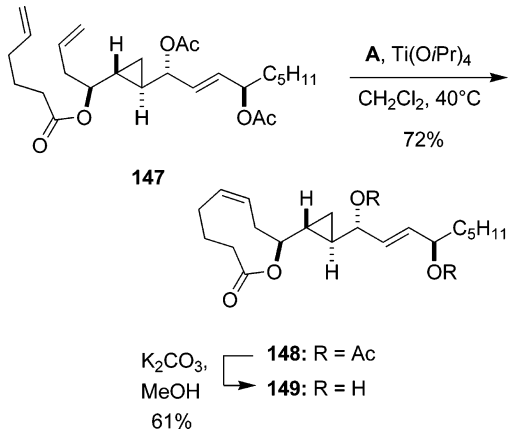
The formation of medium-size lactones by RCM constitutes a considerable challenge, since the inherent ring strain predisposes cycloalkenes containing

Scheme 41



8−11 atoms toward ring-opening metathesis or ring-opening metathesis polymerization. A rare example of preparing the nine-membered lactone moiety of a natural product by RCM was reported by Takemoto in a synthesis of halicholactone (**149**) (Scheme 42).[69]

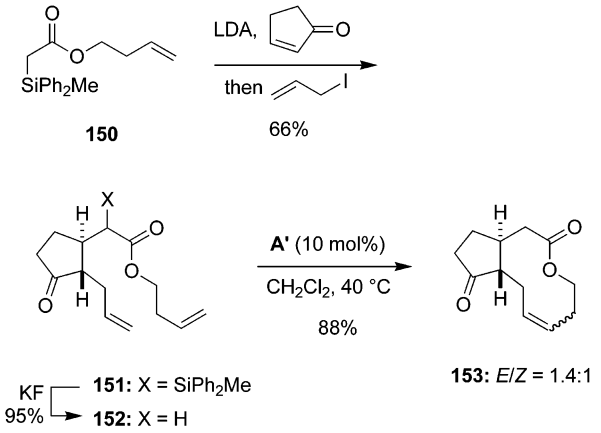
Scheme 42



After considerable experimentation, it was discovered that **147** at high dilution underwent efficient RCM using the binary catalyst system of **A** and Ti(O*i*Pr)$_4$, which was first reported by Fürstner,[70] to give the desired *Z*-isomer **148** as the major product together with 11% of the corresponding dimer. The synthesis of **149** was completed by methanolysis of the two acetyl groups. When these hydroxy groups were protected as their corresponding SEM or MOM ethers, the yield of the RCM reaction was only 19%; 45% of the starting material was recovered as was 8% of a dimer.

The first construction of a 10-membered lactone using a RCM was reported by Fürstner and Müller in 1997 in their synthesis of the jasmine ketolactone (*Z*)-**153**, a minor component of the essential oil of jasmine.[70] The first step in the diastereoselective synthesis of the RCM substrate **152** involved an efficient three-component reaction with the lithium enolate derived from **150**, cyclopentenone, and allyl iodide (Scheme 43). The methyldiphenylsilyl group, which was required for the selective 1,4-addition of the enolate to cyclopentenone, was removed by reacting **151** with KF in aqueous methanol to give **152**. Heating a dilute solution of **152** in the presence of

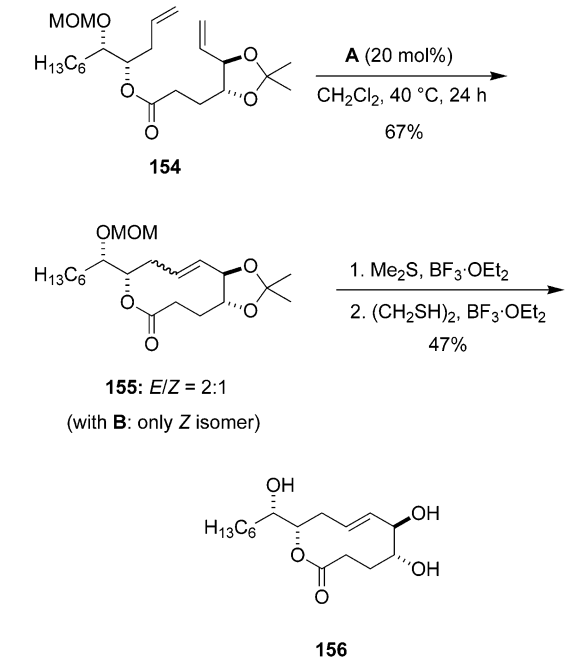
Scheme 43



A' then furnished **153** as a mixture (1.4:1) of *E*/*Z*-isomers in 88% combined yield. The natural product (*Z*)-**153** was separated by chromatography.

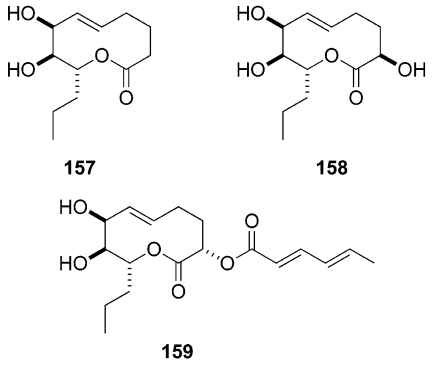
Marco recently reported a total synthesis of microcarpalide (**156**), a naturally occurring nonenolide with cytotoxic and antimicrofilament activity,[71] by an approach that featured the RCM of **154**, which was prepared from (*S*,*S*)-tartaric acid and (*R*)-glycidol. When the RCM was catalyzed by **A**, a mixture (*E*/*Z* = 2:1) of macrocyclic lactones **155** was obtained from which the *E*-isomer was isolated by chromatography (Scheme 44). Alternatively, treatment of **154** with the

Scheme 44



second-generation catalyst **B** furnished almost exclusively the thermodynamically more stable (*Z*)-**155**. This observation is in agreement with those of Grubbs, who found that the *E*/*Z*-ratio in ring-closures using **B** is not kinetically controlled but is rather the result of an equilibration of the products (see Scheme 49).[72] The synthesis of **156** was then completed by global deprotection of **155** in two steps.

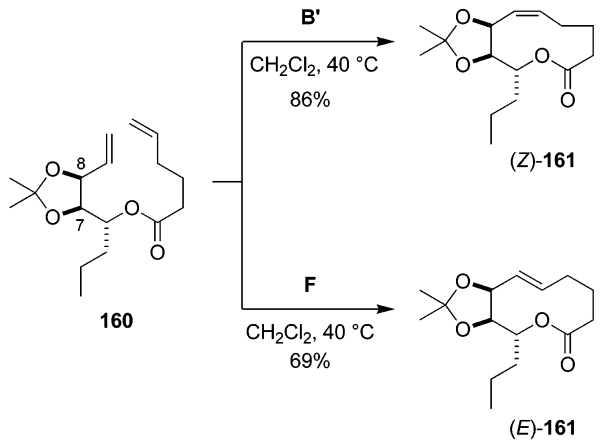
Fürstner reported the first total syntheses of the phytotoxic agents herbarumin I (**157**) and II (**158**) and of the closely related pinolidoxine (**159**).[73] All



possible stereoisomers of **159** were prepared, and the spectra and analytical data of each were compared with those reported for the natural product, thereby unambiguously establishing the structure of this promising herbicidal agent and correcting a previous assignment.[74]

The nonenolides **157**−**159** each contain a carbon−carbon double bond, so RCM clearly emerged as an attractive reaction that could provide a convergent approach to these targets. The salient features of using RCM in these syntheses are illustrated in the steps leading to herbarumin I (**157**) (Scheme 45). The

Scheme 45



diene **160** was prepared from D-ribose in a few steps by standard methods. The isopropylidene protecting group spanning the oxygen atoms at C7 and C8 was expected to stabilize a conformation of **160** that would be predisposed toward ring closure. Semiempirical calculations for **161** revealed that the *Z*-isomer is about 3.5 kcal mol^{-1} more stable than the *E*-isomer. Hence, conducting the RCM of **160** and related dienes under conditions of thermodynamic control would be expected to be counterproductive for obtaining the *E*-alkenes found in **157**−**159**. This prediction then suggested that RCM catalysts known to equilibrate the initial products should not be employed,[72] and it is gratifying that the results obtained using two different RCM catalysts were fully consistent with this hypothesis. Namely, cyclization of **160** with the second-generation catalyst **B**', which was known to provide mixtures enriched with the thermodynamically favored product, led to the selective formation of (*Z*)-**161**. In contrast, exposure of the diene **160** to

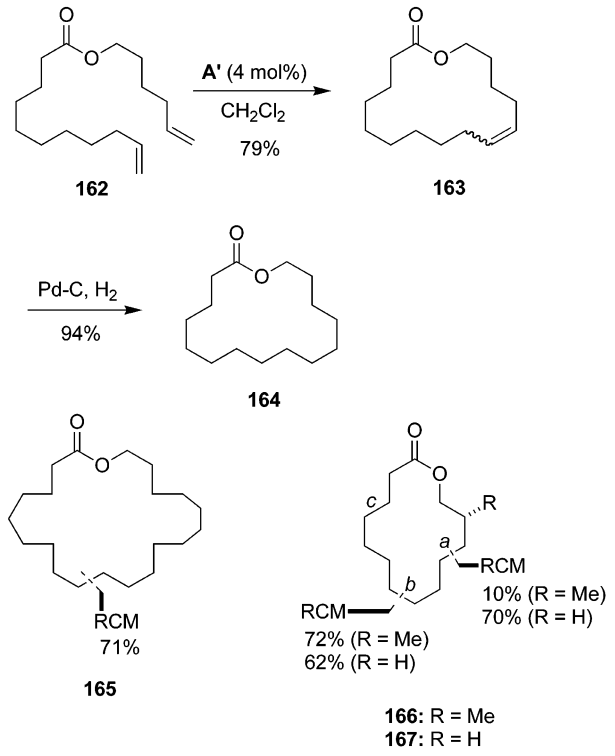
catalytic amounts of the ruthenium indenylidene complex **F**, which has properties very similar to those of **A**, afforded the desired lactone (*E*)-**161** as the major product, but the *Z*-isomer (9% yield) was also isolated. The *E*/*Z*-ratio in this reaction did not evolve over time, suggesting that product formation occurs under kinetic control. Hydrolysis of the acetal moiety in (*E*)-**161** then afforded natural **157**.

2.8. Macrocyclic Lactones

There have been numerous applications of RCM to the syntheses of macrocyclic lactones. Fürstner and Langemann were the first to demonstrate that dienic esters devoid of any conformational constraints could be efficiently cyclized by RCM to produce macrocycles, albeit with variable *E*/*Z*-selectivity.[75] Indeed, they showed that RCM constitutes a general approach to large ring systems that may compare favorably with other alternatives.[76]

Exaltolide (**164**), a saturated 16-membered lactone that is a valuable musk-odored olfactory agent, was the first macrolactone to be prepared via RCM.[75] Thus, acylation of 5-hexenol with 10-undecenoyl chloride yielded the diene **162**, which underwent cyclization upon treatment with **A**' to give the macrolactone **163** (*E*/*Z* = 46:54) (Scheme 46). Hydrogenation of the double bond gave **164** in excellent yield. This synthesis of **164** represented a significant improvement over previous approaches.[77] Inspired by this result, Fürstner then prepared the 21-membered lactone **165** analogously; the RCM leading to **165** proceeded in good yield and gave a mixture (55:45) of *E*/*Z*-isomers.[75]

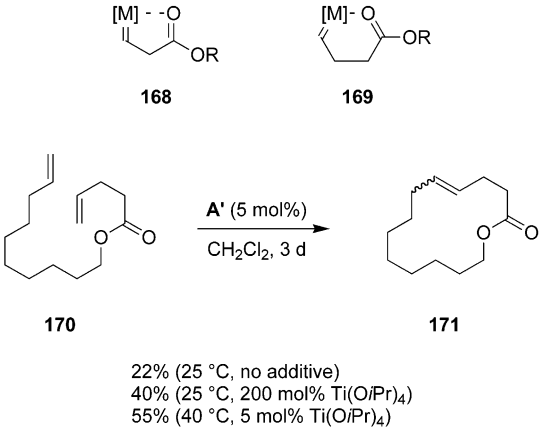
Scheme 46



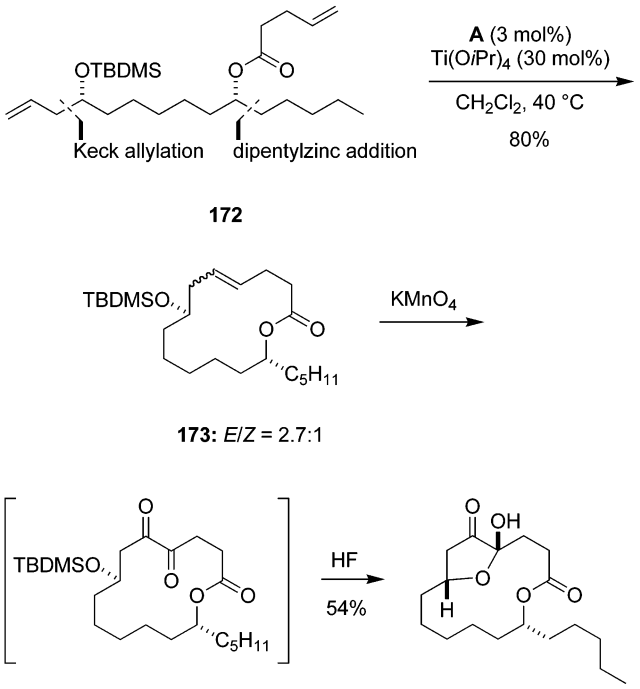
Work directed toward applying RCM to the synthesis of the enantiomerically pure 14-membered lactone **166** (R = Me), a musk-odored and minor component of *Angelica* root oil, revealed that the site of ring closure was more important than ring size in determining the efficiency of the cyclization. For example, attempts to effect RCM with **A**' to generate a double bond at *a* in **166** (R = Me) delivered the cyclized product in only 10% yield, whereas formation of bond *b* occurred in 72% yield (*E*/*Z* = 96:4).[75] This dramatic difference can probably be attributed to a steric effect involving the adjacent methyl group, because a systematic study on forming 14-membered lactones and lactams using **A** by Weiler showed that bond *a* in **167** (R = H) was produced in the highest yield (*E*/*Z* = 87:13).[78] Bond *b* of **167** (R = H) was also formed in good yield (*E*/*Z* = 99:1). On the other hand, when bond *c* of **167** (R = H) was produced by RCM, the yield was poor (*E*/*Z* = 50:50).

The difficulty observed in cyclizing a but-3-enoic acid derivative by constructing bond *c* was rationalized as arising from the formation of a stable five-membered chelate as **168** between the ester carbonyl group and the Lewis acidic metal of the intermediate alkylidene carbene (Scheme 47).[75b] Indeed, the involvement of such chelates in problematic cyclizations of unsaturated amides via RCM had been previously proposed by Grubbs.[79] The generation of six-membered chelates such as **169** also undermines RCM reactions. One solution to this problem was discovered by Fürstner, who developed a binary catalyst system that could be used to cyclize dienes that would otherwise react with RCM catalysts to form unreactive chelates related to **168** and **169**. When the diene **170** was treated with Grubbs' catalyst **A**' for 3 days, only 22% of the product lactone **171** was isolated, and starting material was recovered. Presumably the reaction of **170** with **A**' produced a stable six-membered chelate like **169**. However, if the reaction was conducted under identical conditions, except in the presence of 200 mol% of the Lewis acid Ti(O*i*Pr)$_4$, the yield of macrolactone **171** nearly doubled. Increasing the reaction temperature to 40 °C and using catalytic amounts of Ti(O*i*Pr)$_4$ produced **171** in 55% yield.[25] Clearly, Ti(O*i*Pr)$_4$ had a significant, beneficial impact on the efficiency of the cyclization of **170**. The generality of this tactic has not yet been fully established, and the precise nature of the effect of adding Ti(O*i*Pr)$_4$ to the mixture is unknown. How-

Scheme 47



Scheme 48



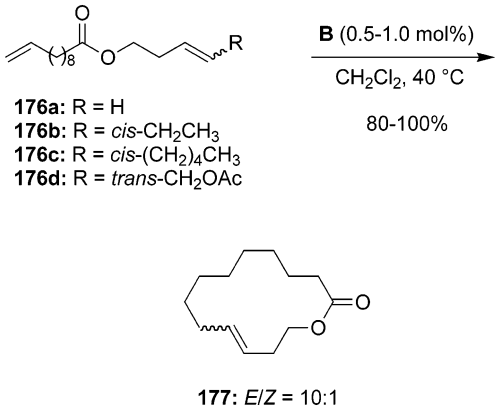
ever, it presently seems reasonable to suggest that the Ti(O*i*Pr)$_4$ either interferes with the generation of the unreactive chelate or it destabilizes such a chelate once formed.

Fürstner used this binary catalyst system in a RCM reaction leading to the total synthesis of the macrolide (−)-gloeosporone (**175**) (Scheme 48),[25] a germination self-inhibitor that was isolated from *Colletotrichum gloeosporioides*. The requisite diene **172** was synthesized in six steps by a sequence wherein the stereogenic centers were introduced by an asymmetric Keck allylation and an asymmetric dipentylzinc addition. Although **172** did not undergo RCM in the presence of **A**, it did cyclize in the presence of **A** and Ti(O*i*Pr)$_4$ to provide the macrolactone **173** as a mixture (2.7:1) of *E*/*Z*-isomers. Because the double bond in **173** was converted into the diketone **174** in the next step, the obtention of geometric isomers in the cyclization was inconsequential. Deprotection of **174** then afforded (−)-gloeosporone (**175**).

At this juncture it should be noted that the second-generation Grubbs' catalyst **B** may be used effectively to catalyze the RCM reactions of substrates that have functionalities suitably disposed for chelation with the ruthenium alkylidene intermediate.[80] Moreover, catalysts in which the metal is already chelated with an ether group, such as Hoveyda's catalyst **E**,[68,81] show high activities for substrates that may produce intermediate chelates.

The formation of lactones from dienic esters using **A** as the catalyst generally provides mixtures of *E*- and *Z*-isomers with low selectivity. The *E*/*Z*-selectivity changes with ring size and position of the olefin, so it is difficult to predict and control the double bond geometry.[75] Studies directed toward the syntheses of epothilone[82] and salicylihalamide (see Scheme 57) have revealed that functionality far from the double

Scheme 49



bonds involved in the RCM can have significant effects upon the *E*/*Z*-ratio of the products. Indeed, control of double bond geometry is a significant problem that is commonly encountered in applying RCM to the synthesis of macrocycles.

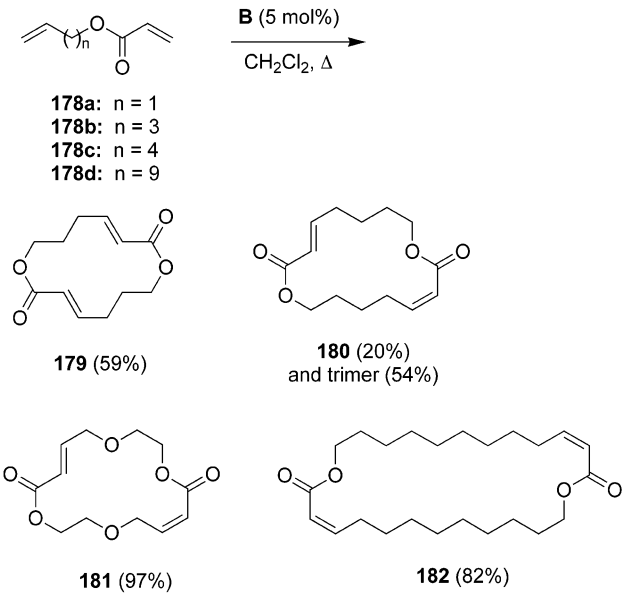
There have thus been a number of investigations directed toward developing tactics that would control double bond geometry in macrolactonizations. For example, Grubbs envisioned that positioning an auxiliary proximal to one of the double bonds involved in the RCM might influence the *E*/*Z*-selectivity.[72] Ideally, the auxiliary group would be removed in the metathesis step. Cyclizations of **176a**−**d** were therefore examined to determine whether substitutions on one of the double bonds might influence the stereochemical outcome of the RCM (Scheme 49). Although initial experiments were conducted with **A** as the catalyst, the second-generation catalyst **B** was preferred, owing to shorter reaction times (minutes instead of hours) and reduced catalyst loading (5−10 times less catalyst). Contrary to initial expectations, the *E*/*Z*-ratios of the product lactone **177** were about 10:1, irrespective of the nature of substitution on one double bond. They also discovered that *E*/*Z*-ratios were lower (about 5:1) at lower conversion and that a mixture of **177** ($E/Z = 4:1$) rapidly isomerized to a mixture of **177** ($E/Z = 10:1$) upon treatment with 1 mol% of **B**. These two observations suggested that the high *E*/*Z*-ratios observed in the cyclizations of **176a**−**d** with catalyst **B** was due to secondary metatheses that equilibrated the initially formed products to provide the isomeric lactones in a thermodynamic ratio. Consistent with this interpretation is that the calculated *E*/*Z*-ratio of **177** is 19:1.[78]

When **A** was used as the catalyst in these cyclizations, no *E*/*Z*-isomerization of the lactone **177** was observed, even though **A** was known to catalyze such isomerizations. For example, Kalesse observed complete *E*→*Z*-isomerization of the *E*-double bond in a 10-membered lactone using 20 mol% of **A** in refluxing CH_2Cl_2. The *Z*-isomer was used as an intermediate in a synthesis of the northern hemisphere of epothilone A.[83] Hence, the effect of catalyst on the geometric ratios of products formed via RCM reactions must be examined on a case-by-case basis.

