Synthethic Methods

Metathesis Reactions in Total Synthesis

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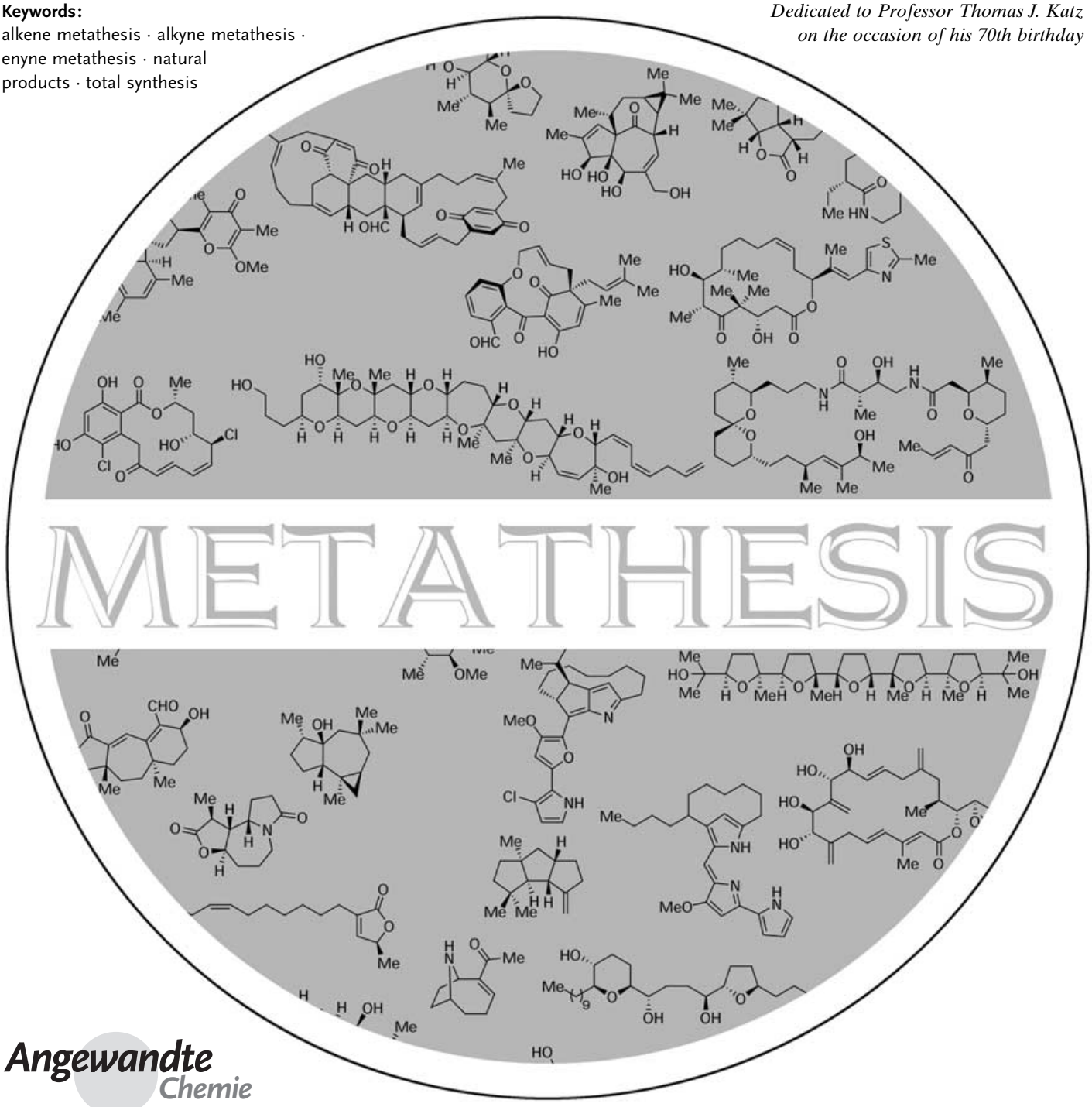
alkene metathesis · alkyne metathesis · enyne metathesis · natural products · total synthesis

Dedicated to Professor Thomas J. Katz on the occasion of his 70th birthday



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With the exception of palladium-catalyzed cross-couplings, no other group of reactions has had such a profound impact on the formation of carbon–carbon bonds and the art of total synthesis in the last quarter of a century than the metathesis reactions of olefins, enynes, and alkynes. Herein, we highlight a number of selected examples of total syntheses in which such processes played a crucial role and which imparted to these endeavors certain elements of novelty, elegance, and efficiency. Judging from their short but impressive history, the influence of these reactions in chemical synthesis is destined to increase.

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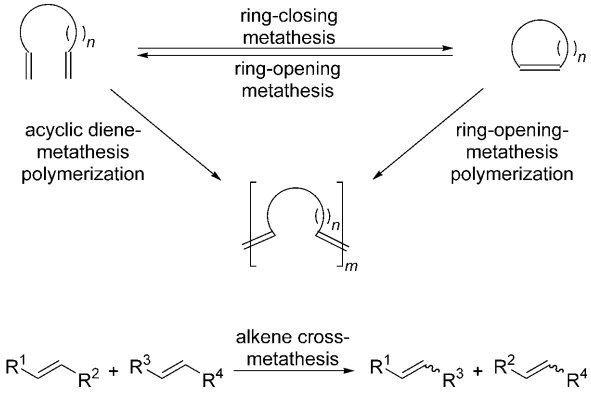
1. Introduction

Ever since the birth of the art of organic synthesis, as marked by Wöhler's synthesis of urea in 1828, progress in this field has, to a large degree, been dependent on our ability to construct carbon frameworks through carbon–carbon bond-forming reactions. The Grignard,[1] Diels–Alder,[2] and Wittig reactions[3] are three of the most prominent such processes that played decisive roles in shaping the science of chemical synthesis as we know it today. During the last quarter of the previous century, two more such reactions emerged as rivals to the aforementioned carbon–carbon bond-forming processes: the palladium-catalyzed cross-coupling reactions and those collectively known as metathesis reactions. As a most stringent test, total synthesis often serves as a measure of the power of a given reaction. Surveys of relevant applications of enabling reactions are, therefore, of importance in that they not only help to underscore the scope and generality of such processes in chemical synthesis, but they also serve to place into perspective that particular reaction within the field, and to inspire future improvements and new applications. In the preceding Review in this issue ("Palladium-Catalyzed Cross-Coupling Reactions in Total Synthesis"),[4] such a critical analysis was provided. The purpose of this Review is to do the same for the alkene, enyne, and alkyne metathesis reactions.[5]

Alkene metathesis, in all its various guises (Scheme 1), has arguably influenced and shaped the landscape of synthetic organic chemistry more than any other single process over the last 15 years.[6] The wealth of synthetic transformations that can be accomplished when this reaction is applied to appropriate substrates is astonishing, since the same catalyst (initiator) systems can promote several different types of reactions, depending on the substrates and reaction conditions employed. The history of alkene metathesis is a fascinating one, beginning with its serendipitous discovery nearly 50 years ago through to the design and application of the latest initiators available today.[7] The elucidation of the mechanistic pathway was, itself, the culmination of nearly two decades of extensive, if not collaborative or competitive, research by numerous groups, and the subject of lively debate in the literature during that period. The generally accepted mechanism of alkene metathesis was originally proposed by



Scheme 1. The most commonly employed alkene-metathesis reactions in organic synthesis.

Hérisson and Chauvin in 1971,[8] with key experimental evidence for its validity subsequently being provided by the Casey,[9] Katz,[10] and Grubbs groups,[11] and invokes metal carbene intermediates as key propagating species in the catalytic cycle. From a practical viewpoint, a key milestone in the evolution of alkene metathesis was the demonstration by Katz and co-workers in 1976 that single-component, well-defined tungsten carbenes, for example $Ph_2C{=}W(CO)_5$, could initiate alkene metathesis without added coactivators.[12,13] This discovery ushered in the modern era of rational catalyst design, and after further development, the alkene-metathesis reaction has developed into one of the most powerful carbon–carbon bond-forming reactions currently available to the synthetic chemist.