Forming large, monocyclic lactones from α,β-unsaturated esters has been fraught with difficulties. For example, attempted cyclizations of dienes of the

general type **178** in the presence of **A** gave "head-to-head", homodimeric linear products as a result of a cross metathesis of the unconjugated double bond.[84] Since the imidazolylidene catalyst **B** was known to catalyze the metathesis of α,β-unsaturated esters, Grubbs treated dienes of type **178** with **B** in refluxing CH_2Cl_2 (3 mM) in anticipation of obtaining simple cyclization products; however, macrocyclic "head-to-tail" dimers **179**−**182** were isolated instead (Scheme 50).[84] Cyclization of **178c** under these conditions did

Scheme 50

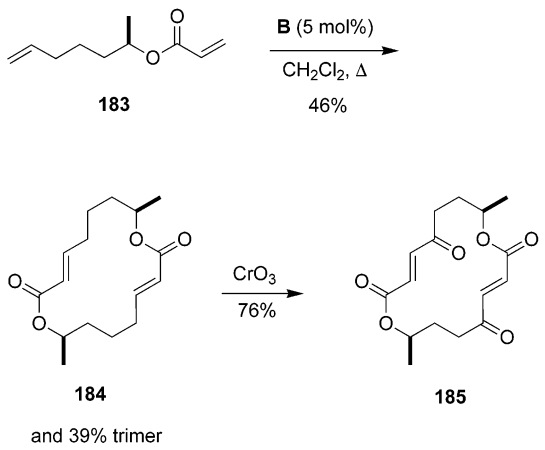


give some of the 16-membered ring lactone **180**, but the major product was a cyclic trimer; the trimer was the only product when the reaction was conducted at higher (100 mM) concentration. On the other hand, the 14-, 16-, and 26-membered lactones **179**, **181**, and **182** were formed in remarkably high yields from the corresponding precursors **178a**, **178b**, and **178d**. In all cases the products were obtained exclusively as their *E*-double bond isomers, a selectivity that was previously observed in the metathesis of other acrylic esters.[85]

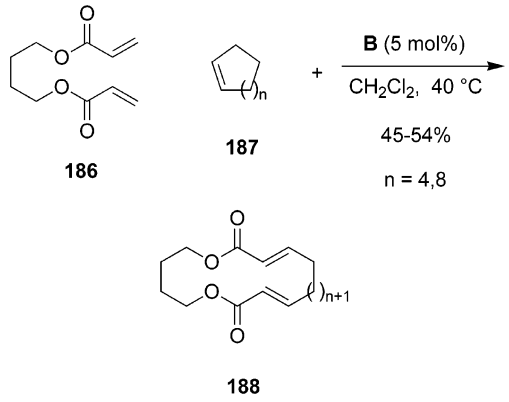
Grubbs then applied this entry to macrocyclic diolides to a synthesis of the antifungal and antibacterial natural product (−)-pyrenophorin (**185**).[84] In the event, cyclization of **183** in the presence of **B** provided the 16-membered diolide **184**, but the corresponding trimer was also isolated. Allylic oxidation of **184** then afforded the natural product **185** (Scheme 51). Fürstner contemporaneously discovered the dimerization of acrylate esters and published an identical approach to **185**.[86]

A novel approach to forming macrolactones has been reported that features tandem ring-opening metathesis (ROM), cross metathesis (CM), and RCM reactions (Schemes 52−54).[87] However, the requirements for successfully effecting this reaction sequence are somewhat demanding as the cycloalkene must first undergo ROM to give an intermediate alkylidene that reacts with a diene via CM to give another intermediate that must then preferentially undergo RCM rather than another CM. The acyclic diene

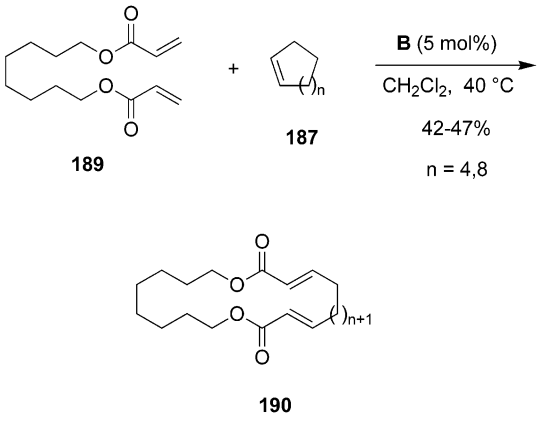
Scheme 51



Scheme 52



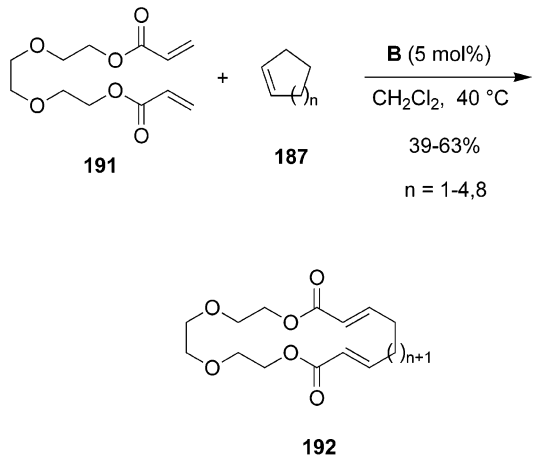
Scheme 53



should not undergo RCM or dimerize via CM. On the basis of these criteria, bis-acrylates appear to be well-suited to participating in such processes, because they react selectively with terminal olefins in the presence of **B** without undergoing competitive RCM.[85] The generality of this route to macrolactones having a variety of ring sizes is illustrated by the reactions of the commercially available cyclic alkenes **187** (n = 1, 2, 3, 4, 8; 1.1−5.0 equiv) with the acyclic dienes **186**, **189**, and **191** to give the lactones **188**, **190**, and **192**, which were isolated exclusively as their *E*-isomers.

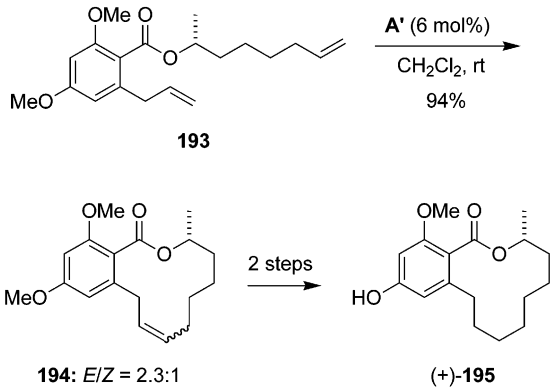
Fürstner's synthesis of (+)-lasiodiplodin (**195**) represents one of the early applications of RCM to the preparation of 12-membered macrolide natural prod-

Scheme 54



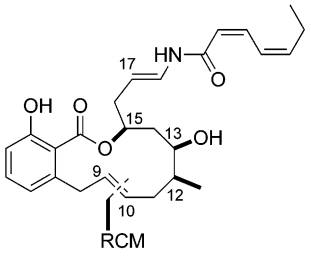
ucts.[88] Cyclization of **193** using **A'** as the catalyst gave **194** as a mixture of double bond isomers (*E*/*Z* = 2.3:1) in excellent yield (Scheme 55). Hydrogenation of

Scheme 55



this mixture and cleavage of one phenolic methyl ether then completed the synthesis of (+)-**195**. Because the double bond formed by the RCM was reduced, the purist may question this approach to saturated, naturally occurring macrocycles based upon its inefficient use of functionality.

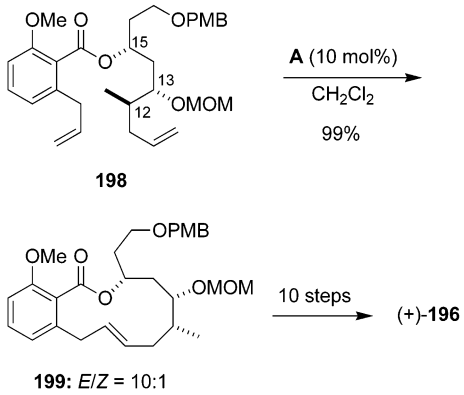
Salicylihalamides A and B (**196** and **197**) comprise a novel class of secondary metabolites isolated from the marine sponge *Haliclona* by Boyd in 1997.[89] Salicylihalamide A (**196**), which displays potent cytotoxicity in the NCI 60-cell line human tumor assay and appears to have a novel mechanism of action, possesses a 12-membered salicylate macrolide and a novel dienyl enamide side chain. The correct absolute stereochemistry of salicylihalamide A was established by De Brabander, who first synthesized both (+)-**196** and (−)-**196**.[90]



196: 17*E*
197: 17*Z*

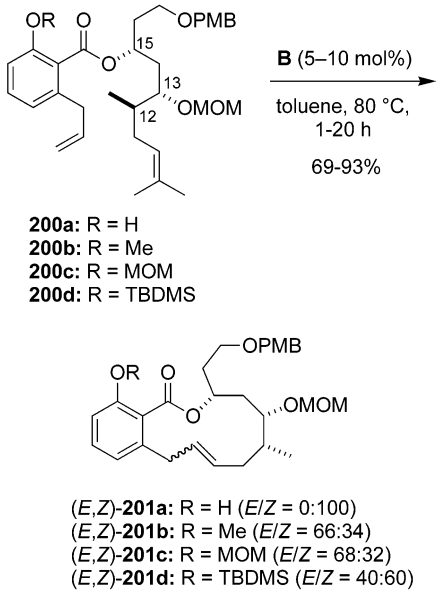
In all of the total syntheses of salicylihalamide A reported to date, the C9−C10 *E*-double bond, and hence the macrocycle, was generated by a RCM reaction. The stereogenic centers in **198**, which was the RCM substrate in De Brabander's synthesis,[90] were constructed by an asymmetric Brown allylation (C15) and an asymmetric aldol reaction employing Oppolzer's sultam (C12 and C13) (Scheme 56). Exposure of **198** to Grubbs' catalyst **A** produced **199** with good *E*/*Z*-selectivity. The synthesis of (+)-**196** was then completed in 10 steps, wherein the 17*E*-enamide moiety was established by addition of a vinyllithium reagent to an isocyanate.

Scheme 56



Shortly after De Brabander's initial account was published, Fürstner reported a very similar approach to the macrolide core of **196** (Scheme 57).[91] The stereocenter at C12 in the RCM substrates **200a**−**d** was generated by an Evans asymmetric alkylation, while the centers at C13 and C15 were formed by an enantioselective hydrogenation. Because one of the double bonds in **200a**−**d** was trisubstituted, the first-generation Grubbs catalyst **A**, which is known to be sensitive to double bond substitution, was ineffective,

Scheme 57



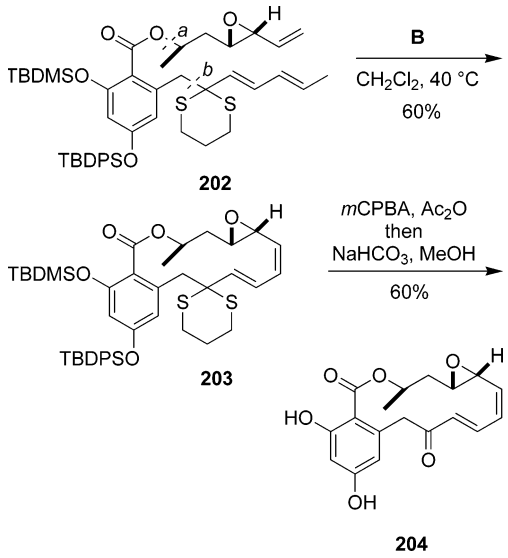
and the more reactive Grubbs catalyst **B** had to be employed. The stereochemical course of the RCM of **200a**−**d** was found to be highly dependent upon whether the phenolic hydroxy group was free or protected, although the exact nature of the protecting group had little effect. Thus, the diene **200a** (R = H) was cleanly converted into (*Z*)-**201a** upon treatment with catalytic amounts of **B**. That the *Z*-double bond was formed exclusively was unexpected, because **B** had been shown to favor production of the more stable *E*-configured products via isomerization.[72]

Fürstner speculated that conformational factors, such as a constraining hydrogen bond between the phenolic hydroxyl and the carbonyl group in **200a**, were responsible for the stereochemical outcome of the RCM cyclization. Indeed, protecting this hydroxyl group as a methyl, MOM, or TBDMS ether had a dramatic effect on the stereochemical outcome of the RCM reaction, providing the products **201b**−**d** in excellent yields and in *E*/*Z*-ratios up to 68:32 favoring the desired *E*-**201**. There was no change in the *E*/*Z*-ratio over the course of the reaction. Fürstner's findings together with those of De Brabander[90] illustrate that the stereochemistry of the double bond formed upon the RCM of even very closely related substrates is not always predictable, even when a second-generation Ru-catalyst is employed.

The findings of De Brabander and Fürstner have been mirrored in subsequent syntheses of (−)-salicylihalamide A (**196**). For example, Snider cyclized dienes very similar to **200a** and **200d** using **A** as the catalyst to obtain primarily a *Z*-olefin when the phenolic hydroxyl group was free and a mixture (4:1) of *E*/*Z*-isomers when it was protected as a TBDMS ether.[92] In Smith's synthesis of (−)-**196**,[93] a diene closely related to **198** was cyclized with **A** (10 mol%) to give a mixture (10:1) of *E*- and *Z*-lactones, a result identical to that of De Brabander. Porco recently reported the total synthesis of oximidine II, another salicylate enamide macrolide closely related to **196**, by a strategy in which a macrocyclic conjugated triene was formed by RCM.[94]

There have been several applications of RCM to prepare naturally occurring 14-membered lactones. For example, Danishefsky recently reported the synthesis of radicicol (**204**), a resorcylic macrolide that exhibits antibiotic and antifungal properties and inhibits the molecular chaperone Hsp90 to suppress the transformed phenotype caused by a variety of oncogenes.[95] Bond *a* in the RCM substrate **202** was formed by a Mitsunobu esterification, whereas bond *b* was generated by alkylation of a lithiated dithiolane, a reaction that unfortunately delivered mixtures of α- and γ-substitution products (Scheme 58). Treatment of **202** with the second-generation catalyst **B** furnished the macrolactone **203** in good yield. This RCM is rather unusual in that it represents a rare example of the metathesis of a vinyl epoxide[85] and of a metathesis involving the terminal double bond of a conjugated diene (see also Scheme 61). Inasmuch as sulfur had been previously implicated as a deactivating ligand in unsuccessful RCM reactions,[96] it is also noteworthy that **202** contains two sulfur

Scheme 58

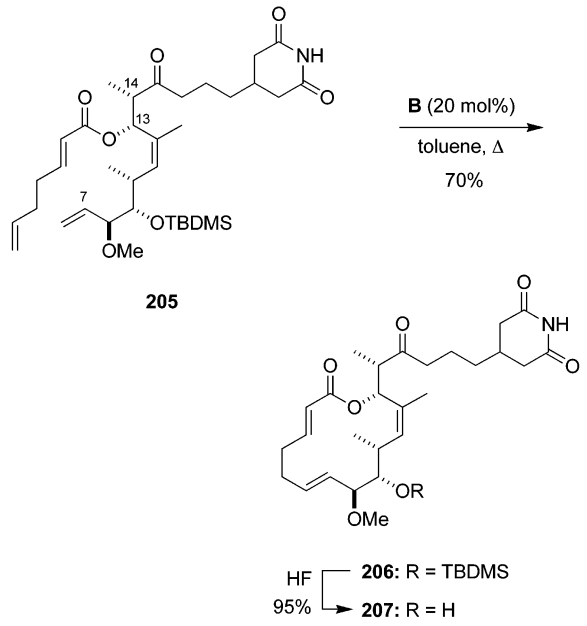


atoms. When the RCM of **202** was attempted with **A** as the catalyst, only trace amounts of cyclized product were obtained. Moreover, if the phenolic hydroxyl group ortho to the ester function was not protected, the yield and the reaction rate decreased. Protection of the phenols as silyl ethers was critical, as the dimethyl ether analogue of **202** did not cyclize as efficiently, and it was not possible to cleave the dimethyl ethers later in the synthesis.[95b] A study on the temperature dependence of the RCM of **202** and derivatives showed that monomeric cyclization products were preferentially formed at 110 °C in toluene.[95c] The dithiolane moiety in **203** was removed under Pummerer conditions that led to the simultaneous conversion of the silyl ethers into acetates that were subsequently hydrolyzed to complete the synthesis of **204**.

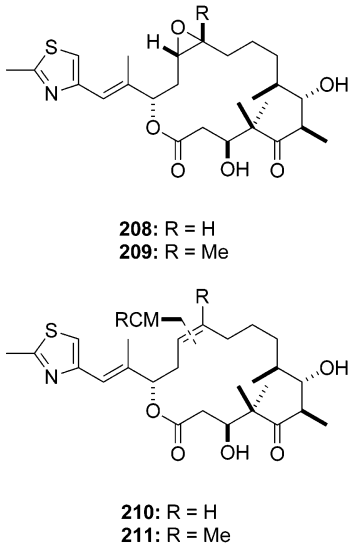
(+)-Migrastin (**207**) is a novel 14-membered macrolide isolated from different strains of *Streptomyces* that was recently synthesized by the Danishefsky group.[97] The C6−C13 fragment of the RCM precursor **205** was assembled in nine steps from commercially available dimethyl-2,3-*O*-isopropylidene tartrate using a hetero-Diels−Alder reaction as a key step; an Evans aldol reaction then set the remaining stereogenic centers at C13 and C14 (Scheme 59). Acylation of the hydroxy group at C13 with the requisite dienoic acid was rather challenging, as many esterification procedures led to either extensive decomposition of starting material or to products containing significant amounts of β,γ-unsaturated ester. Ultimately, the esterification was realized by a modified Yamaguchi procedure leading to the RCM substrate **205**. When **205** was treated with **B** in refluxing toluene, the desired (*E*,*E*,*Z*)-trienyl 14-membered macrolactone **206** was obtained as the sole product. This result is in accord with the expectation that **B** would react first with the less hindered of the two terminal olefins with subsequent cyclization involving the most accessible of the three remaining double bonds. Cleavage of the silyl ether **206** then furnished migrastatin (**207**).

Because of their high activity against a number of tumor cells and their intriguing mode of action, there

Scheme 59



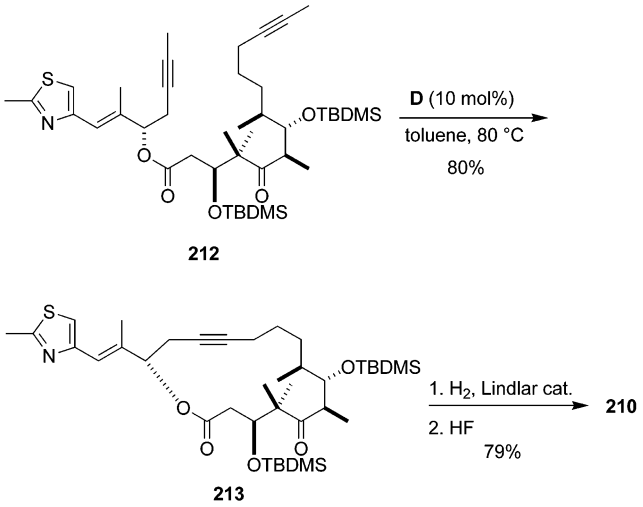
has been intense interest in developing efficient syntheses of the epothilones **208**−**211**. It is thus



noteworthy that a RCM reaction was employed to form the 16-membered lactone in the first three total syntheses of epothilone A (**208**). Although the RCM reactions in these syntheses were chemically efficient, the *Z*/*E*-selectivities were generally poor and largely unpredictable. This result was something of a drawback, because the cyclization was typically conducted toward the end of a labor-intensive sequence, and the two geometric isomers were not easily separable. Nevertheless, efforts directed toward synthesizing the epothilones provided numerous insights into ruthenium alkylidene catalyzed RCM reactions and the compatibility of such conversions with a wide range of functional groups including epoxides, vinyl iodides, thiazoles, and alcohols.[98] Synthetic approaches to the epothilones have been extensively reviewed,[99] particularly in the context of using RCM to form the C12−C13 double bond,[100] so only the most recent developments will be presented herein.

Fürstner reported a novel approach to the epothilones that involved the stereoselective generation of the C12−C13 double-bond by sequential alkyne-RCM and Lindlar hydrogenation.[101] Thus, cyclization of the diyne **212** in the presence of **D** afforded the 16-membered cycloalkyne **213** (Scheme 60). The mild-

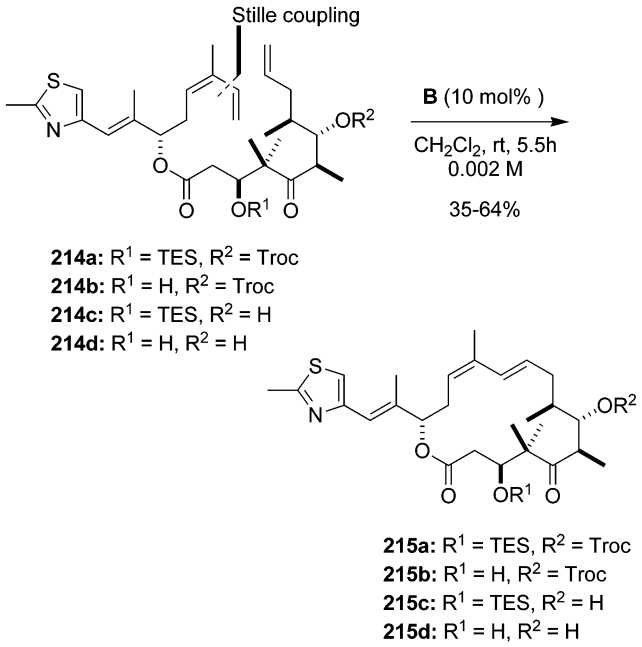
Scheme 60



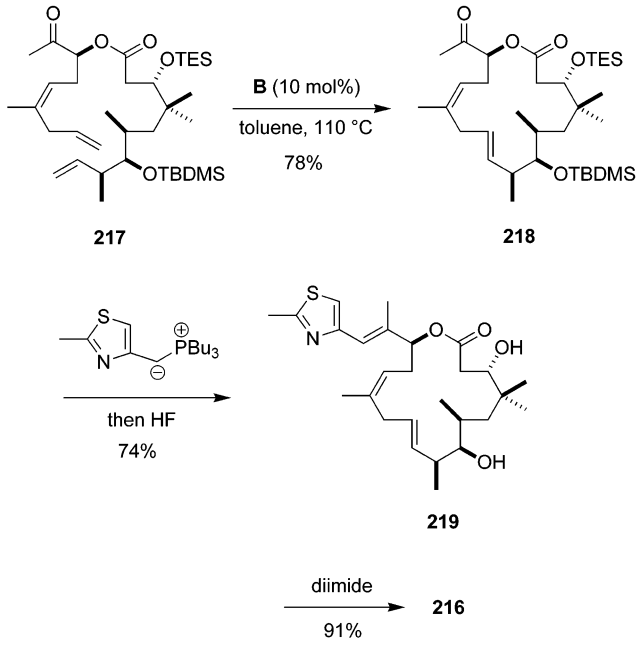
ness of this method is demonstrated by fact that the ester, the silyl ethers, the aldol substructure, and the chiral center adjacent to the carbonyl group remained intact. Moreover, the preexisting alkene and the thiazole ring did not interfere with the catalyst. Lindlar reduction of **213** followed by cleavage of the TBDMS protecting groups then delivered epothilone C (**210**).

In view of the poor stereoselectivities observed in the RCM reactions of α,*ω*-dienes to generate the epothilone ring system, other approaches were developed that did not rely on RCM to form the C12−C13 double bond. For example, the Danishefsky group became interested in desoxyepothilone B (**216**), a compound that is currently being evaluated in human clinical trials, and other novel epothilones such as epothilone 490 (**215d**). Inspired by their successful cyclization of triene **202** in the synthesis of radiciol (**204**) (Scheme 58),[95] Danishefsky envisioned that dienes **214a**−**d** might serve as suitable substrates for forming the C10−C11 double bond of epothilones via a RCM.[102] The diene unit in **214a**−**d** was prepared by a Stille coupling (Scheme 61). Exposure of fully protected **214a** to the second-generation Grubbs catalyst **B** produced a mixture (3:1) of the desired 16-membered lactone **215a** and a 14-membered lactone (not shown) that was formed by competing metathesis of the 12,13-double bond; none of the *Z*-isomer of **215a** was isolated. Removal of either one of the hydroxy protecting groups gave increased amounts of **215b**,**c**. When neither hydroxy group was protected, the 16-membered macrolide epothilone 490 (**215d**) was obtained as the sole product. Selective reduction of the C10−C11 double bond of **215b** with diimide furnished desoxyepothilone B (**216**), thereby completing an efficient synthesis of an epothilone B derivative. A similar sequence of reactions was applied to the synthesis

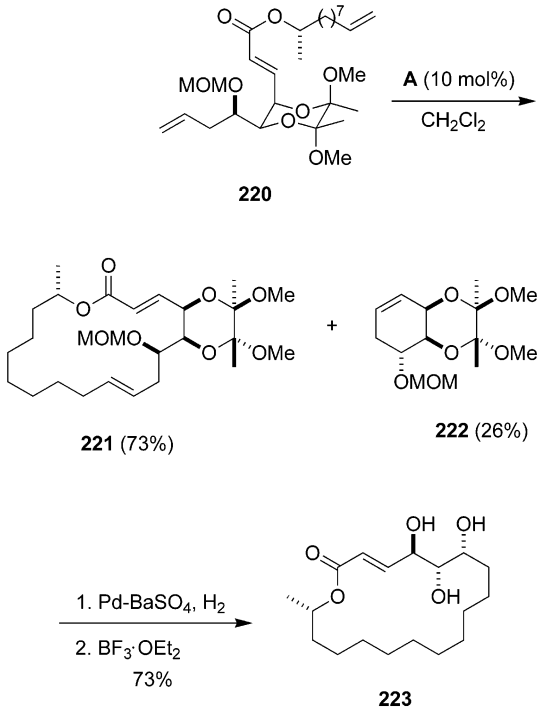
Scheme 61



Scheme 62



Scheme 63



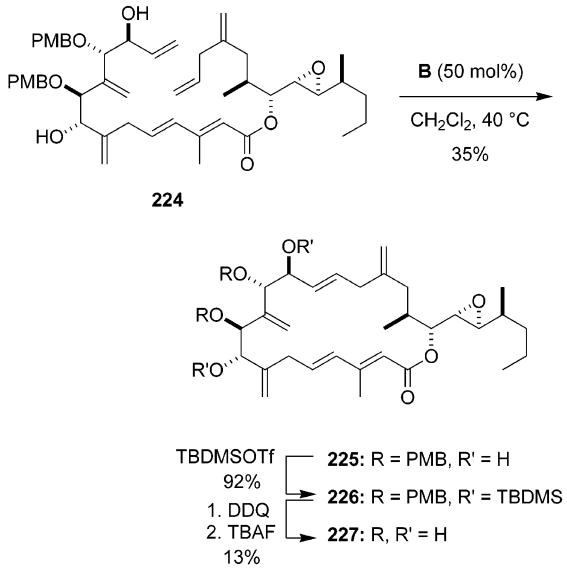
of a 17-membered analogue of 12-trifluoromethyl desoxyepothilone B.[103]

Danishefsky has also unveiled an approach to a new class of 9,10-dehydroepothilones and a superior route to desoxyepothilone B (**216**).[104] The RCM of **217** was effected using **B** to afford exclusively the *E*-isomer **218** (Scheme 62). The conjugated thiazole moiety was introduced by a Wittig reaction, and subsequent deprotection of the hydroxyl groups with HF led to **219**. Diimide reduction of **219** then completed an improved synthesis of **216**.

The 18-membered lactone (+)-aspicilin (**223**) was synthesized by Ley to showcase the utility of enantiomerically pure butane diacetal-protected butanetetrols as readily available building blocks for the construction of naturally occurring polyol motifs.[105] The diene **220** was first prepared and treated with Grubbs catalyst **A** to give the desired macrolactone **221** as a mixture (1:1.5) of *E*- and *Z*-isomers (Scheme 63). Compound **222** was also isolated in 26% yield as a side product from a competing RCM with the double bond of the α,*β*-unsaturated ester. The synthesis of **223** was completed by selective hydrogenation of the unconjugated double bond in **221**, followed by global deprotection under acidic conditions. The formation of **222** during the RCM step and the need to reduce the double bond generated are relatively minor flaws in an otherwise elegant synthesis.

Maleczka reported a synthesis of the polyunsaturated 18-membered lactone **227**, which had been proposed as the structure of amphidinolide A by Kobayashi,[106] using an approach featuring the RCM of a polyunsaturated substrate that proceeded with unprecedented selectivity.[107] The RCM substrate **224** was first exposed to **A** because of its higher selectivity for monosubstituted double bonds; however, this catalyst simply isomerized the terminal allylic alcohol to a methyl ketone.[108] On the other hand, when **224** was treated with the second-generation catalyst **B**, **225** was formed as the only cyclic product (Scheme 64); the C13−C14 double bond was formed exclusively in the *E*-configuration. To remove the various PMB protecting groups, it was first necessary to silylate the remaining two hydroxy groups of **225** to

Scheme 64

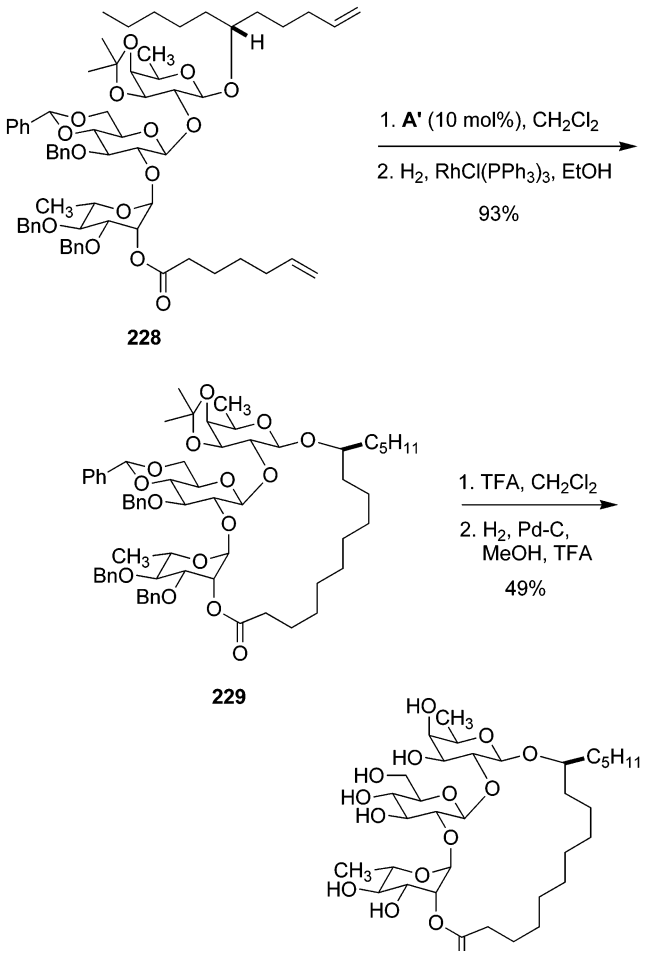


avoid acetal formation. Removal of all protecting groups from **226** then gave the desired **227**. The NMR data of the synthetic material thus obtained did not match those reported for **227**,[106] although they did match those obtained by Pattenden, who prepared **227** independently.[109]

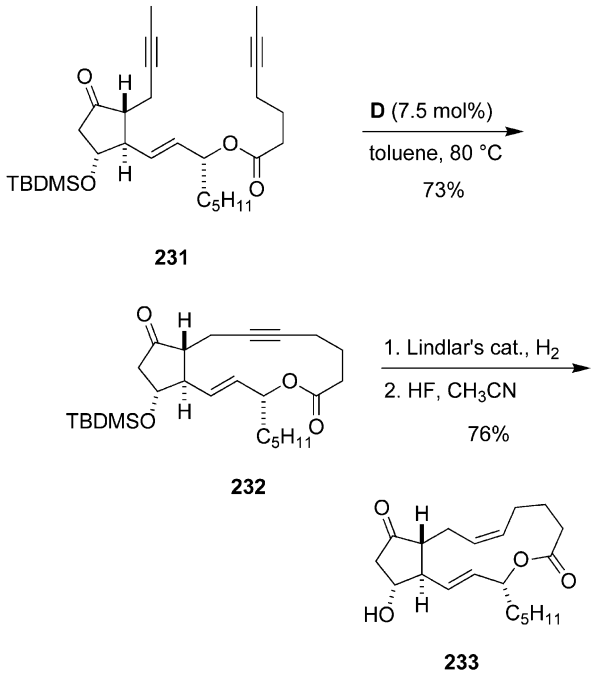
The resin glycosides, of which tricolorin G (**230**) is a representative member, are a complex group of natural products in which jalapinolic acid spans two or more units of an oligosaccharide backbone, giving a macrocyclic lactone. One major challenge in the synthesis of these compounds involves the regioselective formation of the macrolide, and classical macrolactonization procedures have generally been employed toward that end. Fürstner has developed an approach to the resin glycosides using RCM as illustrated by the synthesis of tricolorin G (**230**) (Scheme 65).[110] Cyclization of **228** in the presence of **A**' followed by hydrogenation of the resulting mixture of stereoisomeric alkenes furnished the fully protected tricolorin G (**229**). Owing to the lability of the glycosidic linkages in **229**, it was necessary to remove the protecting groups in two steps under carefully controlled conditions to deliver **230**.

It is readily apparent from many of the foregoing examples that RCM can be used for the efficient production of macrolactones bearing a number of different functional groups. In some cases *E*-double bonds can be formed stereoselectively under equilibrating conditions using the second-generation Grubbs' catalyst **B**. However, tactics for the selective formation of *Z*-configured double bonds are lacking, and this has sometimes proven to be a handicap. To address this critical problem, Fürstner developed a potentially very useful reaction sequence that involves a diyne metathesis followed by *cis*-hydrogenation of the resulting triple bond. The application of this tactic is nicely exemplified in his synthesis of epothilone C (**210**) (Scheme 60).[101] He also applied this strategy to the syntheses of the marine natural product prostaglandin E_2-1,15-lactone (**233**) (Scheme 66)[111] and the 26-membered macrolactone of the resin glycoside sophorolipid lactone (**236**) (Scheme 67).[112]

Scheme 65

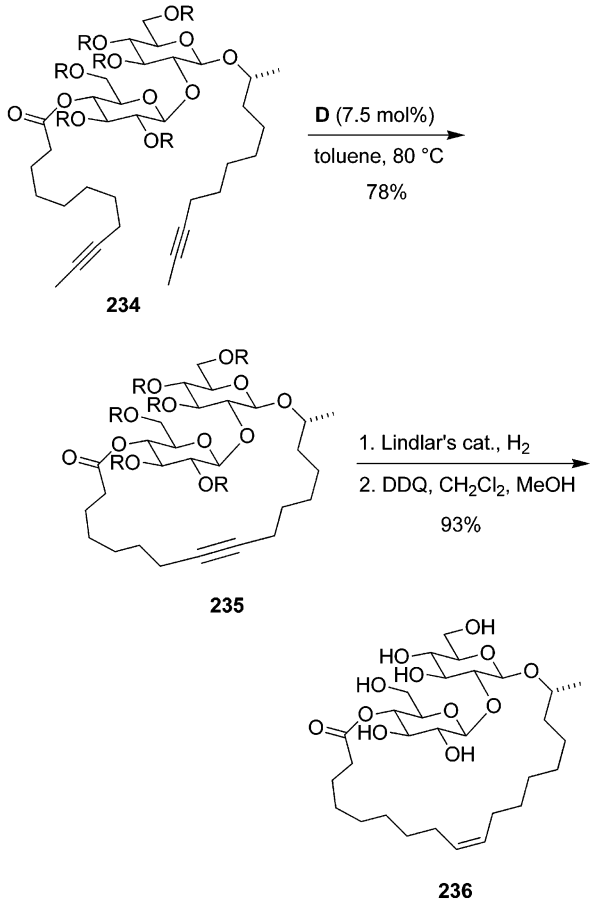


Scheme 66



The diyne **231** required for the synthesis of **233** was constructed by a three-component coupling of a vinyl zincate, a propargyl iodide, and a cyclopentenone (Scheme 66). Cyclization of **231** proceeded smoothly using a catalytic species that was formed in situ from

Scheme 67

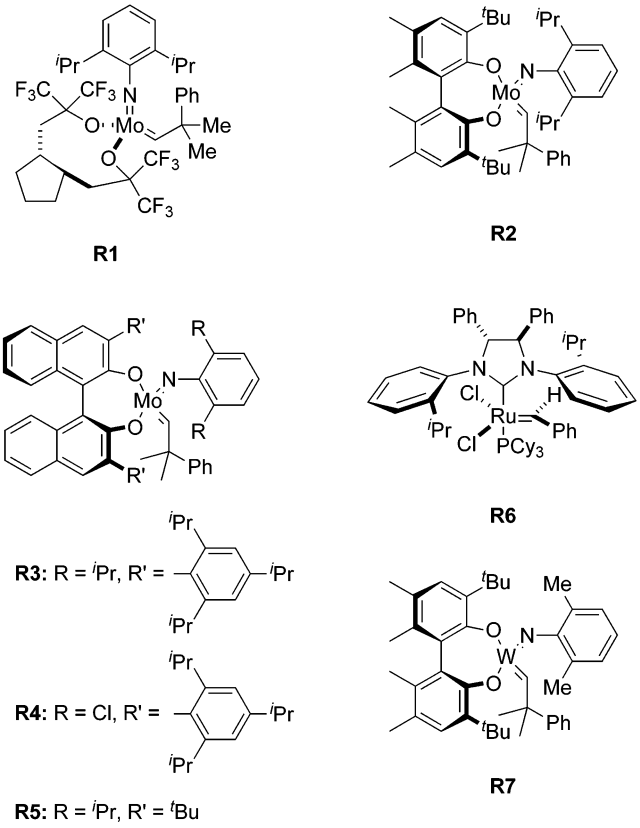


the reaction of the precatalyst **D** with CH_2Cl_2[113] to give the cycloalkyne **232**. Several important features of the **D**-derived catalyst are apparent from this example: It is tolerant of esters, ethers, silyl ethers, amides, thioesters, and pyridine moieties, and it rigorously discriminates between the triple bonds, which are reactive, and double bonds, which are inert. Semihydrogenation of **232** with Lindlar catalyst and deprotection completed the total synthesis of **233**.

In early attempts to prepare sophorolipid lactone (**236**), a diene closely related to the diyne **234** was treated with a variety of RCM catalysts, but the product was always isolated as an *E*/*Z*-mixture (3:1) of cycloalkenes.[110] Thus, the diyne **234** was prepared and cyclized in the presence of **D** to give **235** (Scheme 67); neither the acid-labile PMB ethers nor the glycosidic bonds were affected by the Lewis acidic metal center. Semihydrogenation of the cycloalkyne **235** and global deprotection with an excess of DDQ furnished the natural product **236**.

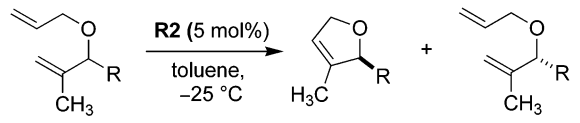
2.9. Enantioselective Cyclizations to Oxygen Heterocycles

Catalytic enantioselective RCM has been reviewed recently,[114] so the following discussion will be restricted to an overview of its applications to the synthesis of oxygen heterocycles. The first examples of enantioselective RCM were reported by Grubbs in 1996 and involved Mo-catalyzed kinetic resolutions using the chiral hexafluoro-Mo catalyst **R1**.[115] On the basis of experiments with the related catalyst **C**, the chiral bis-hydroxy ligands presumably did not dissociate from the metal center during catalysis, but nevertheless, the levels of enantiodifferentiation using **R1** were typically low (k_{rel} < 2.2).



In 1998, Hoveyda and Schrock reported the synthesis of the enantiopure biphenyl-chelated Mo complex **R2**,[116] and they reported that this catalyst could be used to effect the kinetic resolution of allylic ethers **237a**−**d** with good levels of enantiocontrol to yield dihydrofurans **238a**−**d** (Scheme 68).[117] Dienes having

Scheme 68

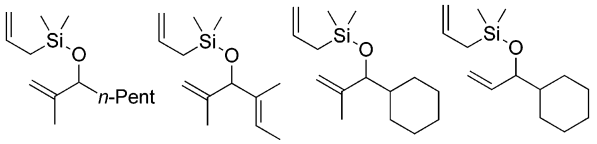


rac-**237a**: R = *n*-Pent	(*S*)-**238a** (63%)	(*R*)-**237a** (92% *ee*)
rac-**237b**: R = *i*-Bu	(*S*)-**238b** (56%)	(*R*)-**237b** (95% *ee*)
rac-**237c**: R = Cychex	(*S*)-**238c** (62%)	(*R*)-**237c** (98% *ee*)
rac-**237d**: R = Ph	(*S*)-**238d** (56%)	(*R*)-**237d** (75% *ee*)

1,2-disubstituted double bonds and those having tertiary ethers rather than secondary ones could not be so resolved.

Because their initial attempts to resolve the 1,7-dienes **239a**−**d** using **R2** as a catalyst were unsuccessful, Hoveyda and Schrock developed the BINOL-derived Mo catalyst **R3**. This catalyst readily promoted the efficient resolution of **239a**,**b**, but it was less effective for resolving the less-substituted dienes **239c**,**d** (Scheme 69).[118] For these substrates, the older catalyst **R2** gave better results. These observations

Scheme 69



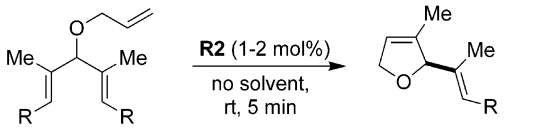
239a **239b** **239c** **239d**

with **R2**	$k_{rel} < 5$	$k_{rel} < 5$	$k_{rel} = 21$	$k_{rel} > 25$
with **R3**	$k_{rel} > 25$	$k_{rel} > 25$	$k_{rel} > 5$	$k_{rel} > 5$

underscore the high level of substrate specificity of these Mo-catalysts.

Perhaps a more important area of enantioselective RCM is the cyclization of prochiral molecules using catalysts that differentiate two enantiotopic carbon−carbon double bonds. Consequently, it was a significant finding that the trienes **240a**,**b** underwent rapid cyclizations in the presence of **R2** to afford dihydrofurans **241a**,**b** in good yields and excellent enantioselectivities (Scheme 70).[116] The reaction could be

Scheme 70



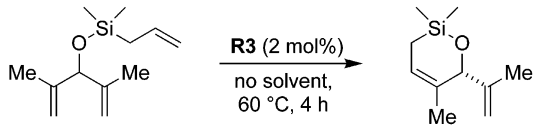
240a: R = H
240b: R = Me

(*R*)-**241a** (93% *ee*)
(*R*)-**241b** (99% *ee*)

conducted with or without solvent. The level of enantiodifferentiation on substrates similar to **240a**,**b** depended upon the degree of substitution on the double bond, presumably because formation of the intermediate metallacyclobutane seems the likely stereochemistry-determining step. Higher levels of enantioselectivity were observed with substrates having more highly substituted double bonds, and trienes with singly substituted double bonds cyclized to give products having only low to moderate ee values.