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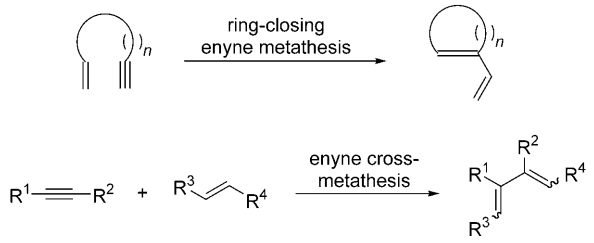
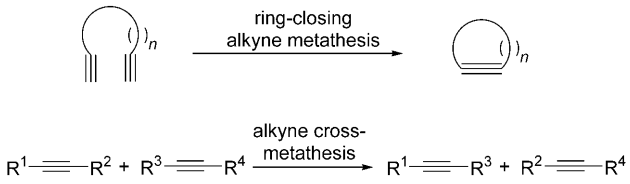
Although alkene metathesis constitutes, by far, the most widely utilized type of metathesis reaction, recent years have witnessed the discovery and development of a number of related processes employing a broader range of substrates. Prominent amongst these is the enyne-metathesis reaction, which involves the union of an alkene with an alkyne to form a 1,3-diene system (Scheme 2).[14] Unlike the corresponding



Scheme 2. Enyne-metathesis reactions in organic synthesis.

alkene-metathesis reactions, enyne metatheses are wholly atom economical (that is, no olefin-containing by-product is released during the process)[15] and are therefore driven by enthalpic rather than entropic factors, principally the stability of the conjugated diene system thus produced. Another distinction is that enyne metathesis can occur by any one of several independent mechanistic pathways, with the course of the reaction being dictated by whether metal carbene species or low-valent transition-metal complexes mediate the process, although the net outcome is (usually) the same. The enyne-metathesis reaction was discovered by Katz and his group, who reported the first examples of this process in 1985 in the presence of catalytic amounts of tungsten Fischer carbene complexes.[16] At the same time, these workers proposed the currently accepted mechanism for this type of process, invoking a sequence of [2+2] cycloaddition and cycloreversion steps involving metal carbene species, which closely parallels the mechanism of alkene metathesis. Subsequently, the Trost group documented the cycloisomerization of 1,*n*-enyne systems in the presence of palladium(II) complexes to generate 1,3-diene systems, which formally arise as the result of enyne ring-closing metathesis, yet proceed through non-carbenoid mechanistic pathways.[17] This type of transformation forms an important subset of a larger class of transition-metal-mediated reactions.[18–20] This transformation can also be effected by complexes of a number of other late transition metals, including ruthenium,[21] iridium,[22] and platinum.[23] Nevertheless, in terms of both scope and frequency of use, the metal carbene mediated reactions are the most widely employed among the enyne-metathesis processes.

Most recently, it has proven to be the turn of alkyne metathesis to emerge from the shadow of alkene metathesis and become a valuable addition to the armory of the synthetic chemist in its own right.[24] Unlike enyne metathesis, alkyne metathesis is a direct analogue of the alkene-metathesis reaction and involves the mutual exchange of alkylidyne units between two acetylene moieties (Scheme 3). Alkyne meta-



Scheme 3. Alkyne-metathesis reactions in organic synthesis.

thesis can be applied in both inter- and intramolecular contexts, although the application and development of these processes in the field of total synthesis is still very much in its infancy. The first examples of homogeneously catalyzed alkyne-metathesis reactions were reported by Mortreux and Blanchard in 1974,[25,26] with a mechanistic rationale (involving a Chauvin-type series of metal carbyne and metallacyclobutadiene intermediates as the propagating species) being put forward by Katz and McGinnis less than a year later.[10] As was the case with alkene metathesis, however, the acknowledgment that alkyne metathesis could serve as a synthetically useful tool in the construction of complex molecules would be postponed until the development of newer generations of more practical catalyst systems that could operate efficiently under mild conditions and in the presence of sensitive functionality. Breakthroughs in alkyne-metathesis chemistry within the last decade, largely spearheaded by the pioneering work of the Bunz and Fürstner groups, include the development of practical, selective ring-closing and intermolecular (cross) alkyne-metathesis versions. These processes are often complementary to the corresponding alkene-metathesis reactions and have propelled this field to the forefront of the emerging metathesis technology.

The impact of K. C. Nicolaou's career on chemistry, biology, and medicine flows from his contributions to chemical synthesis, which have been described in numerous publications and patents. His dedication to chemical education is reflected in his training of hundreds of graduate students and postdoctoral fellows. His Classics in Total Synthesis series, which he has co-authored with his students Erik J. Sorensen and Scott A. Snyder, are used around the world as a teaching tool and source of inspiration for students and practitioners of the art of chemical synthesis.

Paul G. Bulger was born in London (UK) in 1978. He received his M.Chem in 2000 from the University of Oxford, where he completed his Part II project under Dr. Mark G. Moloney. He obtained his D.Phil in chemistry in 2003 for research conducted under Professor Sir Jack E. Baldwin. In the fall of 2003, he joined Professor K. C. Nicolaou's group as a postdoctoral researcher. His research interests encompass reaction mechanism and design and their application to complex natural product synthesis and chemical biology.

In this Review, we highlight a number of total syntheses that feature one or more of these transition-metal-catalyzed carbon–carbon bond-forming reactions, and we hope to underscore their power in chemical synthesis.[27]

2. The Alkene-Metathesis Reaction

The alkene-metathesis reaction is the most commonly employed of the metathesis-based carbon–carbon bond-forming reactions. In the context of total synthesis, it has been primarily the alkene ring-closing metathesis reaction and, more recently, the alkene cross-metathesis reaction that have found the most widespread and gainful use. The success of the alkene-metathesis reaction and the many stunning and ingenious situations in which it has been applied are largely due to the advent of today's readily available catalyst systems that display high activity and excellent functional-group tolerance. The three such catalysts most routinely used by organic chemists (all of which are commercially available) are shown in Figure 1. The molybdenum-based catalyst **1** was

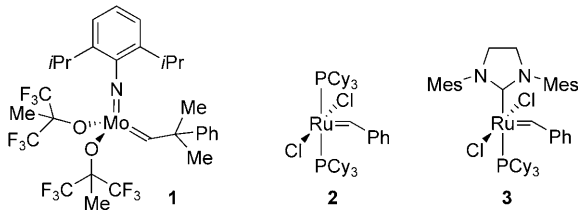


Figure 1. Commonly used alkene metathesis initiators (catalysts).

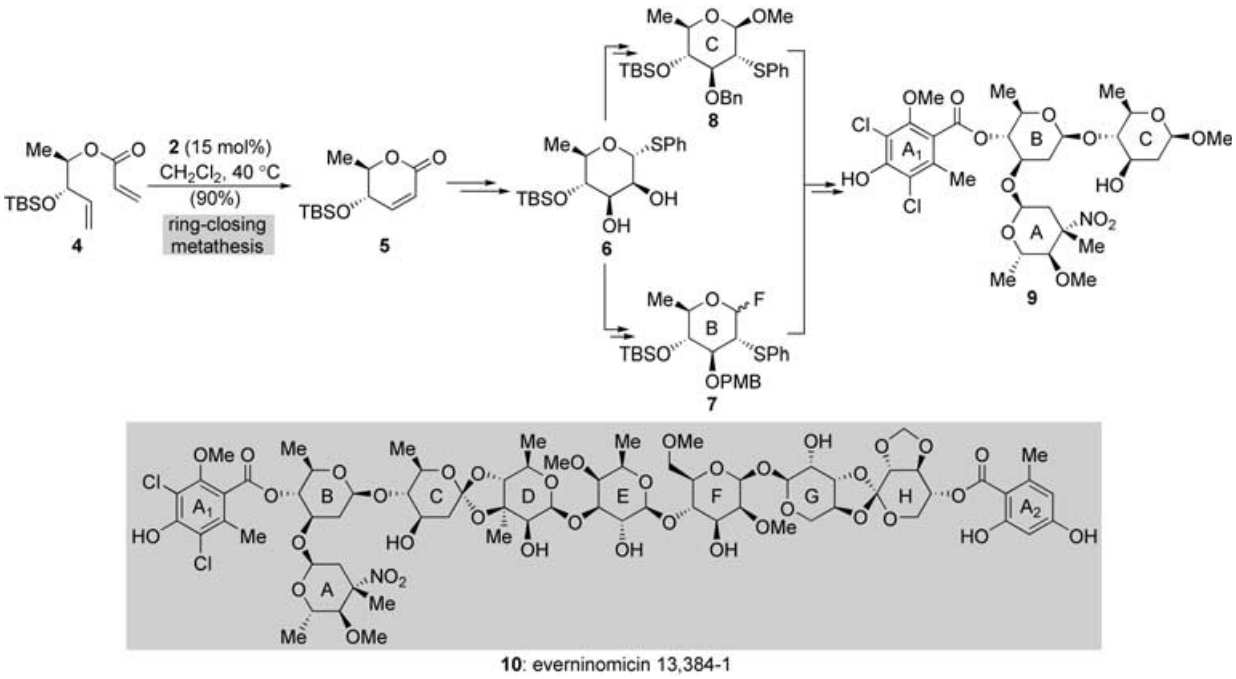
introduced by the Schrock group in 1990,[28] and represented the first real groundbreaking advance in catalyst design since the tungsten carbenes initially used by Katz and co-workers.[12] Catalyst **1** displays superb metathesis activity with a wide variety of alkene substrates, and is particularly useful for the formation of sterically crowded systems.[29] The singular drawback of catalyst **1** is its pronounced sensitivity to oxygen, moisture, and certain polar or protic functional groups owing to the electrophilicity of the high-oxidation-state transition-metal center.[30] Grubbs and co-workers subsequently introduced ruthenium-based carbene complexes,[31] initially optimized to **2**,[32] as general and practical metathesis catalysts.