In another series of experiments, Hoveyda and Schrock discovered that the silyloxy triene **242** cyclized in the presence of **R3** to provide **243** in nearly quantitative yield and >99% ee (Scheme 71).[119] The

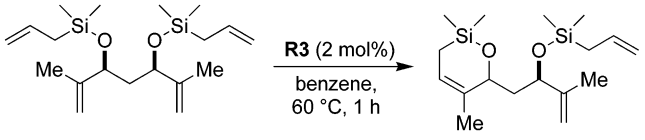
Scheme 71



242 (*R*)-**243**

meso compound **244** could also be desymmetrized by treatment with **R3** to give **245** as the only isolable product in >99% ee (Scheme 72). The absence of any meso bicyclic product illustrates the exceptionally high degree of stereodifferentiation that may be induced by the chiral Mo complex **R3**. Mo-alkylidenes derived from both enantiotopic terminal double bonds in **244** are presumably formed in this reaction, but because alkylidene formation is apparently rapidly

Scheme 72

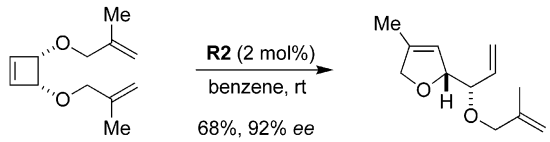


244 **245**

reversible, cyclization occurs only between the *matched* portion of the tetraene.[119]

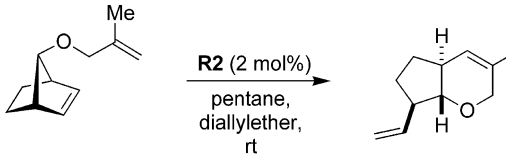
The desymmetrization of meso compounds via an enantioselective ROM followed by RCM offers a powerful method for preparing complex molecules in a single step as illustrated in Schemes 73 and 74.[120]

Scheme 73



246 **247**

Scheme 74



248 **249**

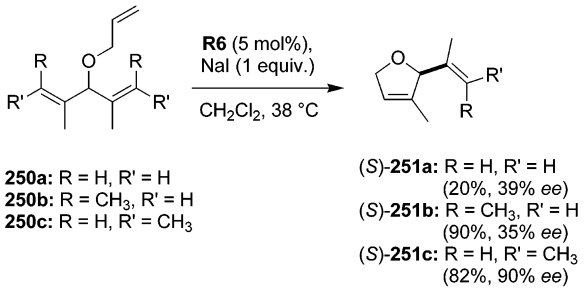
The step that determines the stereochemistry in these processes is presumably the enantioselective formation of an Mo-alkylidene from interaction of the catalyst **R2** with the more reactive internal double bonds in **246** and **248**. RCM then provides the observed products **247** and **249** in good yields and excellent enantioselectivities. Formation of the bicycle **249** required the presence of diallyl ether, presumably to initiate formation of the reactive Mo=CH_2 complex (Scheme 74). This is a potentially useful trick that might be more generally employed when the double bonds of a substrate are unreactive toward the precatalyst used.

Other chiral Mo complexes that induce enantioselective RCM reactions are **R5** and **R4**.[121] While **R5** shares structural features with both the biphenyl and the BINOL-based complexes **R2** and **R3**, **R4** has electron-withdrawing chlorine atoms incorporated in the imido substituent to increase the Lewis acidity of the metal center and potentially give higher levels of catalytic activity. This catalyst is particularly well suited for forming chiral acetals. It has been found that adding 10 equiv of THF to reaction mixtures involving **R3** and **R4** may lead to enhanced enantioselectivities.[122] Another recently developed catalyst for asymmetric metathesis reactions is the tungsten catalyst **R7**.[123]

Chiral ruthenium catalysts for enantioselective RCM reactions have been prepared and developed by Grubbs.[124] A series of modifications to the original complex **B** led to the design of **R6**, the structure of which was established by X-ray analysis. In studies

of the enantioselective desymmetrizations of trienes **250a**−**c** using **R6**, it was discovered that changing the halide ligands from chloride to iodide improved the enantioselectivity (Scheme 75). When the 1,1-disubstituted olefin **250a** was treated with **R6** in the presence of NaI, both the conversion and the ee were low. However, introducing an additional methyl group onto each of the enantiotopic double bonds had significant effect. For example, cyclization of the (*Z*)-isomer **250b** proceeded in excellent yield but low ee, whereas the corresponding (*E*)-isomer **250c** cyclized to give **251c** in 90% ee. Variations in solvent (THF, CH_2Cl_2, C_6H_6) and temperature (−15, 0, 38 °C) had little effect upon the enantioselectivity. Although these represent the only examples of enantioselective RCM reactions using ruthenium catalysts, further developments can be expected owing to the extensive functional group tolerance and the stability toward air and moisture of ruthenium-derived catalysts.

Scheme 75



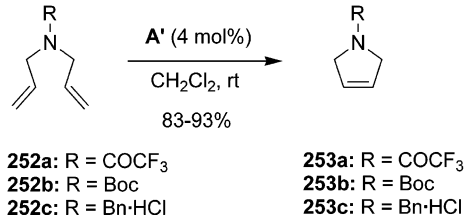
Only simple oxygen heterocycles have been formed by enantioselective RCM reactions, and to date the only practical application of such a cyclization is found in Burke's synthesis of *exo*-brevicomin synthesis (see Scheme 35).[61a] Indeed, the application of such processes in organic synthesis will be limited until catalysts are found that are not subject to the high degree of catalyst-substrate specificity typical of known complexes. Moreover, catalysts that do not have specific requirements for substitution on the enantiotopic double bonds must be identified. In this regard, the modular structure of the Mo-alkylidene catalysts may address the necessity to design catalysts for a specific substrate.

3. Nitrogen Heterocycles

3.1. Five- and Six-Membered Azacycles

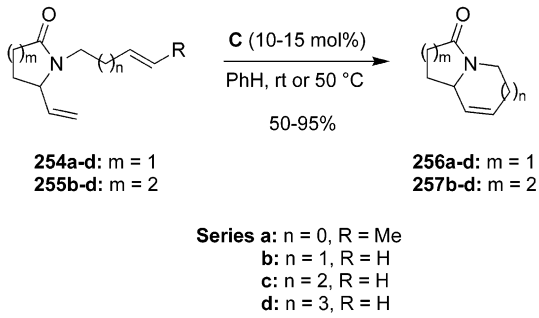
The use of RCM to form nitrogen heterocycles was first reported by Grubbs and Fu, who found that the *N*-trifluoroacetyl diene **252a** underwent cyclization in the presence of Schrock catalyst **C** to give the dihydropyrrole **253a**.[1b,125] Shortly thereafter they discovered that the more easily handled Ru-alkylidene complex **A'** catalyzed the reaction of **252b** to **253b** in excellent yield, even when reagent-grade, undistilled solvents were used and the reaction was carried out in the presence of air (Scheme 76).[125b] Although a basic amine function was not compatible with the catalyst **A'**,[6] the hydrochloride salt **252c** cyclized readily in good yield.

Scheme 76



Stimulated by these early reports, Martin and coworkers were the first to demonstrate that RCM could be employed to construct fused nitrogen heterocycles that were common subunits in alkaloid natural products.[126] Thus, the α,ω-dienes **254a**−**d** and **255b**−**d**, which were readily accessible from succinimide and glutarimide, cyclized smoothly in the presence of Schrock's catalyst **C** to form the fused bicyclic products **256a**−**d** and **257b**−**d** (Scheme 77).

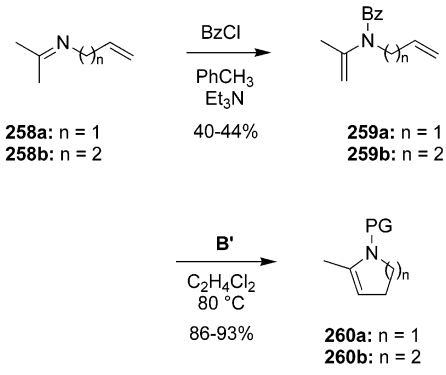
Scheme 77



That RCM could be employed for the synthesis of eight-membered rings was particularly noteworthy. These findings clearly established the potential of RCM for alkaloid synthesis, and since this initial report others reported similar routes to bicyclic lactams.[127]

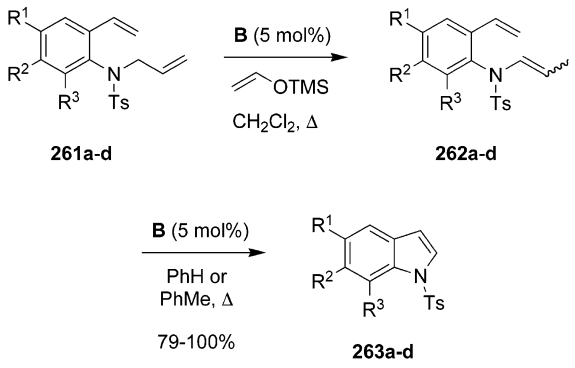
Acyclic enamides are good substrates for RCM, as illustrated by the cyclizations of the enamides **259a**,**b**, which were prepared by acylation of the corresponding imines **258a**,**b**, in the presence of the catalyst **B'** to furnish the corresponding five- and six-membered cyclic enamides **260a**,**b** (Scheme 78).[128] These cyclic enamides are versatile intermediates that may be used as substrates for *N*-acyliminium ion chemistry or Heck reactions.

Scheme 78



Nishida and co-workers recently reported a novel synthesis of indoles by a process that featured the RCM of an enamide that had been formed by isomerization of an allyl amide (Scheme 79).[129] Thus,

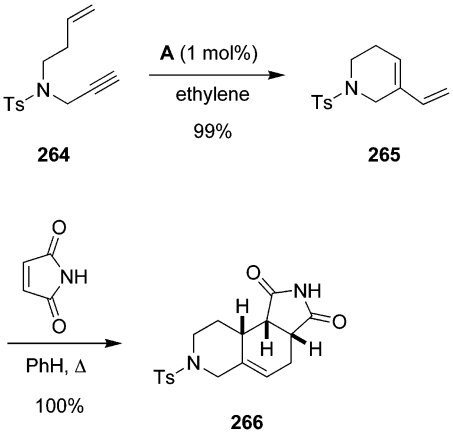
Scheme 79



allylamides **261a**−**d** were isomerized to the enamides **262a**−**d** using vinyloxytrimethylsilane and Grubbs catalyst **B**. The mechanism of this double bond isomerization is unknown, although the available evidence suggests that the reaction of **B** with trimethylsilyl vinyl ether generated a new catalyst that isomerized the olefin but was incapable of inducing the RCM of the product enamide. When the enamides **262a**−**d** were isolated and then heated in the presence of Grubbs catalyst **B**, the indoles **263a**−**d** were obtained in very good overall yields from **261a**−**d**.

Mori and co-workers have employed enyne metathesis to construct five-, six-, and seven-membered heterocycles.[130] For example, when **264** was treated with **A** under ethylene gas, cyclization ensued at room temperature to give **265** (Scheme 80). Conduct-

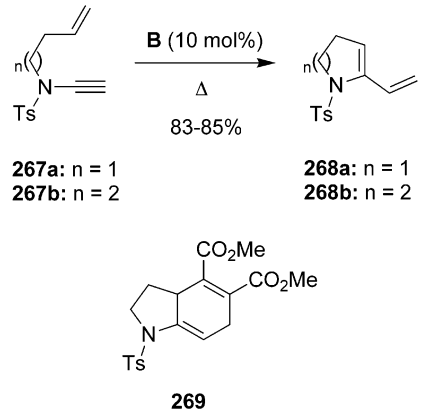
Scheme 80



ing the reaction under an atmosphere of ethylene rather than argon greatly facilitated the ring closure. Dienes such as **265** are useful intermediates for the synthesis of more complex heterocyclic systems. For example, the Diels−Alder reaction of **265** with maleimide furnished the tricycle **266** as a single diastereomer. This methodology was later extended to the synthesis of fused and monocyclic azacyclooctenes.[131]

Mori also discovered that enynamides undergo RCM to form five- and six-membered cyclic vinyl enamides, as illustrated by the cyclizations of **267a**,**b** in the presence of the second-generation Grubbs catalyst **B** to give **268a**,**b** (Scheme 81).[132] When the

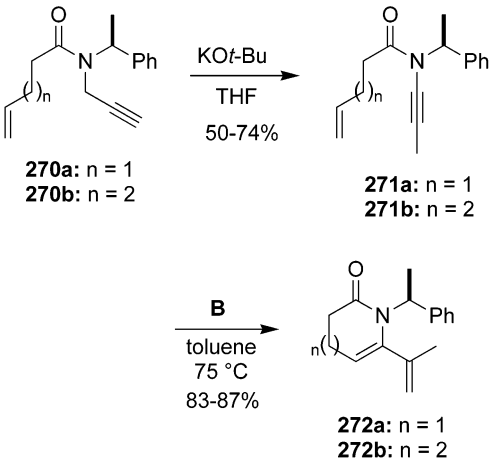
Scheme 81



ruthenium alkylidene **A** was employed as the catalyst, only trace amounts of cyclic products were obtained. To illustrate the potential of vinyl enamides as intermediates for heterocycle synthesis, **268a** was allowed to react with dimethyl acetylenedicarboxylate (DMAD) in a one-pot operation to give the Diels−Alder adduct **269**.

In a similar fashion, Hsung and co-workers reported that the substituted enynamides **271a**,**b**, which were generated by isomerizing the corresponding propargyl amides **270a**,**b** with strong base, cyclized in the presence of Grubbs' catalyst **B** to give the dienes **272a**,**b** in excellent yields (Scheme 82).[133]

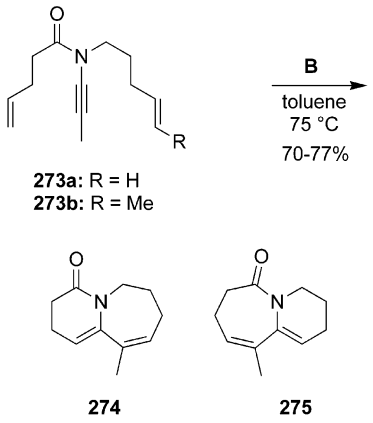
Scheme 82



The less reactive alkylidene **A** promoted the cyclizations in <10% yield.

This methodology was extended to the preparation of bicyclic products using a tandem RCM reaction, as shown in Scheme 83. When the enynamide **273a** was heated in the presence of the ruthenium alkylidene **B**, a mixture (1:1) of **274** and **275** was obtained, because the catalyst reacted with each of

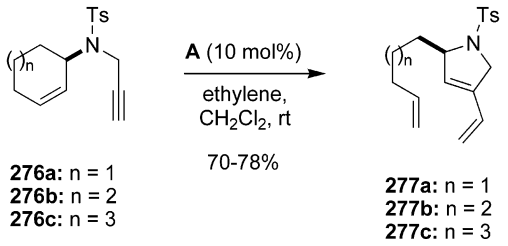
Scheme 83



the terminal alkenes at essentially the same rate. On the other hand, the cyclization of **273b** was more selective, giving **274** and **275** in a 6:1 ratio, because the initial loading of **B** occurred preferentially on the less substituted carbon−carbon double bond. This case represents another nice example of how the course of RCM reactions can be controlled by varying the degree of substitution on the reacting double bonds.

Mori has developed an interesting route to substituted dihydropyrroles **277a**−**c** by treating enynes **276a**−**c** with **A** under an atmosphere of ethylene gas.[134] The employed reaction cascade consists of a ROM followed by a RCM to generate a Ru-alkylidene that then underwent cross metathesis with ethylene, furnishing compounds **277a**−**c** in good to excellent yields (Scheme 84). If the reaction was conducted

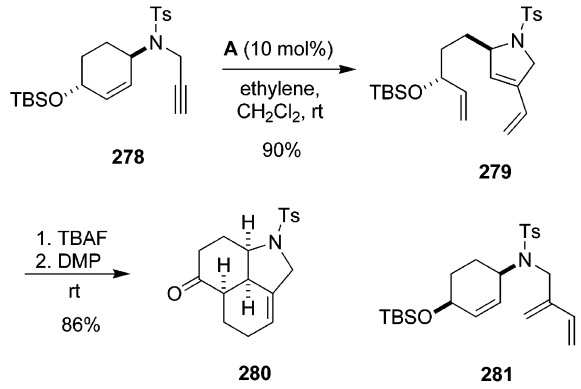
Scheme 84



under argon, no cyclized product was obtained. Thus, ethylene gas can sometimes, but not always (vide infra), be a crucial additive when terminal alkynes are substrates for metathesis reactions.[130a,135]

The trienes obtained by this sequence are useful intermediates, as illustrated by the synthesis of the tricyclic product **280** (Scheme 85). Reaction of the *trans*-1,4-disubstituted cyclohexene **278** with **A** in the presence of ethylene gave the triene **279**. Desilylation of **279** followed by Dess−Martin oxidation of the resultant allylic alcohol gave an enone that spontaneously underwent a diastereoselective, intramolecular Diels−Alder reaction to furnish **280**. Interestingly, treatment of the *cis*-isomer of **278** with **A** gave only **281** (95% yield), which is the product of a CM of the intermediate vinyl ruthenium−alkylidene with ethylene. The ROM of the ruthenium−alkylidene derived from the *cis*-isomer of **278** is presumably hindered by the OTBDMS group, so CM with ethylene occurs preferentially. Hence, conducting the RCM

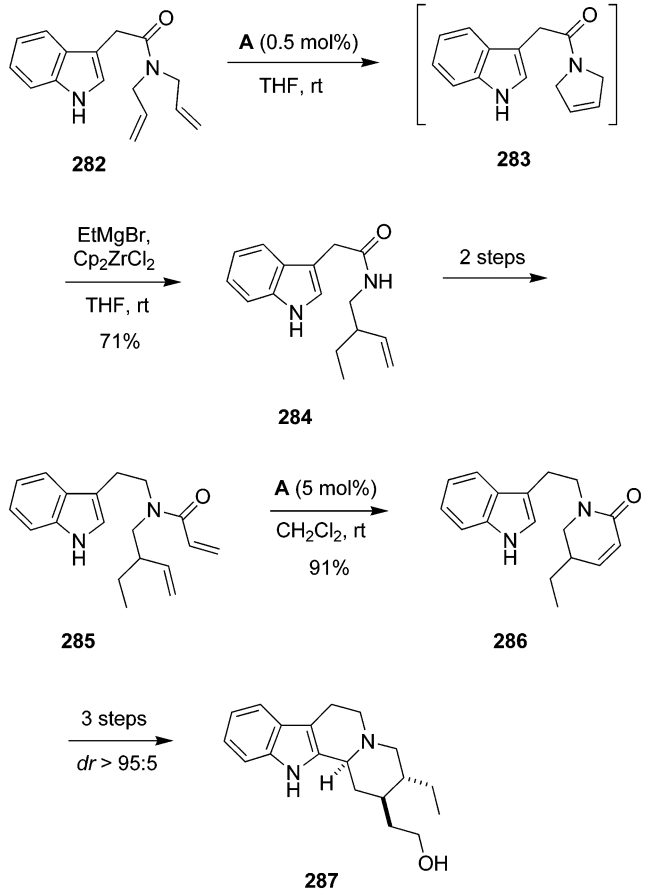
Scheme 85



of enynes under an atmosphere of ethylene is not always advantageous, and its use may be accompanied by undesired CM reactions.

Martin recently reported a stereoselective total synthesis of dihydrocorynantheol (**287**) by a sequence requiring only eight steps and featuring two RCM reactions (Scheme 86).[136] The synthesis commenced

Scheme 86

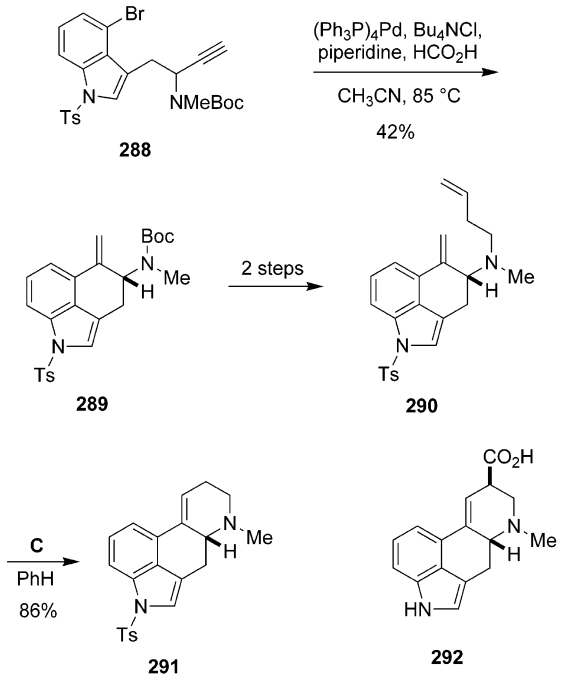


with the conversion of the diallyl amide **282** into the homoallylic amide **285** by an efficient one-pot procedure that involved the RCM of **282** to furnish an intermediate dihydropyrrole **283**[137] that was subjected in situ to a carbomagnesation−elimination reaction. Compound **284** was converted in two steps into the diene **285**, which underwent a RCM reaction upon treatment with Grubbs catalyst **A** to deliver the

α,β-unsaturated lactam **286**.[138] Subjection of **286** to sequential diastereoselective cuprate addition, Bischler−Napieralski cyclization, and hydroboration−oxidation then furnished **287**. It is noteworthy that no protecting groups were used at any stage of the synthesis.