David Sarlah was born in Celje, Slovenia in 1983. He is currently student in the Faculty of Chemistry and Chemical Technology, University of Ljubljana (Slovenia). Since 2001, he has been a research assistant at the Laboratory of Organic and Medicinal Chemistry at the National Institute of Chemistry (Slovenia) where he carried out research on asymmetric catalysis under the direction of Dr. B. Mohar. During the summer of 2004, he was engaged in total synthesis endeavors as a member of the azaspiracid team under Professor K. C. Nicolaou.

Although less active than the Schrock molybdenum-based systems **1**, the "first-generation" Grubbs initiator **2** exhibits much greater functional-group tolerance and has opened up new vistas in synthetic applications, most notably in the total synthesis of complex products, both natural and designed. Recent developments in catalyst (re)design have focused largely on the specific tailoring of catalyst reactivity through modifications of the ancillary ligands bound to the ruthenium center. In particular, the replacement of one of the phosphine ligands in **2** with an N-heterocyclic carbene ligand,[33] as reported independently by several groups,[34,35] increases the catalytic activity, thermal stability, and functional-group tolerance of the complex. The "second-generation" catalyst **3** engenders metathesis reactions with particularly high levels of activity, in certain cases approaching that of the Schrock system **1**, and with a unique reactivity profile that nicely complements both earlier catalysts **1** and **2**.[36] Despite these advances, the search for increasingly efficient and selective metathesis catalysts continues unabated.[37] It should be mentioned that the complexes used in metathesis reactions are more accurately described as "initiators" rather than "catalysts", since they are generally not recovered unchanged at the end of the process. Nevertheless, the use of the term "catalyst" is so entrenched in the metathesis literature that, in this Review, we use both descriptors interchangeably, being mindful of the somewhat lax use of terminology that results.

2.1. Alkene Ring-Closing Metathesis

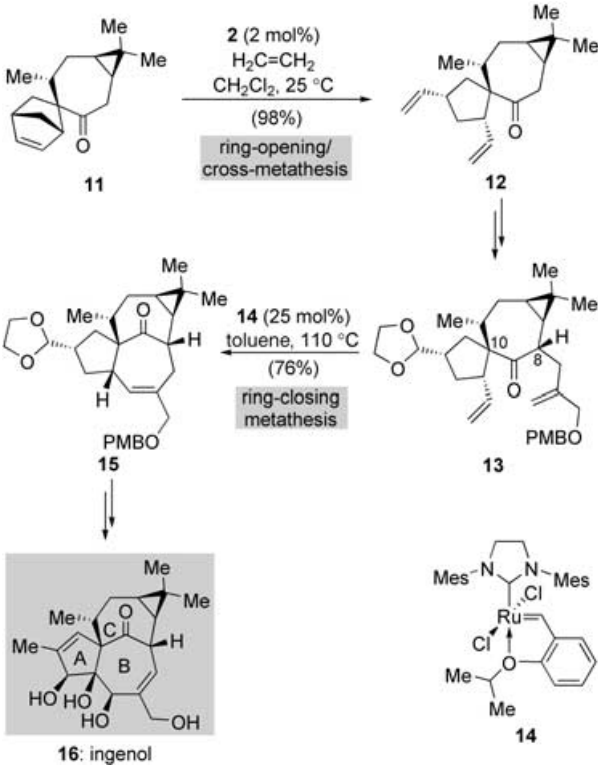
Alkene ring-closing metathesis has developed into one of the most powerful and reliable methods for ring formation. A seemingly limitless array of ring systems, be they common, medium or large, carbocyclic or heterocyclic,[38] can be fashioned by this tool, with the limits of its feasibility continually being probed and expanded. Alkene ring-closing metathesis reactions are now so routinely embedded within multistep target-oriented synthesis that the complexity of the target molecule can obscure possible connections to the metathesis event. A case in point is the early studies toward the synthesis of the ornate oligosaccharide antibiotic everninomicin 13,384-1 (**10**, Scheme 4) reported by the Nicolaou group.[39] In an effort to increase the degree of synthetic convergence, a strategy was sought that would enable the preparation of both the B- and C-ring carbohydrate building blocks from a common intermediate. Whilst the array of functionality present in these units in their final format (i.e. **10**) does not reveal any obvious metathesis disconnection, retrosynthetic analysis suggested that both **7** (B-ring) and **8** (C-ring) could likely be constructed from **6**, which in turn could be derived from α,β-unsaturated intermediate **5**. With simplification to this initial goal structure, the connection of these ring systems to metathesis becomes readily apparent. Indeed, the use of this metathesis-based strategy ultimately proved fruitful, as the complete tetracyclic $A_1B(A)C$-ring assembly (i.e. compound **9**) of the target compound **10** was synthesized following the alkene ring-closing metathesis of α,ω-diene **4** in the presence of the first-generation Grubbs ruthenium catalyst **2** (15 mol%, CH_2Cl_2, reflux, 90%



Scheme 4. Ring-closing metathesis in the fashioning of the B- and C-ring carbohydrates of everninomicin $A_1B(A)C$-ring model system (**9**) (Nicolaou and co-workers, 1998).[39]

yield).[40] Although this ring-closing reaction would appear far from groundbreaking today, the use of metathesis in this situation engendered a particularly concise feature to this complex natural product that would have otherwise been challenging to achieve with equal efficiency.[41]

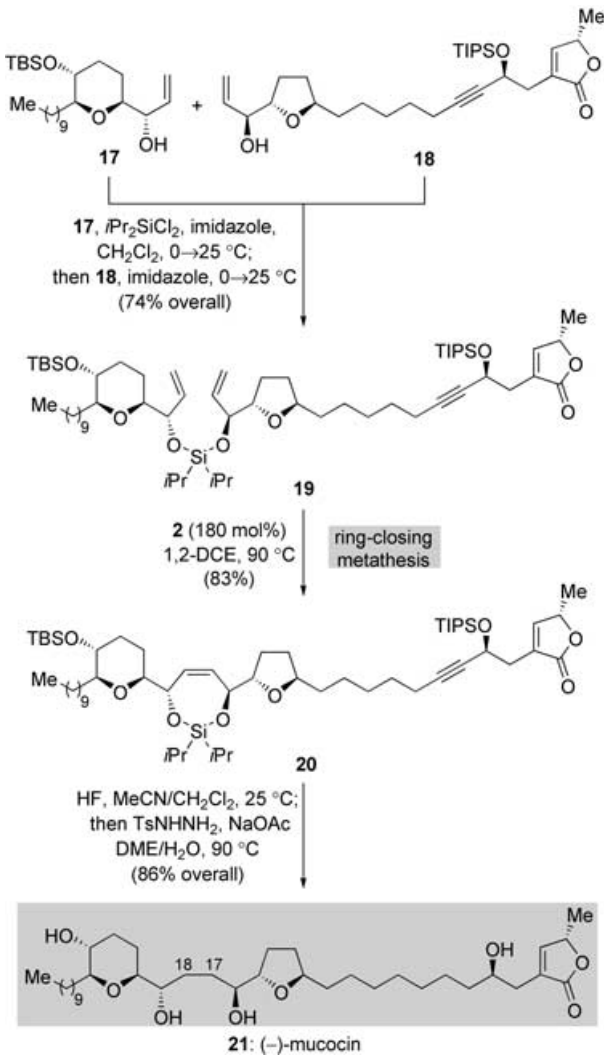
Brilliant use of olefin metathesis reactions in a complex setting was made by Wood and co-workers in their recent total synthesis of ingenol (**16**, Scheme 5).[42] The parent member of a large class of ingenane diterpenes, ingenol (**16**) has captivated the attention of synthetic chemists for more than 20 years.[43] The irresistible lure of this natural product is due partly to its promising biological activity,[44] but also to its rather remarkable polycyclic, highly oxygenated molecular architecture, the most distinctive feature of which is the strained "inside–outside" (*trans*) intrabridgehead stereochemistry of the bicyclic BC-ring system.[45] Indeed, the stereoselective synthesis of this motif has inspired several ingenious approaches, whilst at the same time proving to be the undoing of many more.[46,47] The Wood team proposed that it would be prudent to establish the stereochemical relationship between C8 and C10 before the formation of the BC-ring system, and that the latter task could be accomplished through a ring-closing-metathesis reaction (i.e. **13**→**15**). In an insightful piece of retrosynthetic analysis, they further proposed that **13** could, in turn, arise from diene **12**, the product of a ring-opening cross-metathesis reaction of the norbornene derivative **11**. Indeed, they found that the readily available, enantiomerically pure precursor **11** underwent smooth ring opening upon exposure to initiator **2** (2 mol%) under an ethylene atmosphere (1 atm) in CH_2Cl_2 at ambient temperature to afford diene **12** in nearly quantitative yield. Note that the alternative metathesis pathway available to precursor **11**, namely ring-opening-metathesis polymerization, was efficiently suppressed due to both the relatively high dilution conditions (initially 0.007 M in **11**) and the vast excess of (gaseous) ethylene employed.[48] Following the



Scheme 5. Ring-opening/cross-metathesis and ring-closing-metathesis reactions in the total synthesis of ingenol (**16**) (Wood and co-workers, 2004).[42]

uneventful advancement of diene **12** to give intermediate **13**, the stage was set for the pivotal ring-closing-metathesis reaction. While the team could take heart from previous model studies which had demonstrated the viability of related reactions,[49,50] its successful execution in the present case, and in such an elaborate setting, was by no means a foregone conclusion. To their delight, they found that the desired ring closure could, indeed, be effected in good yield (76%), provided that the novel "phosphine-free" catalyst **14** was employed. Introduced concomitantly and independently by the Hoveyda[51] and Blechert groups[52] in 2000, the cleverly designed complex **14** has proven itself to be a valuable alternative to the second-generation Grubbs catalyst **3** in ring-closing-metathesis processes, particularly in the formation of trisubstituted alkene systems. The incorporation of the cyclopentane A-ring into the cyclization precursor **13** was found to be essential for the formation of the strained BC-ring system by ring-closing metathesis to occur; it is presumed that the presence of this ring biases the conformation of the precursor such that the olefinic termini are in closer proximity and, thus, more amenable to undergo ring closure.[49] Whilst the "southern" portion of cyclized compound **15** looks relatively barren when compared with the targeted structure **16**, the trisubstituted allylic alcohol functionality concomitantly introduced into compound **15** during the metathesis event provided a sufficient handle for its ultimately victorious elaboration, over a number of steps, to the coveted final product **16**.[53]

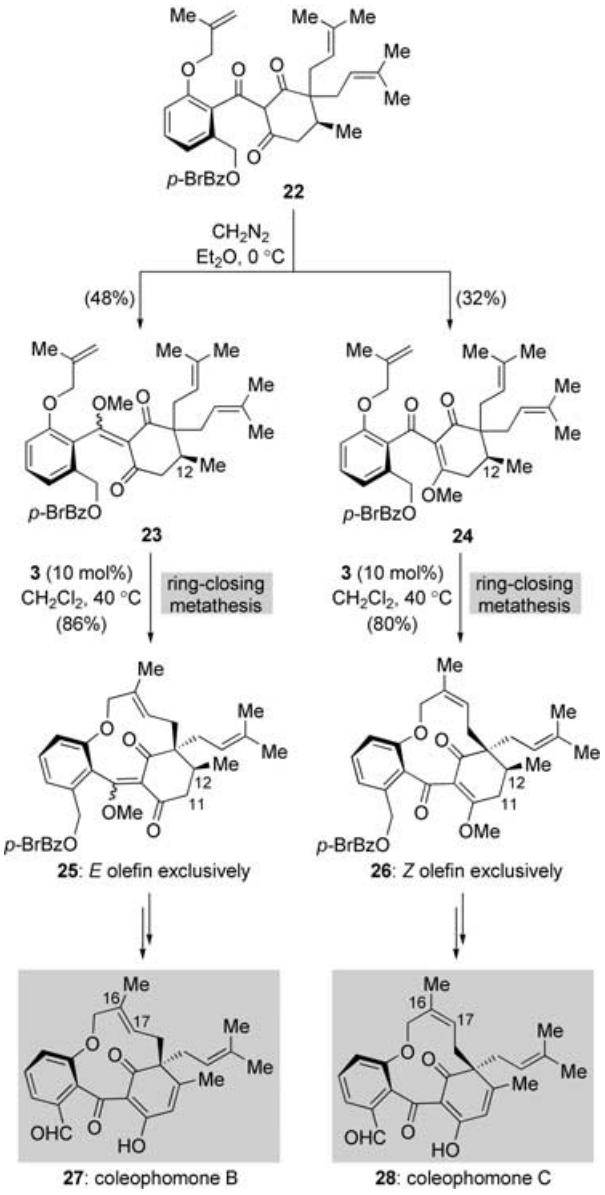
An interesting development in the alkene-metathesis field has been the employment of temporary silicon-based tethers in ring-closing-metathesis reactions, the utility of which has been elegantly exemplified in the total synthesis of the antitumor agent (−)-mucocin (**21**, Scheme 6) by Evans and co-workers.[54] Although the target compound **21** contains three rings that would appear to be prime candidates for construction through ring-closing metathesis, it was, in fact, only the C17–C18 carbon–carbon bond that was forged by this methodology. While this linkage could conceivably be formed through a selective cross-metathesis reaction (see below) between precursors **17** and **18**, it may not, at first glance, be readily apparent how it could be derived from a ring-closing-metathesis event. A clue lies in the two secondary hydroxy groups flanking the two sides of the C17–C18 bond in the target compound. Thus, if precursors **17** and **18** were to be linked together through these hydroxy groups, formation of the C17–C18 bond would then entail an intramolecular as opposed to an intermolecular process. This could endow the reaction with not only entropic advantages, but also higher levels of chemo-, regio-, and stereoselectivity. Temporary silicon tethers have proven to be versatile disposable linkers in a myriad of applications,[55] and the present case represents an instructive addition to this repertoire.[56,57] Thus, as shown in Scheme 6, the mixed bis(alkoxy)silane was readily formed by treatment of allylic alcohol **17** with excess diisopropyldichlorosilane to afford the corresponding monoalkoxychlorosilane, followed by the removal of the excess silylating agent and addition of the second allylic alcohol **18**. The cyclization of the silicon-tethered diene **19**, which can also be viewed as a fragment-coupling reaction, then proceeded as planned upon exposure to ruthenium carbene **2** in refluxing 1,2-dichloroethane. Referring to complex **2** as a "catalyst" would in this case be something of a misnomer, since an excess (180 mol% with respect to **19**, added slowly as a solution in 1,2-dichloroethane over 34 h) was required to drive the reaction to completion. This requirement did not come as a complete surprise to the team, as they had previously shown that the construction of *trans*-1,4-silaketals through ring-closing metathesis was often quite a challenging event.[58] Nevertheless, the cyclized (or coupled) product **20** was obtained in good yield (83%) without any competing and undesired participation of either the alkyne or the butenolide groups. Having fulfilled their various purposes in an exemplary manner, the three silicon groups in compound **20** were then cleaved upon exposure to hydrofluoric acid, with a subsequent chemoselective reduction of both the alkyne and the C17–C18 alkene groups with diimide then unveiling the final product **21**.[59,60]



Scheme 6. Use of a temporary silicon tether to facilitate a ring-closing-metathesis reaction in the enantioselective total synthesis of (−)-mucocin (**21**) (Evans and co-workers, 2003).[54]

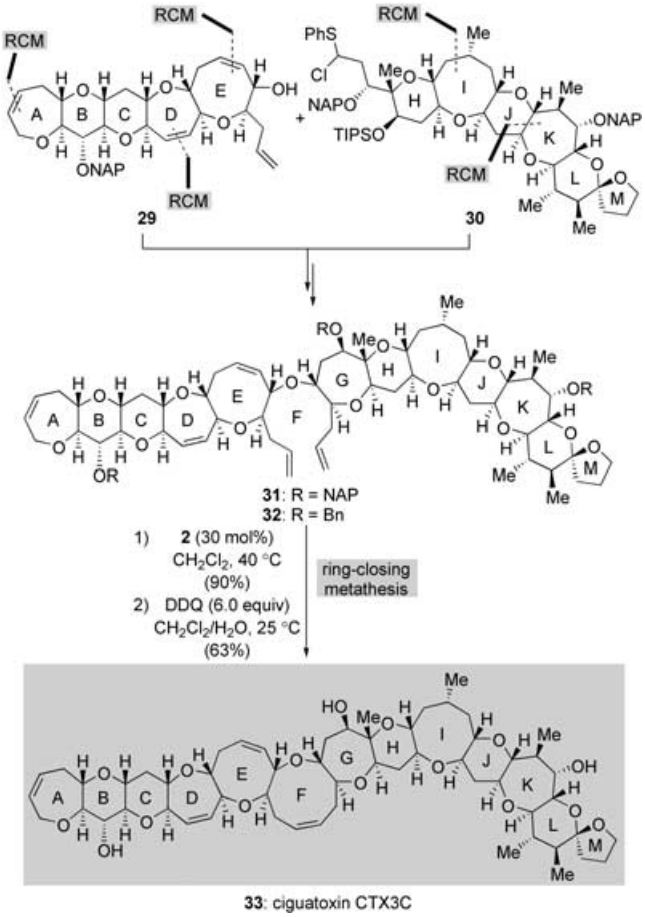
There also has been a burgeoning interest in recent years in the formation of medium-sized rings through ring-closing metathesis.[61] An unfortunate complicating factor in this