Martin has also reported a novel entry to the tetracyclic ring system found in the *Ergot* alkaloid lysergic acid (**292**) by an approach that featured formation of the six-membered D-ring via a RCM (Scheme 87).[139] The key tricyclic intermediate **289**

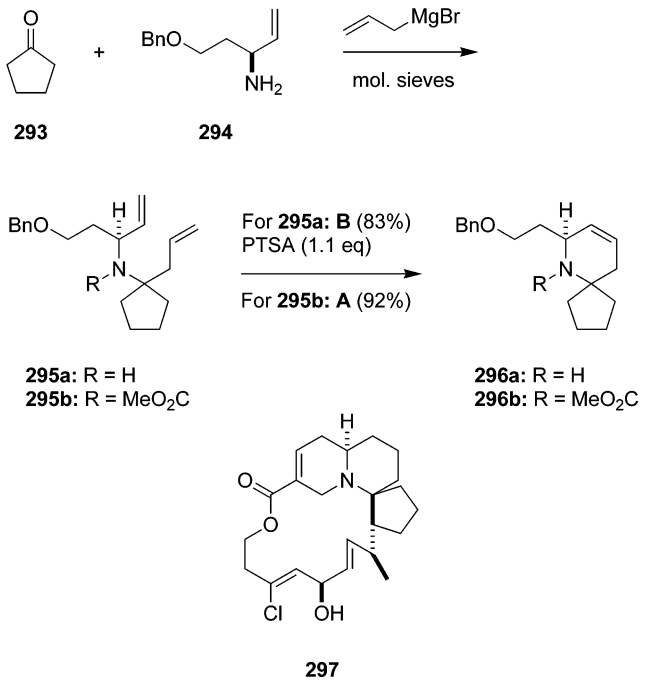
Scheme 87



was formed by the Heck cyclization of **288**, which was prepared in eight steps from 4-bromoindole. Removal of the Boc protecting group from **289** followed by *N*-alkylation gave **290**. Although **290** did not undergo significant cyclization in the presence of the Grubbs catalyst **A**, the more reactive Schrock catalyst **C** induced the desired RCM to give **291**. This cyclization is noteworthy, because there are relatively few examples of RCM reactions involving exocyclic olefins.[140]

In work directed toward the development of entries to spirocyclic piperidines, Wright and co-workers reported a concise entry to the spirocyclic core of halichlorine (**297**) using RCM as a key step.[141] The requisite dienic substrates **295a**,**b** were quickly assembled by condensing cyclopentanone (**293**) with the enantiomerically pure amine **294**, followed by reaction of the intermediate imine with allylmagnesium bromide (Scheme 88). When the unprotected amine **295a** was treated with the catalyst **A** in the presence of *p*-toluenesulfonic acid to form an ammonium salt in situ, the azaspirocycle **296a** was obtained in only 33% yield, even after 20 d and portionwise addition of 60 mol% of **A**. The low yield in this and related cyclizations was attributed to inhibition of the catalyst by the ammonium salt and progressive degradation of the catalyst. However, these problems were

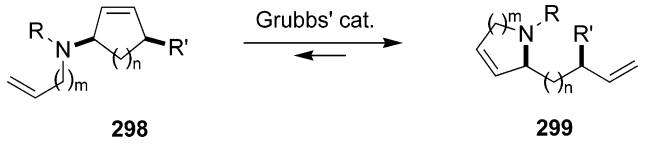
Scheme 88



solved either by using a more reactive catalyst or by protecting the amino group as a carbamate. Thus, the ammonium salt of **295a** underwent facile cyclization to give **296a** using 10 mol% of the second-generation Grubbs catalyst **B**, whereas the carbamate **295b** cyclized in the presence of **A** to deliver **296b**.

Grubbs' strategy[47] for preparing polycyclic ethers has been adapted by Blechert and co-workers in developing a route toward five- and six-membered nitrogen heterocycles. The approach involves the tandem intramolecular ROM and RCM of nitrogen-substituted cycloalkenes **298** to give **299** according to the general plan outlined in Scheme 89.[2g] The ratio

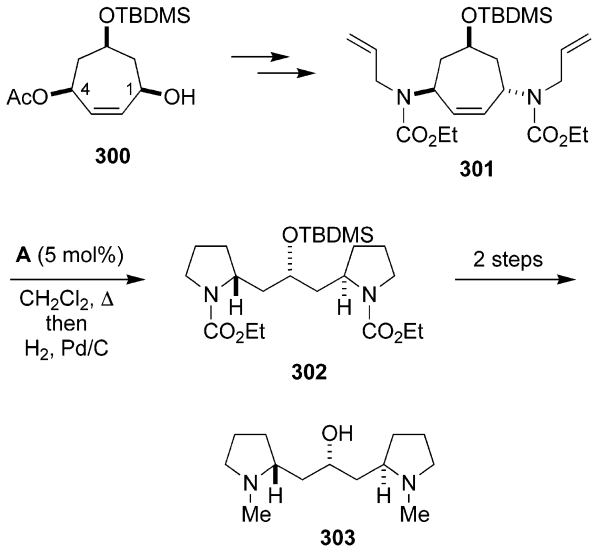
Scheme 89



of rearranged product to starting material largely depends on thermodynamic effects such as ring strain. When enantiomerically pure carbocycles were employed as starting materials, the chiral information was transformed into the heterocycle without loss of optical purity. Blechert has applied this basic entry to nitrogen heterocycles as a key step in the synthesis of a variety of natural products, as illustrated in the several examples that follow.

The synthesis of (+)-dihydrocuscohygrine (**303**), which bears two pyrrolidine moieties, features the tandem ROM and RCM of the bis-allylcarbamate **301** (Scheme 90).[142] The known alcohol **300**[143] was converted into the diene **301** in five steps and good overall yield by a process that involved a Mitsunobu reaction to invert the stereochemistry at C1 followed by a double nucleophilic displacement at C4 that led to retention of stereochemistry at that center. Treat-

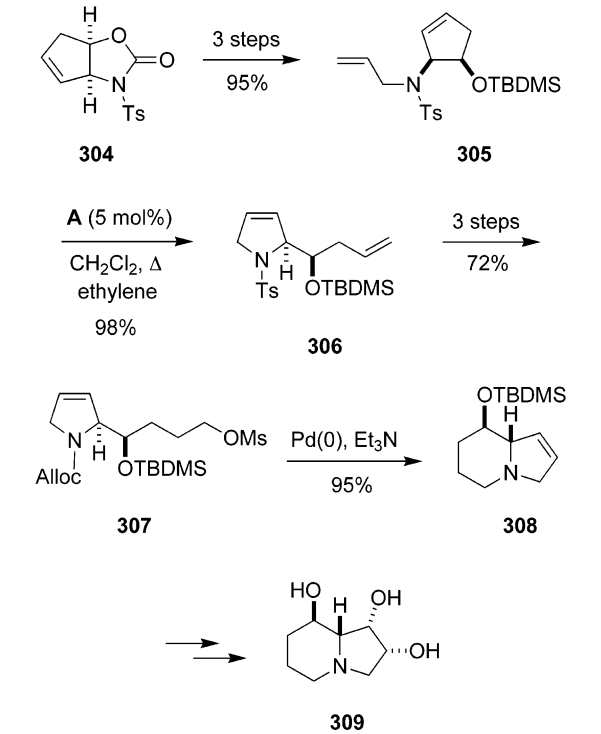
Scheme 90



ment of **301** with **A** gave a bis-dihydropyrrole that was unstable in the presence of decomposed Ru-alkylidene catalyst, so it was reduced directly by catalytic hydrogenation to give **302**. Subsequent reduction of the carbamates and cleavage of the silyl ether provided the natural product **303**.

Blechert has also used a tandem ROM and RCM sequence in a synthesis of swainsonine (**309**), an important polyhydroxylated indolizidine alkaloid.[144] Treatment of **305**, which was obtained in three steps from the known carbamate **304**,[145] with **A** under an atmosphere of ethylene gas afforded **306** in almost quantitative yield (Scheme 91). This transformation

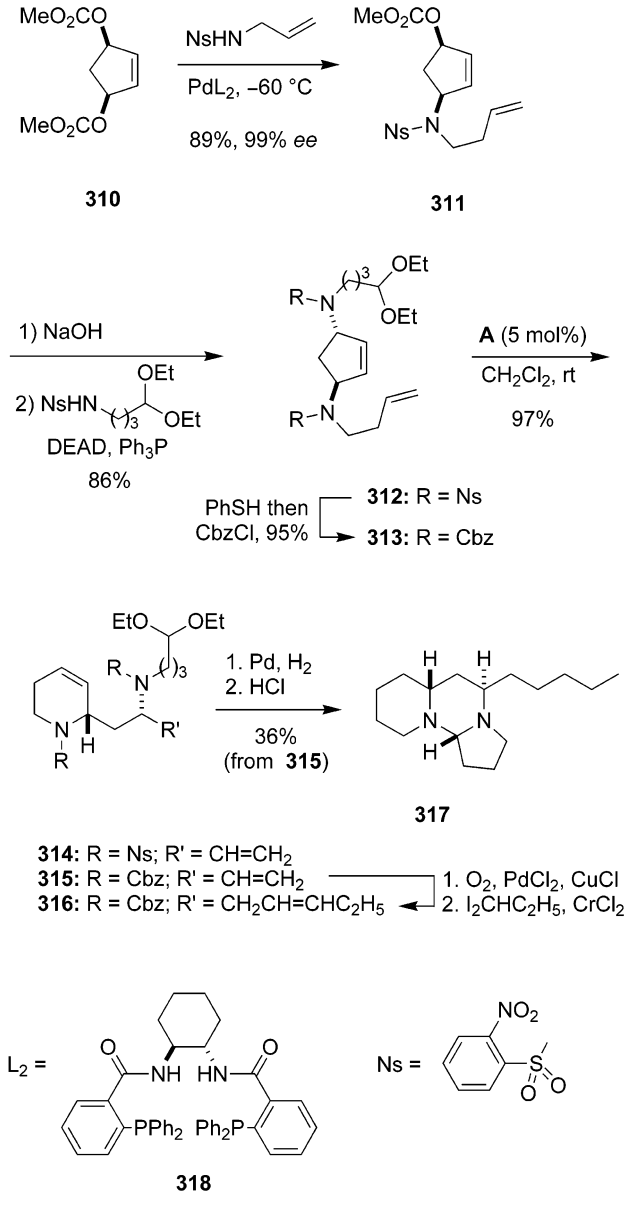
Scheme 91



was favored when the sterically demanding TBDMS group was used to protect the secondary alcohol function, as lower yields were obtained when a benzyl ether was employed instead. Compound **306** was converted in three steps to **307**, and subsequent deprotection of **307** gave the indolizidine **308**. Although the double bond in **308** did not undergo diastereoselective dihydroxylation with OsO_4, high stereoselectivity was obtained by employing the Sharpless protocol and AD-mix α. Pyne has also reported a synthesis of swainsonine (**309**) in which the pyrrolidine ring was formed by RCM.[146]

In another study, Blechert reported the enantioselective synthesis of the tricyclic alkaloid tetraponerine T7 (**317**), which is a major component of the contact poison of the New Guinean ant *Tetraponera sp.*, using the Ru-catalyzed ROM and RCM of **313** as a key step to form the piperidine A-ring (Scheme 92).[147] The *meso*-dicarbonate **310** was first desym-

Scheme 92

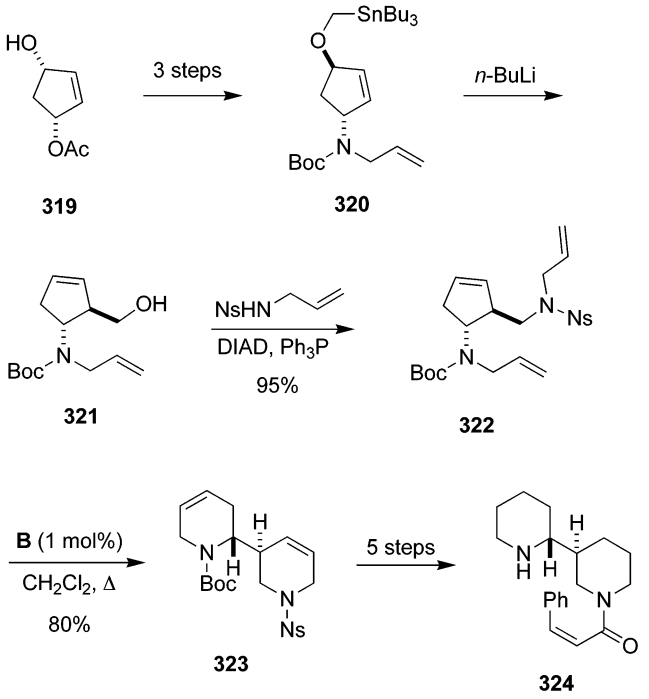


metrized by an asymmetric Pd-catalyzed amination using the Trost ligand **318**[148] to give **311** in 99% ee. Hydrolysis of **311** followed by a Mitsunobu coupling

of the resultant allylic alcohol provided **312**. Initial attempts to induce the ROM/RCM on **312** led to a mixture (1:2) of the starting material **312** and the tetrahydropyridine **314**, so the nitrogen-protecting groups were simply changed to Cbz to give **313**. Exposure of **313** to **A** afforded the desired tetrahydropyridine **315**. To complete the synthesis of **317**, it was then necessary to elongate the side chain. Because a strategy involving a cross-metathesis with allyltrimethylsilane was unsuccessful, an unprecedented Wacker oxidation of an allylic amine to an aldehyde followed by a Takai olefination of the resultant aldehyde was performed to give **316**. The synthesis was completed by catalytic hydrogenation followed by acid-catalyzed cleavage of the acetal and cyclization to give **317**.

In a nice extension of this strategy for tandem ROM and RCM reactions, Blechert has reported the synthesis of (+)-astrophylline (**324**), a *cis*-cinnamoyl alkaloid isolated from the shrub *Astrocasia phyllanthoides*.[149] The synthesis commenced with the straightforward conversion of the readily available, enantiomerically pure cyclopentene **319** into the allylamine derivative **320** (Scheme 93). A diastereoselective

Scheme 93

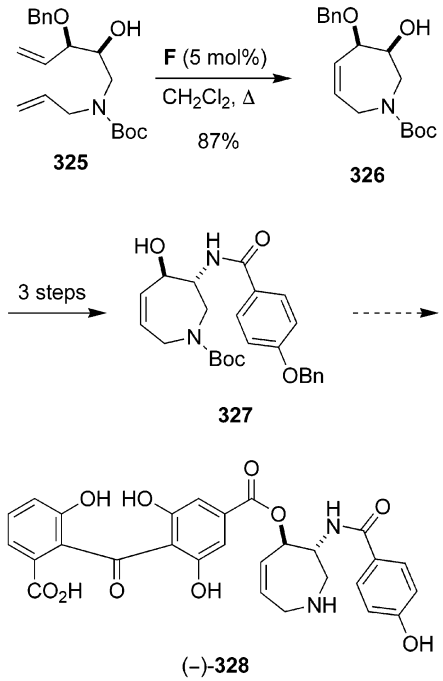


[2,3]-Wittig rearrangement then furnished **321** that was transformed via a Mitsunobu reaction into **322**. When **322** was treated with Grubbs catalyst **B**, it underwent a RCM/ROMP/RCM cascade to establish the two new piperidine rings in **323**. Unlike the problem that was encountered with the ROM/RCM of **312**, the Ns-group on **322** did not seem to interfere with the second-generation catalyst **B**. The key intermediate **323** was then converted into (+)-astrophylline (**324**) in five steps. Blechert has exploited similar reaction sequences for the syntheses of a number of other *N*-heterocyclic compounds.[150]

3.2. Seven-, Eight-, and Nine-Membered Azacycles

Fürstner reported a short, enantioselective route to **327**, a known intermediate in the synthesis of (−)-balanol (**328**), which is an important lead for selective inhibitors of the therapeutically important enzyme protein kinase C (Scheme 94).[151] The approach fea-

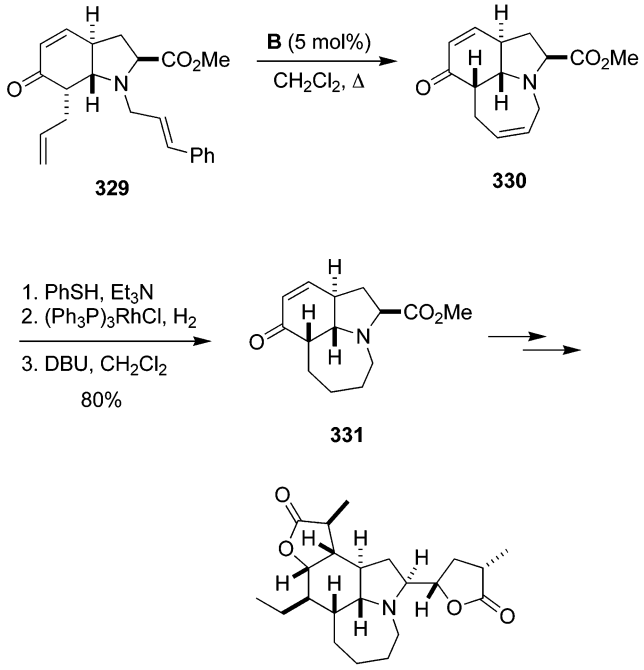
Scheme 94



tured the preparation of the protected amino diol **325** from divinyl carbinol by a four-step sequence that involved a Sharpless asymmetric epoxidation and ring opening with allylamine. The RCM of **325** to give the dehydroazepane **326** was best catalyzed by the easily synthesized ruthenium indenylidene complex **F**. Compound **326** was then converted in three steps into **327**, thereby completing the formal synthesis of **328**.

Wipf exploited a RCM to construct the azepane subunit in the *Stemona* alkaloid (−)-tuberostemonine (**332**) (Scheme 95).[152] The RCM substrate **329** was synthesized in 10 steps from Cbz-protected L-tyrosine. Heating a solution of **329** in the presence of **B** furnished **330**. This transformation is interesting, because ruthenium RCM catalysts may be incompatible with basic amino groups.[6,153−155] Although the reason for having a phenyl ring on one of the double bonds in **329** was not provided, its presence presumably led to the initial reaction of **B** with the terminal double bond in **329**, so **B**, rather than the more fragile methylidene derivative, was regenerated upon ring closure in the last step of the RCM. The presence of the α,β-unsaturated ketone moiety in **330** did not allow selective reduction of the isolated double bond in the azepane ring in **330**, so it was necessary to employ a three-step sequence to convert **330** into **331**. The tricyclic intermediate **331** was then elaborated into (−)-tuberostemonine (**332**) via a series of reactions in which the two γ-butyrolactone rings and the ethyl substituent were installed.

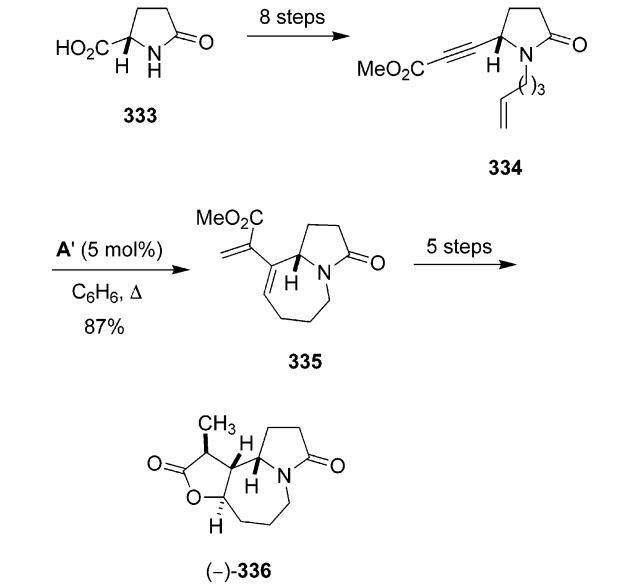
Scheme 95



329 330 331 (–)-**332**

In an elegant synthesis of the related *Stemona* alkaloid (−)-stemoamide (**336**), Mori constructed the enantiomerically pure bicyclic intermediate **335** by the RCM of the enyne **334**, which was prepared in eight steps from (*S*)-pyroglutamic acid (**333**) (Scheme 96).[156] When **334** was heated with **A'**, a facile enyne

Scheme 96

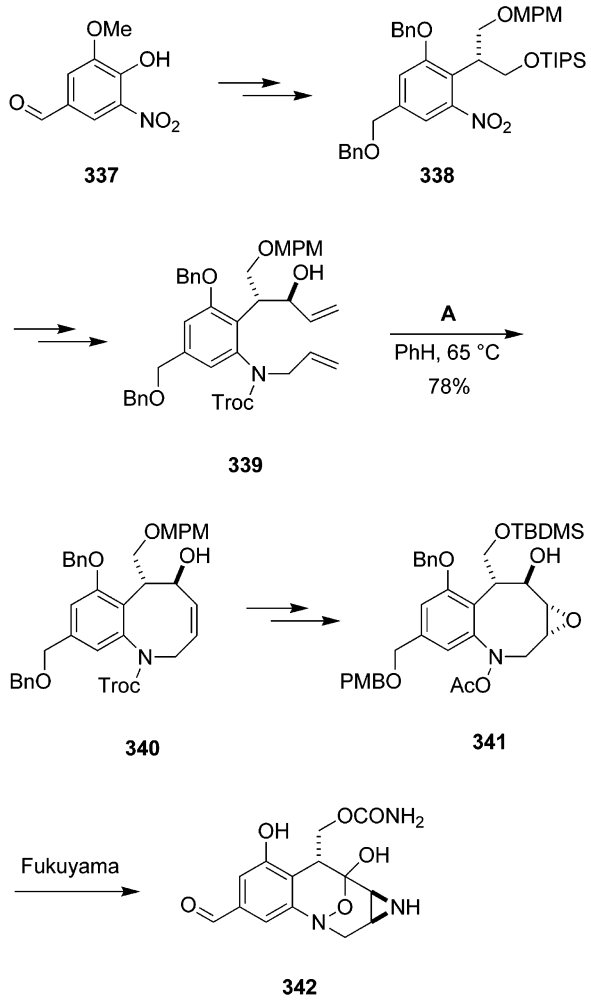


333 334 335 (–)-**336**

RCM ensued to produce the diene **335** in very good yield. Elaboration of **335** to introduce the butyrolactone then led to (−)-**336.**

RCM has been used in several instances to generate heterocyclic eight-membered rings that were then elaborated into bicyclic ring systems via a subsequent transannular reaction.[157] In the context of model studies directed toward the synthesis of FR900482 (**342**), Martin[158] and Grubbs[159] independently demonstrated that RCM could be used to form functionalized benzoazocines (see also Scheme 77). Martin extended these preliminary findings to a formal synthesis of FR900482 by an approach that is outlined in Scheme 97.[160] Commercially available **337**

Scheme 97

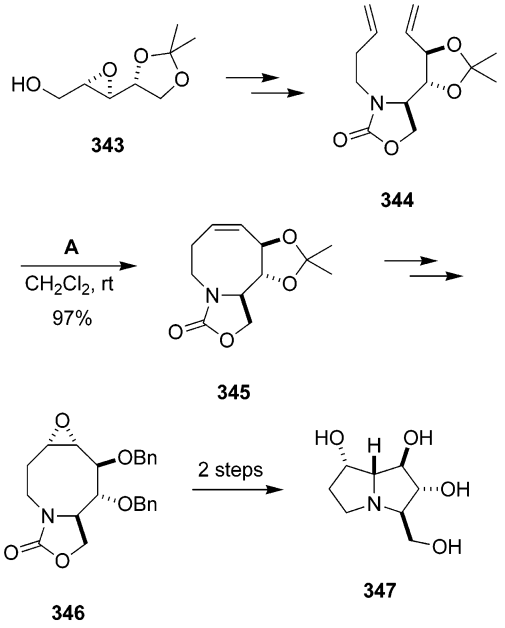


337 338 339 340 341 342

was first converted into enantiomerically pure **338** in 11 steps by a sequence that featured an enzymatic desymmetrization. Stereoselective elaboration of **338** into the RCM substrate **339** required five steps. When a dilute solution of **339** in benzene was heated in the presence of the Grubbs catalyst **A**, the benzoazocine **340** was isolated. The efficiency of this cyclization might result from conformational constraints imposed by the benzene ring and the amide nitrogen atom in the chain linking the two double bonds in **339**. The subsequent transformation of **340** into **341**, which had been previously converted into FR900482 by Fukuyama,[161] completed the formal synthesis of **342**.