application is that, in addition to the difficulties inherent in the construction of medium-sized rings by any cyclization method, the ring strain present in medium-sized cycloalkenes renders them rather prone to the reverse metathesis processes, namely ring-opening metathesis or ring-opening-metathesis polymerization. A commonly employed tactic to circumvent this problem is the incorporation of some form of conformational constraint (be it cyclic or acyclic) into the cyclization precursor, in order to force (or at least encourage) it to adopt a conformation suitable for ring closure, as was applied in the synthesis of ingenol described above. Another such application is in the total synthesis of coleophomones B (**27**) and C (**28**, Scheme 7) by the Nicolaou group.[62] These two compounds differ only in the geometry of the C16–C17 alkene located within the *ansa* bridge, and while a metathesis-based strategy to fashion this motif would seem particularly appealing, its viability in practice would rest on the answers to two key questions: 1) Would the formation of a trisubstituted alkene system in such a rigid, strained setting by ring-closing metathesis, in fact, be feasible? 2) If so, what would be the stereoselectivity of the process? The latter factor, which could hardly be anticipated a priori, clearly stood as a critical element in reaching both **27** and **28**. As events transpired, it was found that both isomers **27** and **28** could be obtained in their pure geometrical forms in separate metathesis reactions simply through the subtle modification of a common advanced intermediate. The final strategy towards these natural products is illustrated in Scheme 7. Thus, having reached the advanced staging area represented by intermediate **22** (itself a poor metathesis substrate), the rather labile tricarbonyl moiety was "protected" by treatment with CH_2N_2. This step was nonselective and led to the formation of both **23** and **24**, which differ only in the site at which methylation occurred; however, this result proved critical to the success of the overall approach. Separate exposure of **23** and **24** to catalyst **3** (10 mol%) in CH_2Cl_2 at reflux effected the desired metathesis to form the corresponding 11-membered cycloalkene ring systems in good yield, but as singular (and different) geometrical isomers. Remarkably, whereas the cyclization of **23** furnished the *E*-alkene-containing product **25** as the sole isomer, ring-closure of **24** afforded the corresponding *Z*-geometric isomer **26** exclusively. Furthermore, these metathesis reactions were also superbly diastereoselective, in that only the prenyl group *cis* to the vicinal C12 methyl group participated in each ring-closure. In hindsight, this outcome is plausible in light of the fact that such a reactive conformation would place the remaining prenyl group *trans* to the C12 methyl group, an arrangement that would correspond to a more favorable equatorial conformation for both groups on the cyclohexane ring. A few cursory modifications involving the introduction of the final C11–C12 alkene and global deprotection then provided the natural products **27** and **28** from these advanced intermediates **25** and **26**, respectively.[63]



Scheme 7. Stereoselective ring-closing-metathesis reactions in the total synthesis of coleophomones B (**27**) and C (**28**) (Nicolaou and co-workers, 2002).[62]

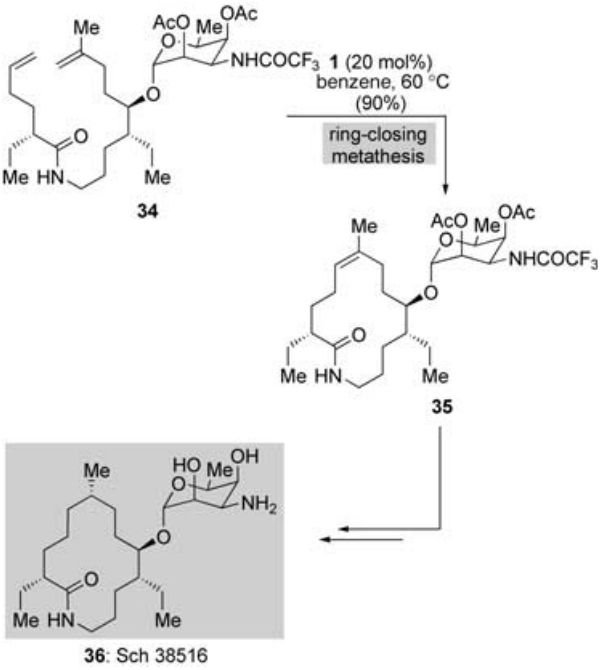
No fewer than six alkene ring-closing-metathesis reactions were used by Hirama and co-workers in their epic total synthesis of ciguatoxin CTX3C (**33**, Scheme 8).[64] Their convergent approach to the daunting polycyclic framework of this remarkable marine metabolite called for the synthesis of two separate fragments **29** and **30**, which correspond to the ABCDE- and HIJKLM-ring domains, respectively, followed by their late-stage union and subsequent formation of the final two ether rings. In the event, alkene ring-closing metathesis was employed in a diverse variety of settings, not only to construct rings A, D, and E in fragment **29**, but also, and perhaps rather less obviously, to forge rings I and J in the complementary hexacyclic fragment **30**. The successful union of the two domains **29** and **30** was then followed by a short sequence of steps to arrive at the advanced intermediate **31**. At this juncture the team was tantalizingly close to the target molecule and needed only to form the final (and thirteenth!) ether ring and then to liberate the three protected secondary hydroxy groups. That the formation of this nine-membered ring was left until the very end of the synthesis bears



Scheme 8. Multiple use of ring-closing-metathesis (RCM) reactions in the total synthesis of ciguatoxin CTX3C (**33**) (Hirama and co-workers, 2002).[64]

testament to the confidence placed by the team in the reliability of the ring-closing-metathesis reaction, trust which had no doubt been garnered in part by its successful implementation at many earlier points in the route. Indeed, it was found that the treatment of diene **31** with initiator **2** (30 mol %) in CH_2Cl_2 at reflux effected the desired cyclization in an astonishing yield of 90 %. Ironically, whereas the potentially troublesome formation of the nine-membered ring proceeded perfectly, it was, in fact, the final deprotection step that caused the team the most consternation. Originally, they had labored heroically to produce the corresponding tris(benzyl ether) **32**, which also underwent efficient ring-closing metathesis to form the corresponding nine-membered ring, only to witness the destruction of most of this precious material during its deprotection to afford the target product **33**, as this step could be achieved in a maximum yield of only 7 %. Thus, in their "second-generation" synthesis, the corresponding 2-naphthylmethyl ether protecting groups were employed, with it being anticipated (and, much to their relief, experimentally demonstrated) that the final deprotection event would proceed much more efficiently.[64b] Indeed, by changing the nature of the protecting groups, the efficiency of this final step was increased by nearly an order of magnitude, occurring in 63 % yield.

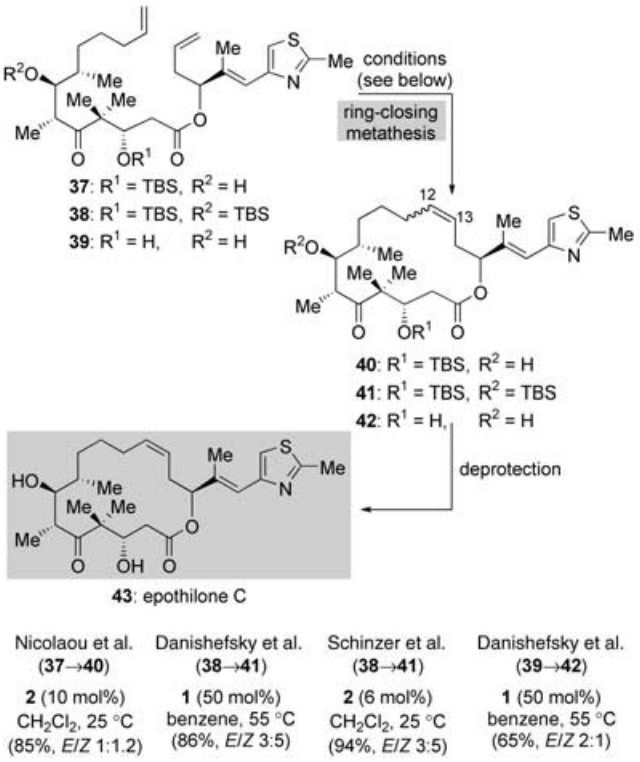
It could be argued that some of the most spectacular applications of alkene ring-closing metathesis have been in effecting macrocyclizations. Indeed, one of the first reported uses of a ring-closing-metathesis reaction in total synthesis was the remarkably efficient macrocyclization of diene **34** (Scheme 9), catalyzed by the Schrock molybdenum carbene **1**,



Scheme 9. Ring-closing metathesis in the total synthesis of Sch 38516 (**36**) (Hoveyda and co-workers, 1996).[65]

in the synthesis of the antifungal agent Sch 38516 (**36**) by the Hoveyda group.[65] Early applications such as this, which were admirably daring at the time and which are still noteworthy today, paved the way for more ambitious and challenging ring-closing-metathesis macrocyclizations, while at the same time providing insight into the essential parameters for successful macrocyclization.[66]

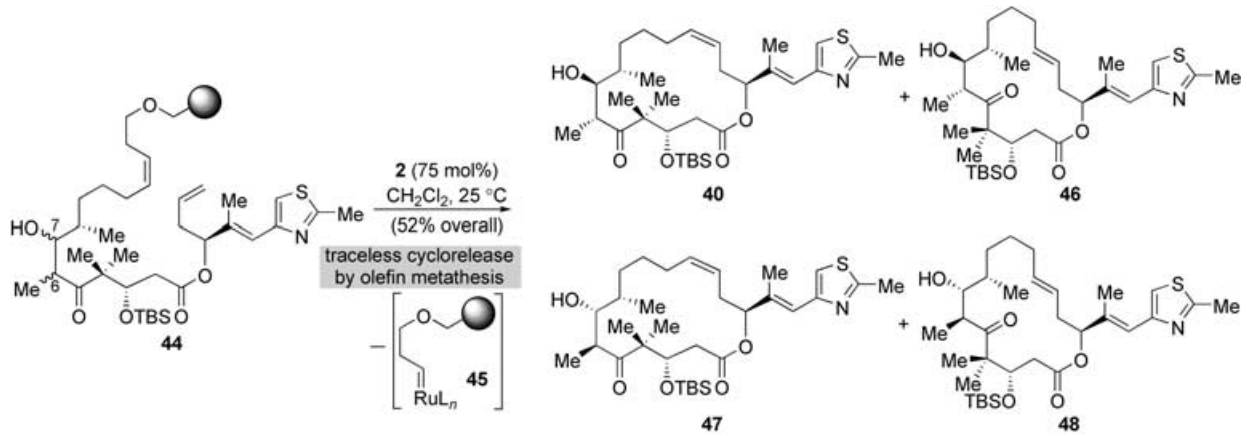
In particular, the first approaches to the total synthesis of epothilone C (**43**, Scheme 10) provided an early testing ground for ring-closing-metathesis macrocyclizations, and these studies served to highlight both the advantages and limitations of this methodology.[67] The first olefin-metathesis-based total synthesis of epothilone C (**43**) was reported by the Nicolaou group who, seeking to form the 16-membered macrocyclic ring by a route other than macrolactonization, anticipated that the power of ring-closing metathesis could potentially be employed to fashion the C12–C13 alkene in **40** from a precursor such as **37**. In those early days of the development of olefin metathesis in complex situations, however, several variables in the proposed transformation constituted unexplored territory in the metathesis landscape. Not only was the compatibility of the functionality in precursor **37**, in particular the unprotected hydroxy group and the thiazole unit, with the (then recently developed) ruthenium-based catalysts, such as **2**, questionable, but there were concerns over the stereochemical outcome of the



Scheme 10. Ring-closing-metathesis reactions in the total synthesis of epothilone C (**43**) (Nicolaou and co-workers, 1997; Danishefsky and co-workers; 1997, Schinzer and co-workers, 1999).[68,69,71]

cyclization. Fortunately, these worries proved to be relatively unfounded, as exposure of **37** to the Grubbs catalyst **2** (10 mol%) in CH_2Cl_2 at ambient temperature for 20 h effected macrocyclization to **40**, which was obtained as a 1:1.2 mixture of *E*/*Z* isomers in 85% combined yield.[68] Standard cleavage of the lone silyl protecting group in **40** then afforded the targeted product **43**. While the team was amply satisfied with the overall conversion of **37** into **40**, they were nonetheless surprised to find the degree to which seemingly subtle modifications of the array of functionality situated on the backbone of the eventual macrocyclic system dictated the *E*/*Z* ratio of the resultant cycloalkene products. Parallel studies by both the Danishefsky[69,70] and the Schinzer groups,[71] in their explorations of the same type of ring-closing reaction, provided further evidence for this phenomenon. For example, the Danishefsky team showed that the stereoselectivity of the macrocyclization could be dramatically reversed, from being marginally *Z* selective (**38**→**41**) to displaying good *E* selectivity (**39**→**42**), simply by liberating the protected hydroxy groups prior to cyclization. In contrast, the comparable results obtained by the Schinzer group in their conversion of **38** into **41** and the Danishefsky group in their ring-closing metathesis of the same substrate indicates that, at least in this case, changing reaction parameters such as solvent, temperature, or even metathesis catalyst leads to the cycloalkene products in only a slightly altered ratio. In other situations this is often not the case, and changing these latter parameters can exert a drastic influence on *E*/*Z* selectivity.[72] Even though subsequent experimentation in numerous contexts has revealed that most metathesis-based macrocyclizations provide predominantly *E* alkenes,[73] the variability of these results should serve as a reminder that we still lack the ability to reliably predict (or achieve) product geometry for certain ring-closing-metathesis reactions in complex situations. Indeed, this sometimes unpredictable formation of stereoisomeric mixtures represents one of the few significant blots on the landscape of ring-closing-metathesis macrocyclization.

The Nicolaou group subsequently investigated solid-phase synthetic approaches to epothilone C (**43**), with the aim of applying metathesis technology in the context of combinatorial chemistry, in order to generate novel natural product analogues with which the molecular basis for the promising anticancer activity of the epothilones could be probed. To facilitate such screening of diverse epothilone-like structural congeners, these researchers sought to extend their original metathesis approach to generate libraries of analogues by utilizing the power of split-and-pool combinatorial synthesis.[74] In this regard, it was anticipated to fashion an intermediate such as **44** (Scheme 11), poised for a ring-closing-metathesis reaction, in which the tether between the epothilone scaffold and the solid support was appended to the

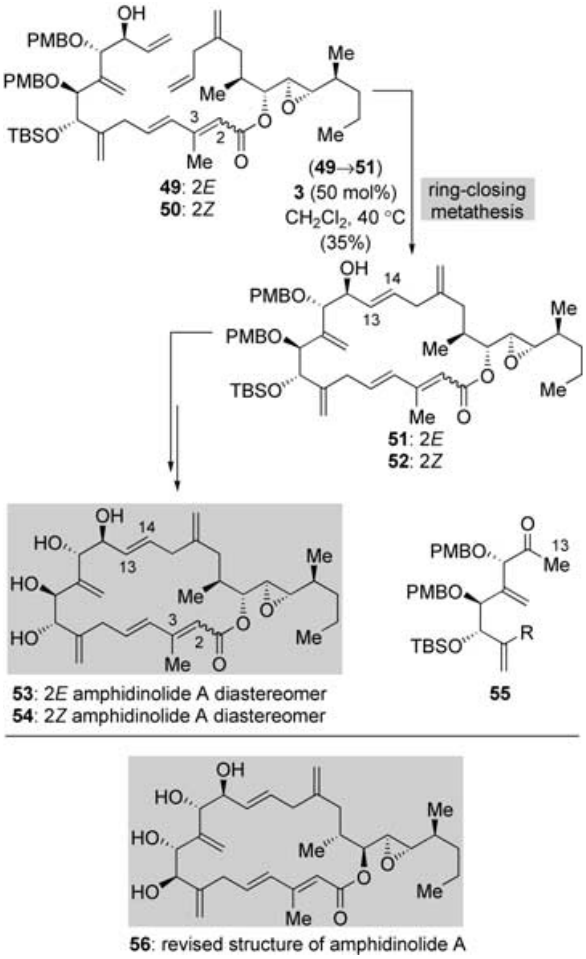


Scheme 11. Solid-phase synthesis of epothilone C and analogues through a ring-closing-metathesis cyclorelease strategy (Nicolaou and co-workers, 1997).[76]

terminal position of one of the olefins that would ultimately participate in the key macrocycle-forming metathesis event. Although the increased steric hindrance imposed by incorporating the alkyl tether at this site could, conceivably, make metathesis more challenging to achieve, the benefits of linking in this manner would far outweigh any potential risk, as ring closure would be attended by traceless cleavage of the desired product from the resin, meaning that no remnants of the original tether that joined the epothilone scaffold to the polystyrene support would remain.[75] This result would be in contrast to most conventional solid-phase approaches, where some signature of the original tether (whether as a hydroxy group or other functional handle) usually remains following cleavage. Perhaps more significantly, appending the solid support in this mode would impart a safety feature to this cyclorelease strategy in that only material capable of undergoing metathesis would ultimately be freed from the resin. As such, any precursor that had not reacted properly during a step leading to **44** would remain attached, thereby ensuring that the products obtained from the metathesis reaction would not be contaminated with undesired by-products.

This strategy proved relatively easy to explore, with **44** being synthesized in short order. Following exposure of this intermediate to carbene initiator **2** in CH_2Cl_2 at ambient temperature, the desired metathesis-based cyclorelease was indeed effected in 52% overall yield over the course of 2 days.[76] However, the ruthenium complex is concomitantly "captured" by the resin during each cyclorelease event, hence the need for the high "catalyst" loading. At the end of this process, a mixture of four products, **40**, **46**, **47**, and **48**, was isolated. Their formation resulted from the anticipated lack of *Z*/*E* selectivity in the metathesis step combined with a 1:1 mixture of C6/C7 *syn* diastereomers within the starting material **44** from an earlier aldol addition. Fortunately, the polarity differences between these four compounds were sufficient to allow their separation by TLC or HPLC. Repetition of this sequence with novel building blocks then led to several hundred distinct analogues, whose biological screening established a clear structure–activity profile for the epothilones, ultimately paving the way for the rational design of novel epothilone-like structures with comparable or even higher antitumor activities than the parent natural product.