White reported a synthesis of (+)-australine (**347**), a member of the family of pyrrolizidine alkaloids that exhibit antiviral activity, employing a strategy to construct the pyrrolizidine core that featured RCM and subsequent transannular cyclization.[162] The approach is potentially applicable to the preparation of polyhydroxylated indolizidines. The synthesis commenced with converting the known epoxy alcohol

Scheme 98

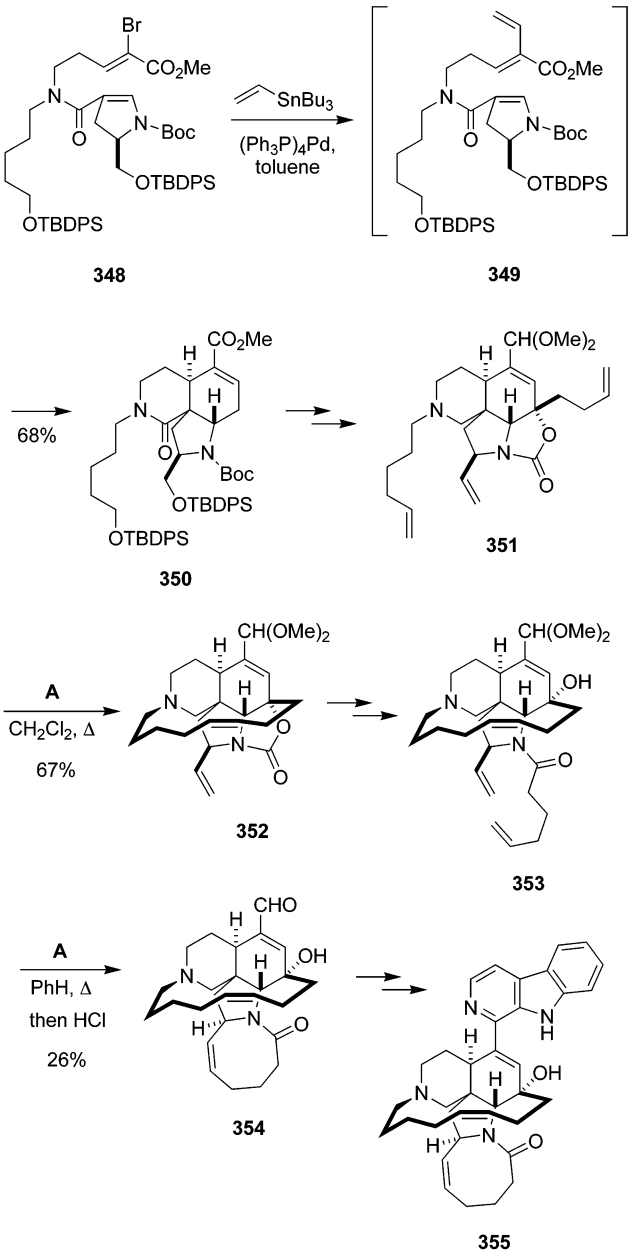


343[163] in four steps into the diene **344** (Scheme 98). The RCM of **344** using **A** as the catalyst furnished **345**, which was then converted into the epoxide **346**. Upon hydroxide-induced cleavage of the oxazolidinone ring in **346**, a transannular ring-closure occurred spontaneously to give a pyrrolizidine that was transformed into (+)-australine (**347**) by removal of the benzyl protecting groups.

3.3. Ten-Membered and Larger Azacycles

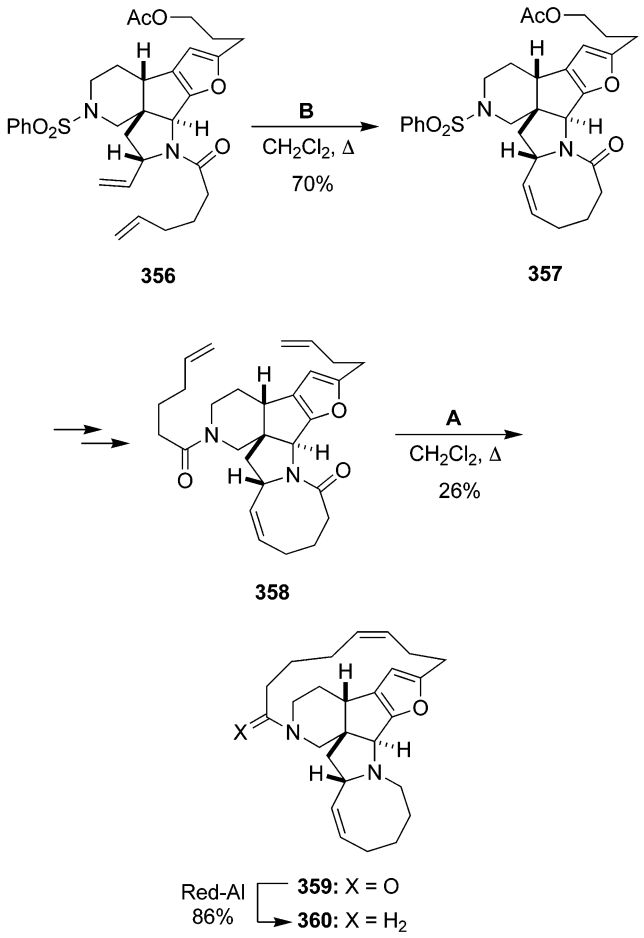
Manzamine A (**355**) is a complex indole alkaloid with an unusual structure that exhibits potent antitumor and antimalarial activity. A concise enantioselective synthesis of **355** has been reported by the Martin group using an approach that featured RCM reactions to form both the fused eight-membered ring and the bridged 13-membered ring.[164] The highlights of this synthesis are summarized in Scheme 99. The key tricyclic intermediate **350** was assembled from **348**, which was prepared from (*R*)-pyroglutamic acid, via **349** by a novel domino Stille/Diels−Alder sequence in which three new carbon−carbon bonds and three new stereocenters were formed in a *single* operation. The cycloadduct **350** was converted in eight steps into the first RCM substrate **351**. Heating **351** in the presence of the Grubbs ruthenium catalyst **A** delivered a mixture of geometric isomers (*Z*/*E* = 8:1) from which (*Z*)-**352** was readily isolated.[165] Although basic amines may sometimes interfere with RCM reactions using **A** as the catalyst,[6,153] protonation of the tertiary amino group in **351** prior to inducing the RCM had no beneficial effect and was unnecessary. In marked contrast to the facility with which **351** underwent RCM, the cyclization of **353**, which was prepared in two steps from (*Z*)-**352**, proved far more difficult for reasons that remain unclear. The yield of the RCM of **353** leading to **354** was only about 30%, even when high catalyst loadings of **A** were used or the more reactive molybdenum catalyst **C** was employed. Compound **354** was then transformed into manzamine A (**355**), thus completing an enantioselective synthesis of **355** that required only 26 chemical operations from commercially available starting materials.

Scheme 99

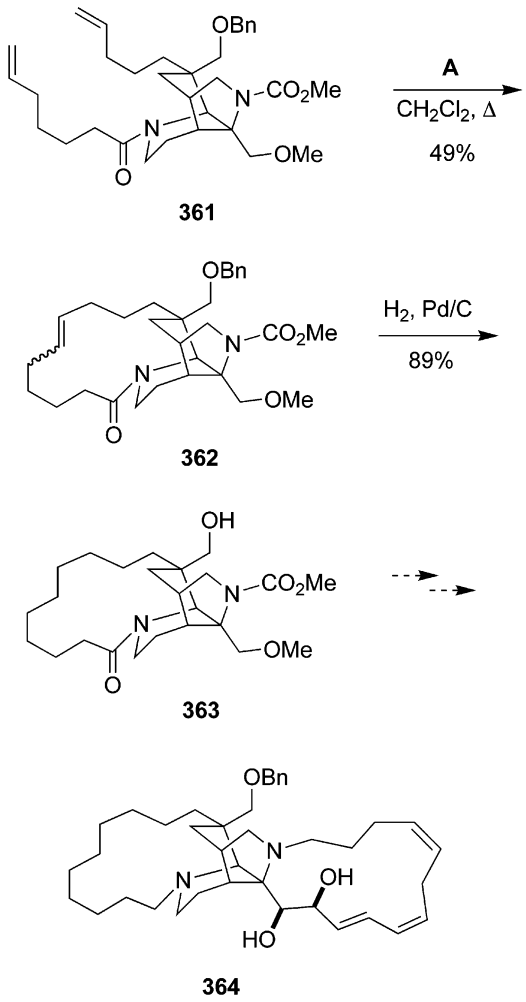


Nishida and co-workers have reported the synthesis of (+)-nakadomarin A (**360**), the enantiomer of an unusual marine natural product that is believed to be a member of the manzamine family. Their approach, which is summarized in Scheme 100, incorporates RCM reactions to construct the eight- and the 15-membered azacycles present in this complex alkaloid.[166] When the advanced intermediate **356** was exposed to the second-generation Grubbs catalyst **B**, a facile RCM reaction ensued to furnish the lactam **357** in good yield. On the other hand, cyclization of **356** using the alkylidene catalyst **A** afforded **357** in only 15% yield. This material was converted in five steps into **358**, thereby setting the stage for the second RCM reaction. Upon treatment with **A**, **358** underwent RCM to give a mixture of

Scheme 100



Scheme 101



double bond isomers (*E*:*Z* = 2:3) from which the desired *Z*-isomer **359** was isolated in low yield. It is tempting to consider that the macrocyclic ring in **359** might be prepared more efficiently using Fürstner's diyne-RCM/hydrogenation strategy.[101] Reduction of the two lactam moieties in **359** then concluded the first total synthesis of (+)-**360**, which is the enantiomer of the natural substance.

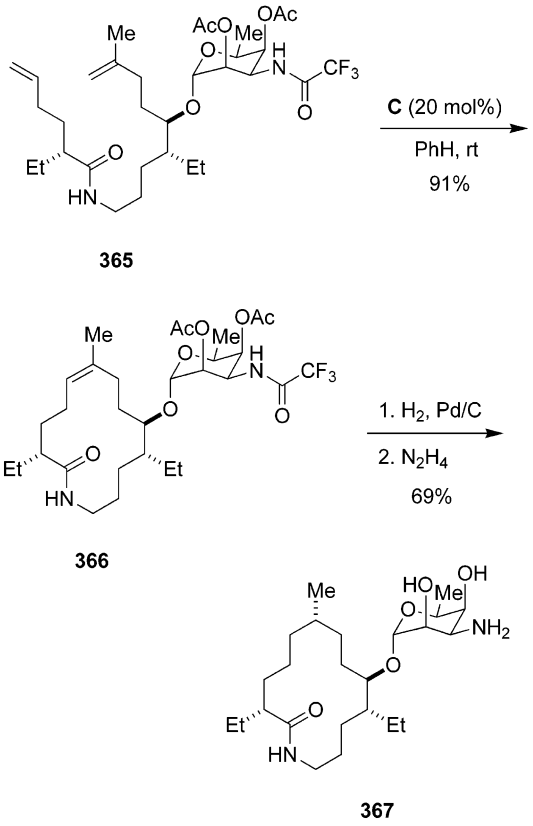
Sarain A (**364**) is another marine alkaloid that has attracted considerable interest, although it has thus far eluded total synthesis. In their approach to **364**, Weinreb and co-workers reported the annelation of the "western" macrocyclic ring onto the previously synthesized tricyclic core using a RCM reaction (Scheme 101).[167] Thus, exposure of the diene **361** to Grubbs catalyst **A** provided the desired macrocyclic lactam **362** as a mixture of geometric isomers (49%), together with a dimeric product (39%) and recovered starting material (7%). Hydrogenation of the double bond in **362** proceeded with concomitant *O*-debenzylation to furnish **363**. In attempts to improve the efficiency of RCM reactions leading to **362**, cyclizations of several substrates related to **361** were examined in which the lengths of the two alkenyl side chains were varied, but these experiments led to inseparable mixtures of cyclic products and dimers. Recently, Cha reported a very similar approach to sarain A in which a diene almost identical to **361** was cyclized with the second-generation catalyst **B** to give the desired macrocycle.[168]

Hoveyda and co-workers reported the first enantioselective synthesis of the macrocyclic antifungal agent Sch38516 (fluvirucin B1) (**367**) using a RCM to form the macrolactam ring (Scheme 102).[169] When the glycosylated diene **365** was treated with freshly recrystallized Mo-catalyst **C**, facile and highly stereoselective (>98% *Z*) cyclization ensued to give **366**. Interestingly, when a RCM reaction was carried out with a closely related diene lacking the ethyl and hydroxy groups found in **365**, the corresponding cyclized product was obtained in only 2% yield; a "head-to-head" dimer was formed in 52% yield. This experiment clearly illustrates that stereogenic centers may provide conformational constraints that are essential for successful cyclizations via RCM.[159] Stereoselective catalytic hydrogenation of the lactam **366** followed by global deprotection of the carbohydrate subunit gave **367**.

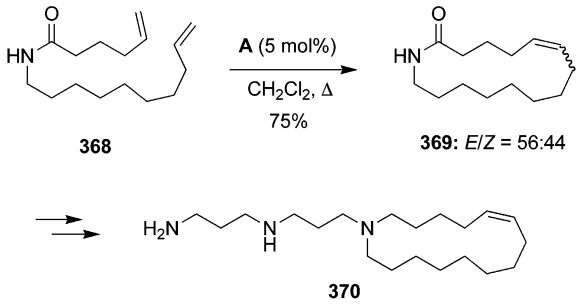
Goldring used a RCM reaction to form the 15-membered ring of the anticancer alkaloid motuporamine C (**370**), as shown in Scheme 103.[170] Reaction of **368** with catalyst **A** provided the macrocyclic lactam **369** as a mixture of double bond isomers (*E*:*Z* = 56:44) that had to be separated by radial chromatography. Conversion of **369** into the natural product **370** was then achieved in four steps.

The lack of stereoselectivity in the cyclization of **368** is symptomatic of a general problem associated

Scheme 102



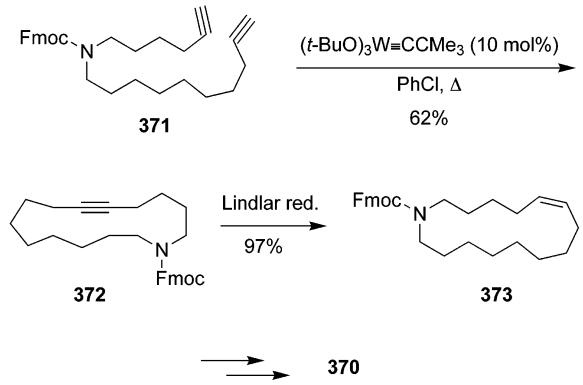
Scheme 103



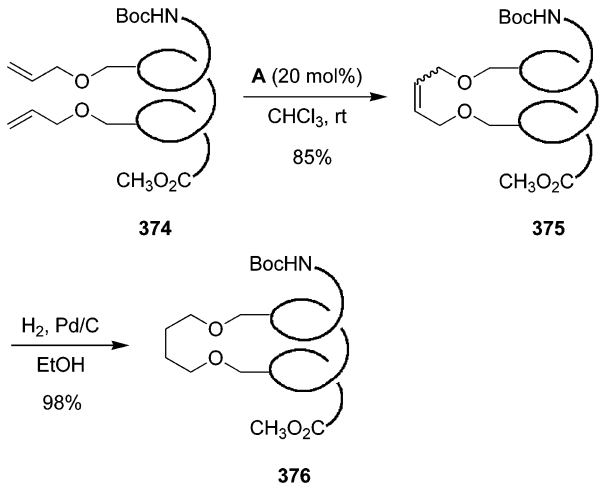
with the stereospecific synthesis of *Z*- and *E*-macrocyclic alkenes by the RCM of α,ω-dienes. As noted previously, one approach to solving this problem involves the RCM of diynes followed by partial reduction of the carbon−carbon triple bond,[101] and Fürstner has applied this tactic to a stereoselective synthesis of motuporamine C (**370**) (Scheme 104).[171,172] Thus, exposure of the diyne **371** to catalytic amounts of the Schrock alkylidyne complex (*t*-BuO)$_3$W≡CCMe$_3$ delivered the macrocyclic alkyne **372**. Reduction of **372** using Lindlar's catalyst gave **373**, which was converted in three steps to **370**.

RCM has also been applied to the syntheses of other macrocyclic lactams[173] and peptides.[174] For example, Grubbs and Blackwell incorporated two *O*-allyl serines into helical peptide scaffold **374** that was then treated with alkylidene **A**. A remarkably facile RCM reaction furnished the 21-membered macrocyclic peptide **375** as a mixture of geometrical isomers. Catalytic hydrogenation yielded the saturated species **376** quantitatively (Scheme 105).[174b]

Scheme 104



Scheme 105



374 = Boc-Val-AllylSer-Leu-Aib-Val-AllylSer-Leu-OMe

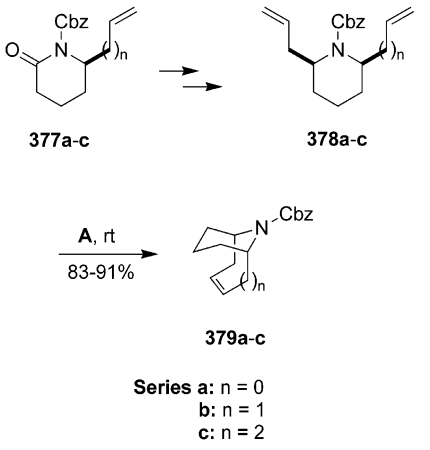
Aib = α-aminoisobutyric acid

The CD spectrum of this rigidified peptide clearly showed that it adopted a helical conformation.

3.4. Bridged Azabicycles

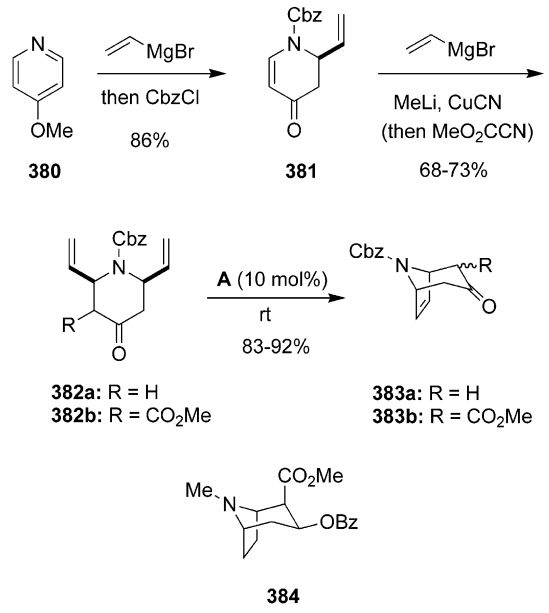
A number of alkaloids and other biologically active substances possess a nitrogen atom in the one-atom bridge of a [n.3.1] bicyclic ring system, so there has been a longstanding interest in developing new tactics for preparing such structural arrays. Martin has recently reported that RCM reactions may be nicely exploited to provide facile access to a number of azabicyclo[n.3.1]alkenes.[175,176] For example, alkenyl-substituted 2-piperidone derivatives **377a**−**c**, which were prepared in four steps from glutarimide, were converted by sequential hydride reduction and reaction with allyltrimethylsilane in the presence of BF_3•OEt_2 into the α,ω-dienes **378a**−**c** with a high degree of stereoselectivity (Scheme 106). Cyclization of **378a**−**c** in the presence of the Grubbs catalyst **A** afforded the corresponding bridged bicyclic products **379a**−**c** in excellent yields. The ease with which **378a**−**c** underwent RCM was attributed to the affect of $A^{1,3}$-strain that would be expected to favor an axial-like orientation for each of the alkenyl side chains, thereby enforcing a conformational bias on the system that was required for cyclization.

Scheme 106



Of the bridged, bicyclic systems that occur in alkaloids, the tropane skeleton is arguably one of the more important, and Martin has developed a concise entry to functionalized members of this family. For example, 4-methoxypyridine (**380**) was allowed to react with vinylmagnesium bromide and Cbz-Cl to give **381**, the reaction of which with a vinylcuprate gave **382a** (dr = 20:1) (Scheme 107).[175] Treatment of

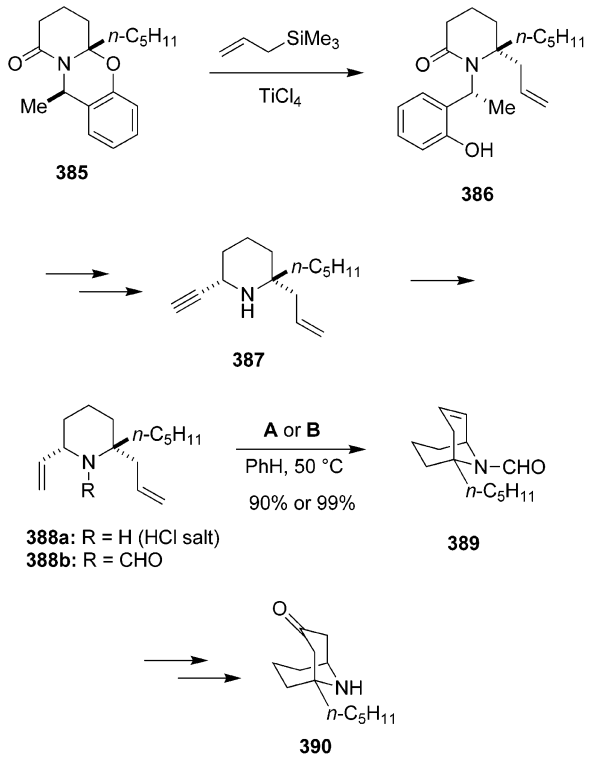
Scheme 107



382a with the first-generation Grubbs' catalyst **A** gave the tropane derivative **383a** in excellent yield. If the enolate generated upon the addition of vinyl cuprate to **381** was trapped with methyl cyanoformate, the keto ester **382b** was obtained. Cyclization of **382b** in the presence of **A** gave **383b**, a potential precursor of cocaine (**384**) and other tropane alkaloids.

Kibayashi subsequently employed a virtually identical strategy for constructing bridged, bicyclic nitrogen heterocycles for the synthesis of (−)-adaline (**390**), the major defensive alkaloid of the European ladybug *Adalia bipunctata*.[177] Enantiomerically pure **385**, which was prepared by condensation of 5-oxodecanoic acid with 2(*R*)-(1-aminoethyl)phenol, was converted via Lewis acid-catalyzed allylation to furnish **386** as a single diastereomer (Scheme 108).

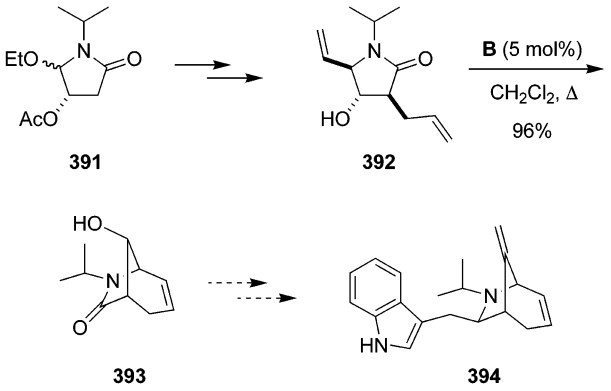
Scheme 108



Stereoselective elaboration of **386** led to the enyne **387**. Semireduction of the triple bond using Lindlar's catalyst gave an intermediate amine that was converted into the hydrochloride salt **388a** to avoid possible complications with the Ru-catalyst.[6,153] This precaution notwithstanding, **388a** did not undergo RCM in the presence of the catalyst **A**. This failure was attributed to the likely diequatorial arrangement of the two alkenyl side chains in **388a**. Hence, **387** was converted into the *N*-formyl derivative **388b**, as it was reasoned that the two alkenyl side chains would adopt diaxial orientations as a consequence of $A^{1,3}$-strain. In support of this hypothesis, **388b** underwent facile RCM with either catalyst **A** (25 mol%) or **B** (15 mol%) to give **389b**, which was subsequently transformed into the natural product **390**.

Martin has recently reported a very concise approach to (−)-peduncularine (**394**), an indole alkaloid that has been the focus of a number of synthetic efforts owing to its anticancer activity and the presence of an unusual 6-azabicyclo[3.2.1]-3-octene subunit.[178] The lactam **391**, which was prepared in two chemical operations from (*S*)-malic acid, was elaborated into **392** in good overall yield (Scheme 109). Although **392** did not undergo RCM using **A** as the catalyst, it did cyclize readily when the more reactive catalyst **B** was used to give **393** in nearly quantitative yield. The bicyclic lactam **393** had been previously converted into (−)-peduncularine (**394**) by Speckamp,[179] so its preparation constituted a formal synthesis of **394**.

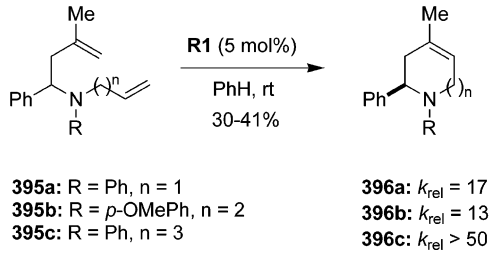
Scheme 109



3.5. Enantioselective Cyclizations to Nitrogen Heterocycles

Hoveyda, Schrock, and co-workers have found that chiral catalysts may be employed to effect the enantioselective synthesis of six-, seven-, and eight-membered nitrogen heterocycles via RCM reactions.[180] The Mo catalyst **R1** was first used to effect the kinetic resolution of the tertiary arylamines **395a**−**c** to provide the cyclized products **396a**−**c** with good to excellent enantioselectivities (Scheme 110).

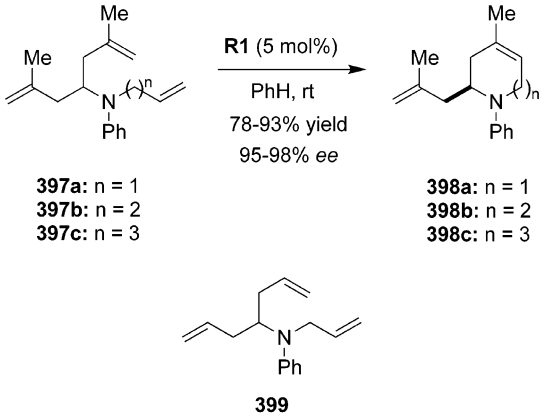
Scheme 110



In contrast to achiral Mo catalysts such as **C**, for which benzylamines and tosylamides are good substrates, the chiral catalyst **R1** appears to have a stringent requirement for the presence of an aryl group on the nitrogen atom. Although it was necessary to conduct the reaction of **395a** in the presence of ethylene gas in order to achieve modest conversion and good selectivity ($k_{rel} = 17$), cyclizations of **395b** and **395c** proceeded with high selectivity without ethylene. Indeed, use of ethylene as an additive in these cases significantly lowered reaction efficiencies. The efficient synthesis of the azocine **396c** is remarkable, given that previous efforts to achieve the enantioselective formation of eight-membered carbocycles and oxacycles led exclusively to homodimeric products.

The chiral catalyst **R1** may also be used to induce the efficient desymmetrization of the unsaturated prochiral amines **397a**−**c** to form the corresponding cyclic amines **398a**−**c** with excellent enantioselectivities (Scheme 111). It was noted that the reactivity and selectivity in cyclizations of other prochiral amines was highly dependent upon the extent of methyl substitution on the alkene moieties. For example, although **399** underwent efficient cyclization in the presence of **R1**, the enantioselectivity of the reaction was <10%. No reactions of substrates with 1,2-disubstituted double bonds were investigated.

Scheme 111



4. Conclusion

Little more than a decade has elapsed since Grubbs and Fu reported that Schrock's molybdenum catalyst **C** could be used to induce efficient cyclizations of functionalized α,ω-dienes to give carbocycles and oxygen and nitrogen heterocycles via RCM. As is evident from the examples cited herein as well as in other reviews,[2−4,181] there has since been a virtual explosion of research in the area. There are an increasing number of applications of RCM to the synthesis of complex and highly functionalized organic molecules of importance in natural product chemistry, chemical biology, and material science. Improved catalysts for specific applications, including enantioselective synthesis, continue to be developed, and it seems likely this area of research will remain fruitful for some time to come. Tandem reactions involving olefin metathesis are becoming more popular, as such processes enable the rapid construction of complex skeletal frameworks. It seems fair to predict that the future holds considerable promise for more advances and applications of RCM not only in heterocyclic chemistry but in other arenas as well.

5. Acknowledgment

We thank the National Institutes of Health, the Robert Welch Foundation, Pfizer, Inc., and Merck Research Laboratories for their ongoing support of our research in ring-closing metathesis. A.D. gratefully acknowledges a Feodor-Lynen postdoctoral fellowship from the Alexander von Humboldt-Foundation for financial support.

6. List of Abbreviations

Ac	acetyl
AIBN	azobisisobutyronitrile
Alloc	allyloxycarbonyl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Cbz	carbobenzoxy
CSA	camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene

DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	diisopropyldiazodicarboxylate
DIBAL-H	diisobutylaluminum hydride
Fmoc	(9-fluorenylmethoxy)carbonyl
HDA	hetero-Diels−Alder
HMDS	hexamethyldisilazane
LDA	lithium diisopropylamide
mCPBA	*m*-chloroperoxybenzoic acid
MOM	methoxymethyl
NIS	*N*-iodosuccinimide
Ns	*p*-nitrobenzenesulfonyl
PMB	*p*-methoxybenzyl
PTSA	*p*-methylbenzenesulfonic acid
RCM	ring-closing metathesis
ROM	ring-opening metathesis
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TES	triethylsilyl
TFA	trifluoroacetic acid
TMS	trimethylsilyl
Ts	methylbenzenesulfonyl

7. References

(1) (a) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426. (b) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856.

(2) Reviews on applications of RCM: (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446. Schmalz, H.-G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1833. (b) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036. (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (d) Fürstner, A. *Top. Organomet. Chem.* **1998**, *1*, 37. (e) Schrock, R. R. *Top. Organomet. Chem.* **1998**, *1*, 1. (f) Schrock, R. R. *Tetrahedron* **1999**, *55*, 8141. (g) Blechert, S. *Pure Appl. Chem.* **1999**, *71*, 1393. (h) Wright, D. L. *Curr. Org. Chem.* **1999**, *3*, 211. (i) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073. (j) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (k) Roy, R.; Das, K. *Chem. Commun.* **2000**, 519. (l) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592. (m) Walters, M. A. In *Progress in Heterocyclic Chemistry*; Joule, J. A., Gribble, G. W., Eds.; Pergamon Press: New York, 2003; Vol. 15, p 1.

(3) Reviews on enyne RCM: (a) Mori, M. *Top. Organomet. Chem.* **1998**, *1*, 133. (b) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1.

(4) Review focusing on CM: Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900.

(5) Review on Ru-catalysts development: Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.

(6) For a comparison of the catalysts **A**, **A'**, and **C**, see: Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371.

(7) Reviews on RCM of *N*-containing compounds: (a) Phillips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75. (b) Pandit, U. K.; Overkleeft, H. S.; Borer, B. C.; Bieräugel, H. *Eur. J. Org. Chem.* **1999**, *959*, 9. (c) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693.

(8) Applications of RCM in synthesis on solid support and in the formation of sulfur- and phosphorus-containing heterocycles are not included in this review.

(9) (a) Farooq, A.; Tahara, S. *Current Top. Phytochem.* **1999**, *2*, 1. (b) Lichtenthaler, F. W. *Mod. Synth. Methods* **1992**, *6*, 273. (c) Schmidt, R. R. *Acc. Chem. Res.* **1986**, *19*, 250.

(10) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875.

(11) (a) Fujimura, O.; Fu, G. C.; Grubbs, R. H. *J. Org. Chem.* **1994**, *59*, 4029. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.

(12) Sturino, C. F.; Wong, J. C. Y. *Tetrahedron Lett.* **1998**, *39*, 9623.

(13) (a) Sutton, A. E.; Seigal, B. A.; Finnegan, D. F.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 13390. (b) Schmidt, B. *Eur. J. Org. Chem.* **2003**, 816.

(14) Tandem RCM/hydrogenation reaction using a single Ru-catalyst: Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312.

(15) van Otterlo, W. A. L.; Ngidi, E. L.; Coyanis, E. M.; de Koning, C. B. *Tetrahedron Lett.* **2003**, *44*, 311.

(16) (a) Burke, S. D.; Ng, R. A.; Morrison, J. A.; Alberti, M. J. *J. Org. Chem.* **1998**, *63*, 3160. (b) Rutjes, F. P. J. T.; Kooistra, T. M.; Hiemstra, H.; Schoemaker, H. E. *Synlett* **1998**, 192.

(17) (a) Kirkland, T. A.; Colucci, J.; Geraci, L. S.; Marx, M. A.; Schneider, M.; Kaelin, Jr., D. E., Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 12432. (b) Berberich, S. M.; Cherney, R. J.; Colucci, J.; Courillon, C.; Geraci, L. S.; Kirkland, T. A.; Marx, M. A.; Schneider, M. F.; Martin, S. F. *Tetrahedron* **2003**, *59*, 6819.

(18) Liu, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 10772.

(19) (a) Corley, D. G.; Herb, R.; Moore, R. E.; Scheuer, P. J.; Paul, V. J. *J. Org. Chem.* **1988**, *53*, 3644. (b) Quinoa, E.; Kakou, Y.; Crews, P. *J. Org. Chem.* **1988**, *53*, 3642. (c) Jefford, C. W.; Bernadinelli, G.; Tanaka, J.-I.; Higa, T. *Tetrahedron Lett.* **1996**, *37*, 159.

(20) Mooberry, S. L.; Tien, G.; Hernandez, A. H.; Plubrukarn, A.; Davidson, B. S. *Cancer Res.* **1999**, *59*, 653.

(21) Account: Mulzer, J.; Öhler, E.; Enev, V. S.; Hanbauer, M. *Adv. Synth. Catal.* **2002**, *344*, 573. See also ref. 24b.

(22) (a) Mulzer, J.; Hanbauer, M. *Tetrahedron Lett.* **2000**, *41*, 33. (b) Enev, V. S.; Kaehlig, H.; Mulzer, J. *J. Am. Chem. Soc.* **2001**, *123*, 10764.

(23) Nadolski, G. T.; Davidson, B. S. *Tetrahedron Lett.* **2001**, *42*, 797.

(24) (a) Ghosh, A. K.; Wang, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11027. (b) Ghosh, A. K.; Wang, Y.; Kim, J. T. *J. Org. Chem.* **2001**, *66*, 8973.

(25) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130.

(26) (a) Messenger, B. T.; Davidson, B. S. *Tetrahedron Lett.* **2001**, *42*, 801. (b) Sivaramakrishnan, A.; Nadolski, G. T.; McAlexander, I. A.; Davidson, B. S. *Tetrahedron Lett.* **2002**, *43*, 213.

(27) Dorling, E. K.; Öhler, E.; Mulzer, J. *Tetrahedron Lett.* **2000**, *41*, 6323.

(28) Paterson, I.; De Savi, C.; Tudge, M. *Org. Lett.* **2001**, *3*, 3149.

(29) Nelson, G. S.; Cheung, W. S.; Kassick, A. J.; Hilfiker, M. A. *J. Am. Chem. Soc.* **2002**, *124*, 13654.

(30) Schweizer, E. E.; Meeder-Nycz, D. 2*H*- and 4*H*-1-Benzopyrans. In *The Chemistry of Heterocyclic Compounds; 31; Chromenes, Chromanones, and Chromones*; Ellis, G. P., Ed.; John Wiley & Sons: New York, 1977; p 11.

(31) Chang, S.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 864.

(32) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994.

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

(34) Visser, M. S.; Heron, N. M.; Didiuk, M. T.; Sagal, J. F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 4291.

(35) Kahnberg, P.; Lee, C. W.; Grubbs, R. H.; Sterner, O. *Tetrahedron* **2002**, *58*, 5203.

(36) Kishuku, H.; Shindo, M.; Shishido, K. *Chem. Commun.* **2003**, 350.

(37) (a) Jung, M. E. *Synlett* **1999**, 843. (b) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1911**, *107*, 1080.

(38) For problems associated with forming simple medium ring ethers, see ref 34.

(39) Linderman, R. J.; Siedlecki, J.; O'Neil, S. A.; Sun, H. *J. Am. Chem. Soc.* **1997**, *119*, 6919.

(40) (a) Crimmins, M. T.; Emmitte, K. A. *Org. Lett.* **1999**, *1*, 2029. (b) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653. (c) Crimmins, M. T.; Tabet, E. A. *J. Am. Chem. Soc.* **2000**, *122*, 5473.

(41) Crimmins, M. T.; Powell, M. T. *J. Am. Chem. Soc.* **2003**, *125*, 7592.

(42) (a) Crimmins, M. T.; Emmitte, K. A.; Choy, A. L. *Tetrahedron* **2002**, *58*, 1817. (b) Crimmins, M. T.; Emmitte, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 1533.

(43) (a) Satake, M.; Murata, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1993**, *115*, 361. (b) Satake, M.; Murata, M.; Yasumoto, T. *Tetrahedron Lett.* **1993**, *34*, 1975.

(44) Reviews: (a) Shimizu, Y. *Chem. Rev.* **1993**, *93*, 1685. (b) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897. (c) Koert, U. *Synthesis* **1995**, 115.

(45) (a) Kadota, I.; Ohno, A.; Matsuda, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, *123*, 6702. (b) Kadota, I.; Ohno, A.; Matsuda, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 3562. (c) Kadota, I.; Takamura, H.; Sato, K.; Ohno, A.; Matsuda, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 46.

(46) (a) Oishi, T.; Nagumo, Y.; Hirama, M. *Chem. Commun.* **1998**, 1041. (b) Maeda, K.; Oishi, T.; Oguri, H.; Hirama, M. *Chem. Commun.* **1999**, 1063. (c) Maruyama, M.; Inoue, M.; Oishi, T.; Oguri, H.; Ogasawara, Y.; Shindo, Y.; Hirama, M. *Tetrahedron* **2002**, *58*, 1835. (d) Hirama, M.; Oishi, T.; Uehara, H.; Inoue, M.; Maruyama, M.; Oguri, H.; Satake, M. *Science* **2001**, *294*, 1904.

(47) Zuercher, W. J.; Hashimoto, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 6634.

(48) Nicolaou, K. C.; Vega, J. A.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4441.

(49) (a) Nicolaou, K. C.; Postema, M. H. D.; Yue, E. W.; Nadin, A. *J. Am. Chem. Soc.* **1996**, *118*, 10335. (b) Nicolaou, K. C.; Postema, M. H. D.; Claiborne, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 1565.

(50) (a) Clark, S. J.; Hamelin, O. *Angew. Chem., Int. Ed.* **2000**, *39*, 372. (b) Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 123. (c) Clark, J. S.; Trevitt, G. P.; Boyall, D.; Stammen, B. *Chem. Commun.* **1998**, 2629. (d) Clark, J. S.; Elustondo, F.; Trevitt, G.