In the appropriate situations, however, ring-closing-metathesis macrocyclizations can proceed with excellent selectivity. One such example is found in the synthesis of the originally proposed structure of amphidinolide A (**53**, Scheme 12) by the Maleczka group in 2002.[77] Having arrived at the late-stage intermediate **49**, the team proposed to generate the macrocyclic ring and concomitantly install the C13–C14 1,2-disubstituted alkene through an alkene ring-closing-metathesis reaction. Given the array of alkene functionality contained within intermediate **49**, such a daring, late-stage metathesis step was not without obvious risks. The main question marks centered on the likelihood of actually being able to direct the reaction down the desired pathway, from amongst the plethora of metathesis opportunities available to the polyolefinic substrate, together with the degree of control of alkene geometry should the desired



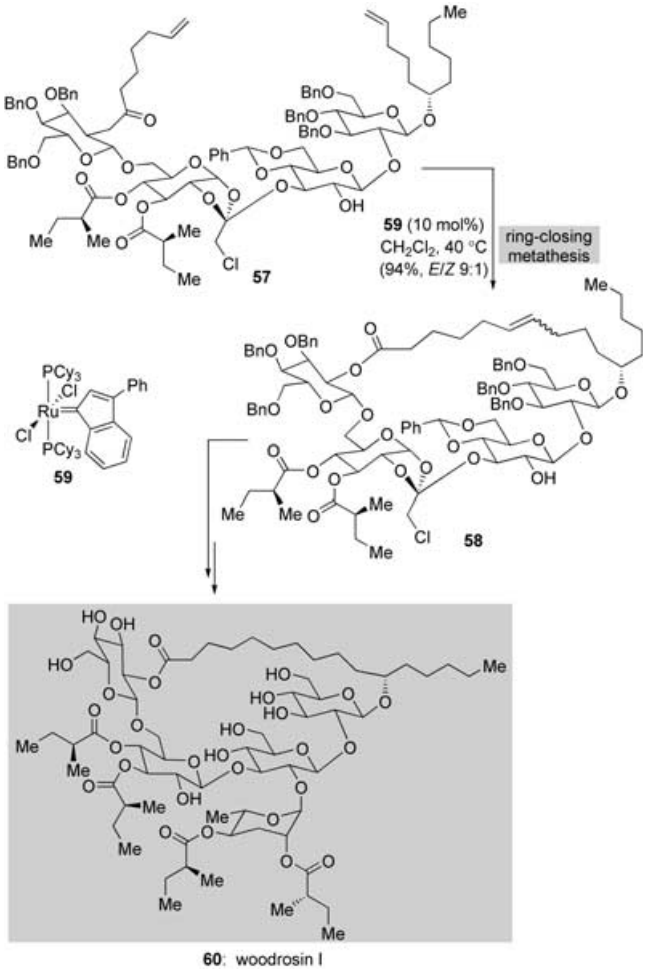
Scheme 12. Ring-closing-metathesis reactions in the total synthesis of amphidinolide A stereoisomers (Maleczka and co-workers, 2002).[77]

reaction indeed prove to be feasible. Much to their delight, the desired macrocyclization of **49** was effected by treatment of the substrate with the second-generation Grubbs ruthenium catalyst **3** in refluxing CH_2Cl_2. Although the ring closure occurred in only moderate yield (35%) and required a relatively high catalyst loading (50 mol%), no other metathesis products were observed. Furthermore, only the desired C13–C14 *E* isomer was formed. This ring closure had, in fact, first been attempted with the less reactive first-generation Grubbs ruthenium carbene **2** in the seemingly logical expectation that a less reactive metathesis catalyst would induce greater selectivity for the less hindered monosubstituted alkenes, and thus the desired C13–C14 metathesis. Surprisingly, exposure of substrate **49** to catalyst **2** merely truncated the allylic alcohol motif to generate the corresponding methyl ketone **55**.[78]

Unfortunately, the team's joy at effecting this macrocyclization was soon to be tempered by the realization that, following the straightforward deprotection of the cyclized product **51** to give the targeted compound **53**, their final product was not the same as natural amphidinolide A. In an effort to uncover the true identity of amphidinolide A, the team subsequently prepared a number of alternative stereoisomers of this structure. One of these compounds was the

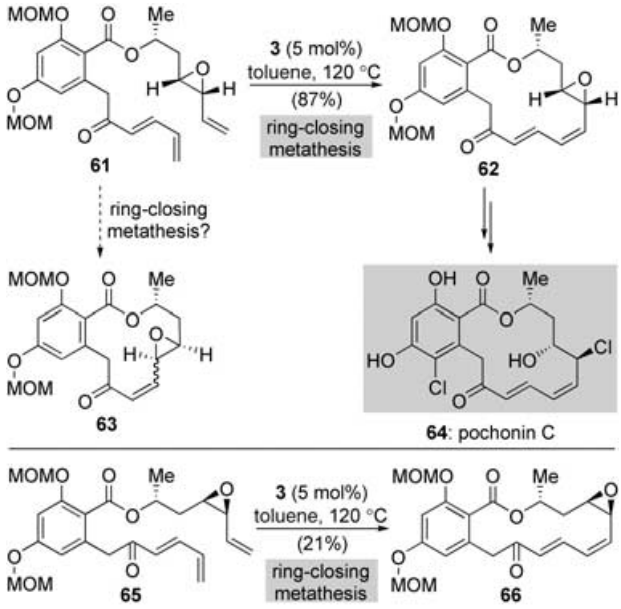
corresponding 2*Z* isomer **54**, which was synthesized through an analogous ring-closing-metathesis macrocyclization strategy. Interestingly, the ring closure of **50** to give **52** proved to be much more efficient proceeding in 88% yield (again with complete *E* selectivity) and requiring only 20 mol% of catalyst **3** to go to completion. This further illustrates the importance of substrate preorganization prior to ring closure. Despite the team's best efforts, however, the mystery surrounding the true structure of amphidinolide A would not be resolved for a further 2 years[79] when the Trost group would provide convincing evidence for its formulation being as compound **56**.[80,81]

In cases in which the stereochemical outcome of ring-closing metathesis is irrelevant (for example, when the resulting alkene system is hydrogenated to give the corresponding alkane), this methodology offers a particularly efficient and practical protocol for the formation of macrocyclic systems, and one which compares favorably with more-traditional methods of macrocyclization. A stunning example of the power of ring-closing metathesis to effect macrocyclization is the total synthesis of woodrosin I (**60**, Scheme 13) by the Fürstner group.[82,83] Having overcome a number of synthetic hurdles during the assembly of the oligosaccharide backbone present in precursor **57**, the team was gratified to find that the anticipated ring-closing-metathesis reaction proceeded smoothly upon exposure of this substrate to a 10 mol% loading of the novel phenylindenylidene complex **59** (championed by the Fürstner group as a useful alternative to the "first-generation" Grubbs catalyst **2**)[37d] in refluxing CH_2Cl_2. Macrocyclic product **58** was obtained in an astonishing yield of 94% (and as an inconsequential 9:1 mixture of *E*/*Z* isomers), with a short sequence of operations involving the hydrogenation of the newly formed alkene, attachment of the rhamnose moiety, and global deprotection, then completing this remarkable total synthesis.



Scheme 13. Ring-closing-metathesis macrocyclization in the total synthesis of woodrosin I (**60**) (Fürstner and co-workers, 2002).[82]

The applicability of ring-closing-metathesis reactions to form higher polyene systems (e.g. conjugated dienes and trienes) in macrocyclic rings has also come under close scrutiny in recent years. An instructive example of this is demonstrated in the total synthesis of pochonin C (**64**, Scheme 14), the most potent member of a small family of

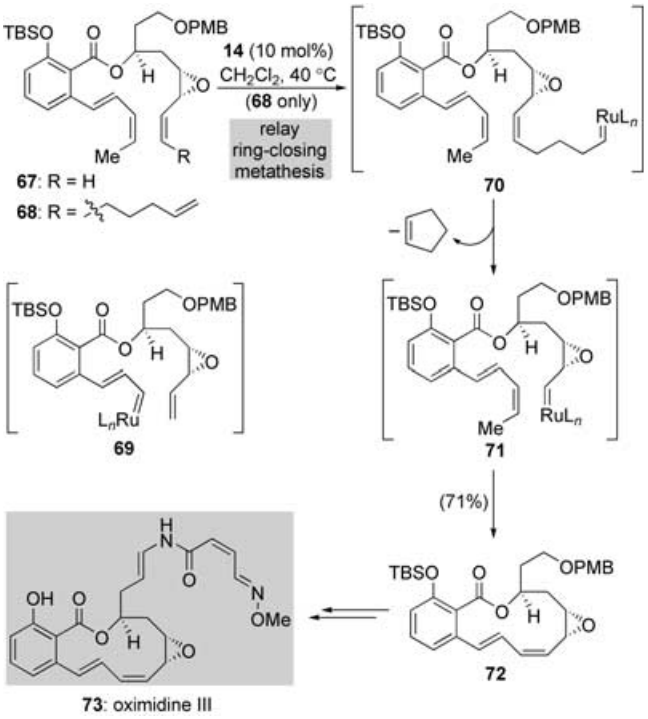


Scheme 14. Ring-closing metathesis to form a diene system in the total synthesis of pochonin C (**60**) (Winssinger and co-workers, 2004).[84]

novel antiviral natural products, reported by Winssinger and co-workers in 2004.[84] While a macrolactonization approach to the 14-membered ring present in the targeted compound **64** would certainly appear to be a viable strategy, these researchers were keen to investigate more modular approaches to the macrocyclic framework, and surmised that the characteristic *E*,*Z*-conjugated diene system could be formed through a ring-closing-metathesis reaction of triene **61**.[85] In addition to the customary questions regarding the stereochemical outcome (i.e. *E* vs. *Z*) of the macrocyclization event, in cases such as these there are also potential regioselectivity issues in that, depending on which double bond of the diene system is engaged in the metathesis event, either the desired diene product (e.g. **62**), or the truncated

monoalkene product (e.g. **63**) could be formed.[86] Again, the outcome can be highly dependent on the reaction parameters, although the former regioselectivity pathway typically predominates. The Winssinger team found that exposure of triene **61** to the second-generation Grubbs catalyst **3** (5 mol%) in toluene at 120°C for 10 minutes (conditions previously developed by the Danishefsky group and shown to be particularly effective in related applications)[87] led to the formation of the required 14-membered ring product **62** as a single regio- and stereoisomer in 87% yield. From intermediate **62**, a few more steps were all that was required to complete the total synthesis of pochonin C (**64**). The influence of the epoxide configuration over the conformational organization of the open-chain metathesis precursor was made evident by the finding that the corresponding *cis*-epoxide **65** underwent metathesis-based ring closure in poor yield (21%), albeit again with excellent regio- and stereoselectivity.