P.; Boyall, D.; Robertson, J.; Blake, A. J.; Wilson, C.; Stammen, B. *Tetrahedron* **2002**, *58*, 1973.
(51) (a) Baylon C.; Heck, M.-P.; Mioskowski, C. *J. Org. Chem.* **1999**, *64*, 3354. (b) Bassindale, M. J.; Hamley, P.; Leitner, A.; Harrity, J. P. A. *Tetrahedron Lett.* **1999**, *40*, 3247. (c) Lautens, M.; Hughes, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 129. (d) Schmidt, B.; Wildemann, H. *J. Org. Chem.* **2000**, *65*, 5817. (e) Wallace, D. J.; Bulger, P. G.; Kennedy, D. J.; Ashwood, M. S.; Cottrell, I. F.; Dolling, U.-H. *Synlett* **2001**, 357. *N*,*O*-Spirocycles: (e) Wallace, D. J.; Goodman, J. M.; Kennedy, D. J.; Davies, A. J.; Cowden, C. J.; Ashwood, M. S.; Cottrell, I. F.; Dolling, U.-H.; Reider, P. J. *Synlett* **2001**, 357.
(52) Heck, M.-P.; Baylon, C.; Nolan, S. P.; Mioskowski, C. *Org. Lett.* **2001**, *3*, 1989.
(53) Wallace, D. J. *Tetrahedron Lett.* **2003**, *44*, 2145.
(54) Burke, S. D.; Quinn, K. J.; Chen, V. J. *J. Org. Chem.* **1998**, *63*, 8626.
(55) Ahmed, A.; Öhler, E.; Mulzer, J. *Synthesis* **2001**, 2007.
(56) Nicolaou, K. C.; Vassilikogiannakis, G.; Montagnon, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 3276.
(57) (a) Arico, F.; Mobian, P.; Kern, J. M.; Sauvage, J. P. *Org. Lett.* **2003**, *5*, 1887. (b) Dietrich-Buchecker, C. O.; Rapenne, G.; Sauvage, J. P. *J. Am. Chem. Soc.* **1999**, *121*, 994. (c) Mohr, B.; Weck, M.; Sauvage, J. P.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1308.
(58) Morehead, A.; Grubbs, R. *Chem. Commun.* **1998**, 275.
(59) (a) Chiu, P.; Lautens, M. *Top. Curr. Chem.* **1997**, *190*, 1. (b) Bernardelli, P.; Paquette, L. A. *Heterocycles* **1998**, *49*, 531. (c) Vogel, P.; Cossy, J.; Plumet, J.; Arjona, O. *Tetrahedron* **1999**, *55*, 13521.
(60) Scholl, M.; Grubbs, R. *Tetrahedron Lett.* **1999**, *40*, 1425.
(61) (a) Burke, S. D.; Müller, N.; Beaudry, C. M. *Org. Lett.* **1999**, *1*, 1827. (b) Keller, V. A.; Martinelli, J. R.; Strieter, E. R.; Burke, S. D. *Org. Lett.* **2002**, *4*, 467. (c) Voight, E. A.; Rein, C.; Burke, S. D. *J. Org. Chem.* **2002**, *67*, 8489.
(62) Dondoni, A.; Marra, A.; Merino, P. *J. Am. Chem. Soc.* **1994**, *116*, 3324.
(63) Other examples of bridged oxabicycles by RCM: de Armas, P.; Garcia-Tellado, F.; Marrero-Tellado, J. J. *Eur. J. Org. Chem.* **2001**, 4423.
(64) Hoye, T. R.; Donaldson, S. M.; Vos, T. J. *Org. Lett.* **1999**, *1*, 277.
(65) Reviews: (a) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 94. (b) Negishi, E.; Kotora, M. *Tetrahedron* **1997**, *53*, 6707. (c) Collins, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1377.
(66) Mizutani, H.; Watanabe, M.; Honda, T. *Tetrahedron* **2002**, *58*, 8929. For the many earlier syntheses of **139**, see the references therein.
(67) (a) Crimmins, M. T.; King, B. W. *J. Am. Chem. Soc.* **1998**, *120*, 9084. (b) Reddy, M. V. R.; Rearick, J. P.; Hoch, N.; Ramachandran, P. V. *Org. Lett.* **2001**, *3*, 19. (c) Reddy, M. V. R.; Yucel, A. J.; Ramachandran, P. V. *J. Org. Chem.* **2001**, *66*, 2512. (d) Cossy, J.; Pradaux, F.; BouzBouz, S. *Org. Lett.* **2001**, *3*, 2233. (e) Trost, Barry, M.; Yeh, V. S. C. *Org. Lett.* **2002**, *4*, 3513. (f) Wang, Y.-G.; Kobayashi, Y. *Org. Lett.* **2002**, *4*, 4615. (g) Falomir, E.; Murga, J.; Carda, M.; Marco, J. A. *Tetrahedron Lett.* **2003**, *44*, 539.
(68) (a) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, Jr. P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791. (b) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.
(69) (a) Takemoto, Y.; Noguchi, I.; Iwata, C.; Tanaka, T.; Ibuka, T. *Tetrahedron Lett.* **2000**, *41*, 3653. (b) Baba, Y.; Saha, G.; Nakao, S.; Iwata, C.; Tanaka, T.; Ibuka, T.; Ohishi, H.; Takemoto, Y. *J. Org. Chem.* **2001**, *66*, 81.
(70) Fürstner, A.; Müller, T. *Synlett* **1997**, 1010.
(71) Murga, J.; Falomir, E.; Garcia-Fortanet, J.; Carda, M.; Marco, J. A. *Org. Lett.* **2002**, *4*, 3447.
(72) Lee, C. W.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 2145.
(73) Fürstner, A.; Radkowski, K.; Wirtz, C.; Goddard, R.; Lehmann, C. W.; Mynott, R. *J. Am. Chem. Soc.* **2002**, *124*, 7061.
(74) de Napoli, L.; Messere, A.; Palomba, D.; Piccialli, V.; Evidente, A.; Piccialli, G. *J. Org. Chem.* **2000**, *65*, 3432.
(75) (a) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 3942. (b) Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792. See also ref 25.
(76) Review on the synthesis of macrocycles: Roxburgh, C. J. *Tetrahedron* **1995**, *51*, 9767.
(77) (a) Becker, J.; Ohloff, G. *Helv. Chim. Acta* **1971**, *54*, 2889. (b) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1977**, *99*, 3867. (c) Mukaiyama, T.; Narasaka, K.; Kibuchi, K. *Chem. Lett.* **1977**, 441.
(78) Goldring, P. D. W.; Hodder, A. S.; Weiler, L. *Tetrahedron Lett.* **1998**, *39*, 4955.
(79) Grubbs, R. H.; Fu, G. C. *J. Am. Chem. Soc.* **1992**, *114*, 7324.
(80) Fürstner, A.; Thiel, O. R.; Lehmann, C. W. *Organometallics* **2002**, *21*, 331.
(81) (a) Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973. (b) Randl, S.; Connon, S. J.; Blechert, S. *Chem. Commun.* **2001**, 1796.
(82) Meng, D.; Su, D.; Balog, A.; Bertinato, P.; Sorensen, E. J.; Danishefsky, S. J.; Zheng, Y.; Chou, T.; He, L.; Horwitz, S. B. *J. Am. Chem. Soc.* **1997**, *119*, 2733.
(83) (a) Gerlach, K.; Quitschalle, M.; Kalesse, M. *Tetrahedron Lett.* **1999**, *40*, 3553. (b) Kalesse, M.; Quitschalle, M.; Claus, E.; Gerlach, K.; Pahl, A.; Meyer, H. H. *Eur. J. Org. Chem.* **1999**, *2817*, 7.
(84) Lee, C. W.; Grubbs, R. H. *J. Org. Chem.* **2001**, *68*, 7155.
(85) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783.
(86) Fürstner, A.; Thiel, O. R.; Ackermann, L. *Org. Lett.* **2001**, *3*, 449.
(87) Lee, C. W.; Choi, T.-L.; Grubbs, R. H. *J. Am. Chem. Soc.* **2002**, *124*, 3224.
(88) Fürstner, A.; Kindler, N. *Tetrahedron Lett.* **1996**, *37*, 7005.
(89) (a) Erickson, K. L.; Beutler J. A.; Cardellina, J. A., II; Boyd M. R. *J. Org. Chem.* **1997**, *62*, 8188. (b) Erickson, K. L.; Beutler J. A.; Cardellina, J. A., II; Boyd M. R. *J. Org. Chem.* **2001**, *66*, 1532.
(90) (a) Wu, Y.; Esser, L.; De Brabander, J. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 4308. (b) Wu, Y.; Seguil, O. R.; De Brabander, J. K. *Org. Lett.* **2000**, *2*, 4241. (c) Wu, Y.; Liao, X.; Wang, R.; Xie, X.; De Brabander, J. K. *J. Am. Chem. Soc.* **2002**, *124*, 3245.
(91) Fürstner, A.; Thiel, O. R.; Blanda, G. *Org. Lett.* **2000**, *2*, 3731.
(92) Snider, B. B.; Song, F. *Org. Lett.* **2001**, *3*, 1817.
(93) (a) Smith, A. B.; Zheng, J. *Synlett* **2001**, 1019. (b) Smith, A. B.; Zheng, J. *Tetrahedron* **2002**, *58*, 6455.
(94) Wang, X.; Porco, J. A., Jr. *J. Am.Chem. Soc.* **2003**, *125*, 6040.
(95) (a) Garbaccio, R. M.; Danishesky, S. J. *Org. Lett.* **2000**, *2*, 3127. (b) Garbaccio, R. M.; Stachel, S. J.; Baeschlin, D. K.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 10903. (c) Yamamoto, K.; Biswas, K.; Gaul, C.; Danishefsky, S. J. *Tetrahedron Lett.* **2003**, *44*, 3297.
(96) Armstrong, S. K.; Christie, B. A. *Tetrahedron Lett.* **1996**, *37*, 9373.
(97) (a) Gaul, C.; Danishefsky, S. J. *Tetrahedron Lett.* **2002**, *43*, 9039. (b) Gaul, C.; Njardason, J. T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 6042.
(98) (a) Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H. Yang, Z. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2399. (b) Yang, Z.; He, Y.; Vourloumis, D.; Vallberg, H.; Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 166. (c) Meng, D.; Bertinato, P.; Balog, A.; Su, D.; Kamenecka, T.; Sorensen, E. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10073. (d) Schinzer, D.; Limberg, A.; Bauer, A.; Böhm, O. M.; Cordes, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 523. (e) 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. (f) Nicolaou, K. C.; He, Y.; Roschangar, F.; King, N. P.; Vourloumis, D.; Li, T. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 84. (g) Schinzer, D.; Bauer, A.; Böhm, O. M.; Limberg, A.; Cordes, M. *Chem. Eur. J.* **1999**, *5*, 2483. (h) Schinzer, D.; Bauer, A.; Schieber, J.; *Chem. Eur. J.* **1999**, *5*, 2492.
(99) (a) Nicolaou, K. C., Roschangar, F.; Vourloumis, D. *Angew. Chem., Int. Ed.* **1998**, *37*, 2014. (b) Nicolaou, K. C.; Ritzén, A.; Namoto, K. *Chem. Commun.* **2001**, 1523.
(100) Nicolaou, K. C.; King, N. P.; He, Y. *Top. Organomet. Chem.* **1998**, *1*, 73.
(101) Fürstner, A.; Mathes, C.; Grela, K. *Chem. Commun.* **2001**, 1057.
(102) Biswas, K.; Lin, H.; Njardarson, J. T.; Chappell, M. D.; Chou, T. C.; Guan, Y.; Tong, W. P.; He, L.; Horwitz, S. B.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 9825.
(103) Rivkin, A.; Biswas, K.; Chou, T. C.; Danishefsky, S. J. *Org. Lett.* **2002**, *4*, 4081.
(104) Rivkin, A.; Yoshimura, F.; Gabarda, A. E.; Chou, T. C.; Dong, H.; Tong, W. P.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 2899.
(105) Dixon, D. J.; Foster, A. C.; Ley, S. V. *Org. Lett.* **2000**, *2*, 123.
(106) Ishibashi, M.; Kobayashi, J. *Heterocycles* **1997**, *44*, 543.
(107) Maleczka, R. E., Jr.; Terrell, L. R.; Geng, F.; Ward, J. S., III *Org. Lett.* **2002**, *4*, 2841.
(108) Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 1123.
(109) Lam, H. W.; Pattenden, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 508.
(110) (a) Fürstner, A.; Müller, T. *J. Am. Chem. Soc.* **1999**, *121*, 7814. (b) Fürstner, A.; Müller, T. *J. Org. Chem.* **1998**, *63*, 424.
(111) Fürstner, A.; Grela, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 1234.
(112) Fürstner, A.; Radkowski, K.; Grabowski, J.; Wirtz, C.; Mynott, R. *J. Org. Chem.* **2000**, *65*, 8758.
(113) Fürstner, A.; Mathes, C.; Lehmann, W. *J. Am. Chem. Soc.* **1999**, *121*, 9453.
(114) (a) Hoveyda, A. H. *Top. Organomet. Chem.* **1998**, *1*, 105. (b) Hoveyda, A. H.; Schrock, R. R. *Chem. Eur. J.* **2001**, *7*, 945.
(115) (a) Fujimura, O.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 2499. (b) Fujimura, O.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 824.
(116) Alexander, J. B.; La, D. S.; Cefalo, D. R.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 4041.

(117) La, D. S.; Alexander, J. B.; Cefalo, D. R.; Graf, D. D.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 9720.
(118) Zhu, S. S.; Cefalo, D. R.; La, D. S.; Jamieson, J. Y.; Davis, W. M.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1999**, *121*, 8251.
(119) Weatherhead, G. S.; Houser, J. H.; Ford, G. J.; Jamieson, J. Y.; Schrock, R. R., Hoveyda, A. H. *Tetrahedron Lett.* **2000**, *41*, 9553.
(120) (a) Weatherhead, G. S.; Ford, J. G.; Alexanian, E. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 2343. (b) Harrity, J. P. A.; La, D. S.; Cefalo, D. R.; Visser, M. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 2343. (c) Weatherhead, G. S.; Ford, J. G.; Alexanian, E. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 1828.
(121) Aeilts, S. L.; Cefalo, D. R.; Bonitatebus, P. J., Jr.; Houser, J. H.; Hoveyda, A. H.; Schrock. R. R. *Angew. Chem., Int. Ed.* **2001**, *40*, 1452.
(122) Teng, X.; Cefalo, D. R.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 10779.
(123) Tsang, W. C. P.; Hultzsch, K. C.; Alexander, J. B.; Bonitatebus, P. J., Jr.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 6337.
(124) Seiders, T. J.; Ward, D. W.; Grubbs, R. H. *Org. Lett.* **2001**, *3*, 3225.
(125) Fu, G.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324.
(126) (a) Martin, S. F.; Liao, Y.; Chen, H.-J.; Pätzel, M.; Ramser, M. *Tetrahedron Lett.* **1994**, *35*, 6005. (b) Martin, S. F.; Chen, H.-J.; Courtney, A. K.; Liao, Y.; Patzel, M.; Ramser, M. N.; Wagman, A. S. *Tetrahedron* **1996**, *52*, 7251.
(127) (a) Arisawa, M.; Takezawa, E.; Nishida, A.; Mori, M.; Nakagawa, M. *Synlett* **1997**, 1179. (b) Tarling, C. A.; Holmes, A. B.; Markwell, R. E.; Pearson, N. D. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1695. (c) Diedrichs, N.; Westermann, B. *Synlett* **1999**, 1127. (d) Lennartz, M.; Steckhan, E. *Synlett* **2000**, 319. (e) El-Nezhawy, A. O. H.; El-Diwani, H. I.; Schmidt, R. R. *Eur. J. Org. Chem.* **2002**, 4137. (f) Hanessian, S.; Sailes, H.; Munro, A.; Therrien, E. *J. Org. Chem.* **2003**, *68*, 7219. (g) Review on bi- and tricyclic-β-lactams: Alcaide, B.; Almendros, P. *Curr. Org. Chem.* **2002**, *6*, 245.
(128) Kinderman, S. S.; Maarseveen, J. H. van; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Org. Lett.* **2001**, *3*, 2045.
(129) Arisawa, M.; Terada, Y.; Nakagawa, M.; Nishida, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4732.
(130) (a) Kinoshita, A.; Sakakibara, N.; Mori, M. *J. Am. Chem. Soc.* **1997**, *119*, 12388. (b) Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082.
(131) Mori, M.; Kitamura, T.; Sakakibara, N.; Sato, Y. *Org. Lett.* **2000**, *2*, 543.
(132) Saito, N.; Sato, Y.; Mori, M. *Org. Lett.* **2002**, *4*, 803.
(133) Huang, J.; Xiong, H.; Hsung, R. P.; Rameshkumar, C.; Mulder, J. A.; Grebe, T. P. *Org. Lett.* **2002**, *4*, 2417.
(134) (a) Kitamura, T.; Mori, M. *Org. Lett.* **2001**, *3*, 1161. (b) Arjona, O.; Csáky, Medel, R.; Plumet, J. *J. Org. Chem.* **2002**, *67*, 1380.
(135) Kinoshita, A.; Mori, M. *Synlett* **1994**, 1020.
(136) Deiters, A.; Martin, S. F. *Org. Lett.* **2002**, *4*, 3243.
(137) For other examples of forming dihydropyrroles by RCM, see: (a) Huwe, C. M.; Blechert, S. *Synthesis* **1997**, 61. (b) Evans, P. A.; Robinson, J. E. *Org. Lett.* **1999**, *1*, 1929. (c) Briot, A.; Bujard, M.; Gouverneur, V.; Nolan, S. P.; Mioskowski, C. *Org. Lett.* **2000**, *2*, 1517. (d) Stürmer, R.; Schäfer, B.; Wolfart, V.; Stahr, H.; Kazmaier, U.; Helmchen, G. *Synthesis* **2001**, 46.
(138) For other examples of preparing α,β-unsaturated piperidinones by RCM, see: (a) Huwe, C. M.; Kiehl, C. O.; Blechert, S. *Synlett* **1996**, 65. (b) Rutjes, F. P. J. T., Schoemaker, H. E. *Tetrahedron Lett.* **1997**, *38*, 677. (c) Arrayás, R. G.; Alcudia, A.; Liebeskind, L. A. *Org. Lett.* **2001**, *3*, 3381 (subsequent $\beta,\gamma \rightarrow \alpha,\beta$-double bond isomerization). (d) Rodríguez, S.; Castillo, E.; Carda, M.; Marco, J. A. *Tetrahedron* **2002**, *58*, 1185.
(139) Lee, K. L.; Goh, J. B.; Martin, S. F. *Tetrahedron Lett.* **2001**, *42*, 1635.
(140) Dirat, O.; Vidal, T.; Langlois, Y. *Tetrahedron Lett.* **1999**, *40*, 4801.
(141) Wright, D. L.; Schulte, J. P. II; Page, M. A. *Org. Lett.* **2000**, *2*, 1847.
(142) Stapper, C.; Blechert, S. *J. Org. Chem.* **2002**, *67*, 6456.
(143) Johnson, C. R.; Golebiowski, A.; Steensma, D. H. *J. Am. Chem. Soc.* **1992**, *114*, 9414.
(144) Buschmann, N.; Rückert, A.; Blechert, S. *J. Org. Chem.* **2002**, *67*, 4325.
(145) Trost, B. M.; Patterson, D. E. *J. Org. Chem.* **1998**, *63*, 1339.
(146) Lindsay, K. B.; Pyne, S. G. *J. Org. Chem.* **2002**, *67*, 7774.
(147) Stragies, R.; Blechert, S. *J. Am. Chem. Soc.* **2000**, *122*, 9584.
(148) Trost, B. M.; Vranken, D. L. Van; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327.
(149) Schaudt, M.; Blechert, S. *J. Org. Chem.* **2003**, *68*, 2913.
(150) (a) Voigtmann, U.; Blechert, S. *Org. Lett.* **2000**, *2*, 3971. (b) Voigtmann, U.; Blechert, S. *Synthesis* **2000**, 893. (c) Zaminer, J.; Stapper, C.; Blechert, S. *Tetrahedron Lett.* **2002**, *43*, 6739. (d) Ovaa, H.; Stapper, C.; van der Marel, G. A.; Overkleeft, H. S.; van Boom, J. H.; Blechert, S. *Tetrahedron* **2002**, *58*, 7503.
(151) Fürstner, A.; Thiel, O. R. *J. Org. Chem.* **2000**, *65*, 1738.
(152) Wipf, P.; Rector, S. R.; Takahashi, H. *J. Am. Chem. Soc.* **2002**, *124*, 14848.
(153) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.
(154) Other examples for the application of Grubbs catalyst in the presence of basic amino groups: (a) Evans, P.; Grigg, R.; York, M. *Tetrahedron Lett.* **2000**, *41*, 3967. (b) Hunt, J. C. A.; Laurent, P.; Moody, C. J. *Chem. Commun.* **2000**, 1771. (c) Davies, S. G.; Iwamoto, K.; Smethurst, C. A. P.; Smith, A. D.; Rodriguez-Solla, H. *Synlett* **2002**, 1146. (d) Hunt, J. C. A.; Laurent, P.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2378
(155) Protonated pyridines are compatible with Grubbs' catalyst; See: (a) Felpin, F.-X.; Vo-Thanh, G.; Robins, R. J.; Villiéras, J.; Lebreton, J. *Synlett* **2000**, 1646. (b) Felpin, F.-X.; Girard, S.; Vo-Thanh, G.; Robins, R. J.; Villiéras, J.; Lebreton, J. *J. Org. Chem.* **2001**, *66*, 6305.
(156) Kinoshita, A.; Mori, M. *J. Org. Chem.* **1996**, *61*, 8356.
(157) Other examples of the formation of eight-membered lactams by RCM: Vo-Thanh, G.; Boucard, V.; Sauriat-Dorizon, H.; Guibé, F. *Synlett* **2001**, 37. See also ref. 126 and 164.
(158) Martin, S. F.; Wagman, A. S. *Tetrahedron Lett.* **1995**, *36*, 1169.
(159) Grubbs, R. H.; Miller, S. J.; Kim, S. H.; Chen, Z. R. *J. Am. Chem. Soc.* **1995**, *117*, 2108.
(160) Fellows, I.; Kaelin, D. E.; Martin, S. F. *J. Am. Chem. Soc.* **2000**, *122*, 10781.
(161) Fukuyama, T.; Xu, L.; Goto, S. *J. Am. Chem. Soc.* **1992**, *114*, 383.
(162) (a) White, J. D.; Hrnciar, P.; Yokochi, A. F. T. *J. Am. Chem. Soc.* **1998**, *120*, 7359. (b) White, J. D.; Hrnciar, P. *J. Org. Chem.* **2000**, *65*, 9129.
(163) Minami, N.; Ko, S. S.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 1109.
(164) (a) Martin, S. F.; Humphrey, J. H.; Ali, A.; Hillier, M. C. *J. Am. Chem. Soc.* **1999**, *121*, 866. (b) Humphrey, J. H.; Liao, Y.; Ali, A.; Rein, T.; Wong, Y.-L.; Chen, H.-J.; Courtney, A. K.; Martin, S. F. *J. Am. Chem. Soc.* **2002**, *124*, 8584.
(165) For a closely related RCM cyclization, see: Pandit, U.; Borer, B.; Bieraugel, H. S. *Pure Appl. Chem.* **1996**, *68*, 659.
(166) Nagata, T.; Nakagawa, M.; Nishida, A. *J. Am. Chem. Soc.* **2003**, *125*, 7484.
(167) Irie, O.; Samizu, K.; Henry, J. R.; Weinreb, S. M. *J. Org. Chem.* **1999**, *64*, 587.
(168) Sung, M. J.; Lee, H. I.; Lee, H. B.; Cha, J. K. *J. Org. Chem.* **2003**, *68*, 2205.
(169) 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.
(170) Goldring, W. P. D.; Weiler, L. *Org. Lett.* **1999**, *1*, 1471.
(171) Fürstner, A.; Rumbo, A. *J. Org. Chem.* **2000**, *65*, 2608.
(172) For more examples of the synthesis of macrocyclic lactams using alkyne RCM, see: Fürstner, A.; Guth, O.; Rumbo, A.; Seidel, G. *J. Am. Chem. Soc.* **1999**, *121*, 11108.
(173) (a) Cabrejas, L. M. M.; Rohrbach, S.; Wagner, D.; Kallen, J.; Zenke, G.; Wagner, J. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2443. (b) Lee, D.; Sello, J. K.; Schreiber, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10648. (c) Bach, T.; Lemarchand, A. *Synlett* **2002**, 1302. (d) Nantermet, P. G.; Selnick, H. G. *Tetrahedron Lett.* **2003**, *44*, 2401.
(174) (a) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606. (b) Blackwell, H. E.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **1998**, *37*, 3281. (c) Prabhakaran, E. N.; Rao, I. N.; Boruah, A.; Iqbal, J. *J. Org. Chem.* **2002**, *67*, 8247. (d) Bijani, C.; Varray, S.; Lazaro, R.; Martinez, J.; Lamaty, F.; Kieffer, N. *Tetrahedron Lett.* **2002**, *43*, 3765.
(175) Neipp, C. E.; Martin, S. F. *Tetrahedron Lett.* **2002**, *43*, 1779; Neipp, C. E.; Martin, S. F. *J. Org. Chem.* **2003**, *68*, 8867.
(176) Application of RCM in other bridged azabicyclic ring systems: Baker, S. R.; Cases, M.; Keenan, M.; Lewis, R. A.; Tan, P. *Tetrahedron Lett.* **2003**, *44*, 2995.
(177) Itoh, T.; Yamazaki, N.; Kibayashi, C. *Org. Lett.* **2002**, *4*, 2469.
(178) Washburn, D. G.; Heidebrecht, R. W. Jr., Martin, S. F. *Org. Lett.* **2003**, *5*, 3523.
(179) Klaver, W. J.; Hiemstra, H.; Speckamp, W. N. *J. Am. Chem. Soc.* **1989**, *111*, 2588.
(180) Dolman, S. J.; Sattely, E. S.; Hoveyda, A. H., Schrock, R. R. *J. Am. Chem. Soc.* **2002**, *124*, 6991.
(181) See also: Grubbs, R. H., Ed. *Handbook of Metathesis*, WILEY−VCH Verlag GmbH & Co. KgaA: Weinheim, 2003; Vols. 1−3.

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