The Porco group has applied the recently developed principle of "relay ring-closing metathesis"[88] to form the conjugated diene system contained within the macrolactone ring of oximidine III (**73**, Scheme 15).[89] Pioneered by the



Scheme 15. Relay ring-closing metathesis in the total synthesis of oximidine III (**73**) (Porco and co-workers, 2004).[89]

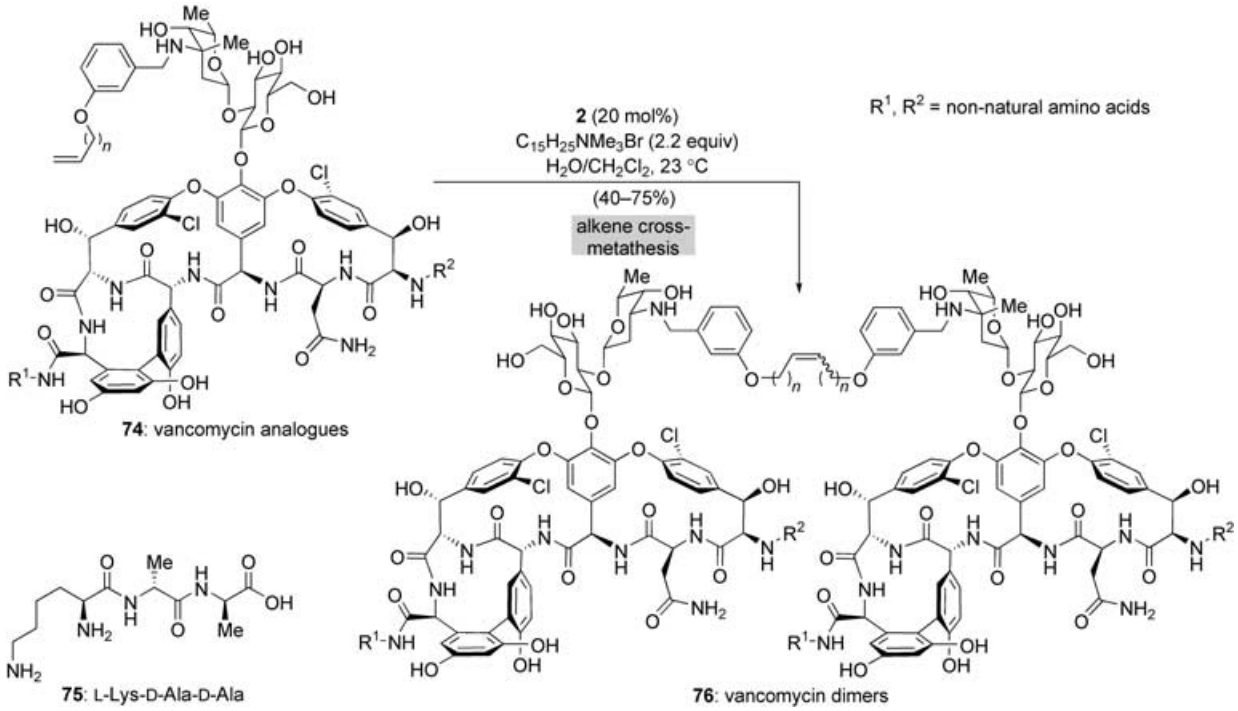
Hoye group,[90] relay ring-closing metathesis has been introduced as a means to enable otherwise sluggish (or entirely unsuccessful) ring-closing-metathesis reactions by moving the site of catalytic initiation away from points of steric hindrance and/or electronic deactivation within a precursor substrate. Thus, as is illustrated in Scheme 15, the addition of precursor **68** to a solution of the Hoveyda–Blechert catalyst **14** (10 mol%) in refluxing CH_2Cl_2 led to the formation of the desired macrocyclic product **72** in good yield (71%). The proposed mechanism of this transformation involves the initial reaction of the ruthenium carbene catalyst with the least hindered terminal double bond to generate carbene complex **70**. This intermediate can then undergo kinetically favorable ring-closing metathesis to extrude cyclopentene and generate the next intermediate **71**, which still contains a metal carbene species and which then undergoes macrocyclization to yield the observed product **72**. The clear superiority, in this instance, of the relay protocol over a conventional ring-closing-metathesis macrocyclization was demonstrated by the observation that when alkene **67** was subjected to the same metathesis conditions, the product **72** was formed in a meager yield of only 15%. In this case, the researchers proposed that the formation of carbene intermediate **69** from alkene **67** competed with the formation of intermediate **71**, with the former species **69** being a stabilized, unreactive ruthenium carbene which shuts down the catalytic cycle, resulting in the low yield. The conversion of precursor **68** into macrocyclic compound **72** was also found to be remarkably stereoselective, with the *E,Z*-diene system being formed exclusively. Having obtained the macrocyclic core of oximidine III (**73**) in this efficient manner, the team was able to manipulate the periphery to complete the total synthesis in a few more steps.[91]

2.2. Alkene Cross-Metathesis

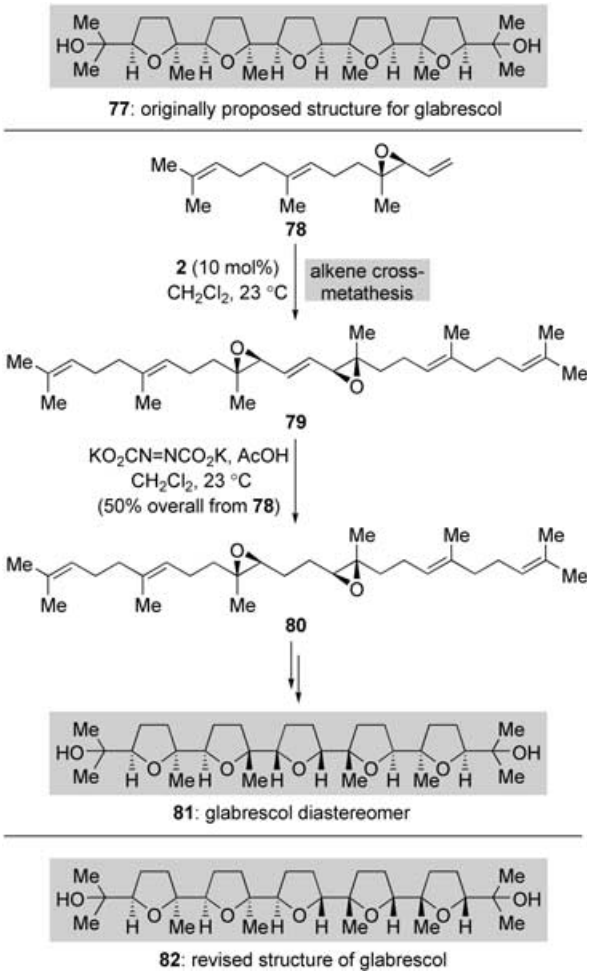
Alkene cross-metathesis has long been of great commercial importance to the industrial sector, but its transition to synthetically viable methodology in total synthesis has been a much more recent affair.[92] Alkene cross-metathesis represents a particularly appealing alternative to other transition-metal-mediated cross-coupling processes (e.g. the Stille or Suzuki reaction) in that readily available alkenes are employed, and no synthetic investment in the preparation of elaborated coupling partners (e.g. vinyl stannanes, vinyl halides, etc.) is required. Furthermore, the mild reaction conditions and functional-group tolerance of modern cross-metathesis often complements the more traditional olefination methods (e.g. the Wittig reaction). Despite its enormous potential for carbon–carbon bond formation, the widespread uptake of alkene cross-metathesis by synthetic chemists has lagged far behind that of the corresponding ring-closing processes. Indeed, until recently, many chemists' experience of cross-metathesis merely involved the unwanted formation of dimeric products arising from a disappointing ring-closing-metathesis event. The biggest challenge in cross-metathesis is the chemo- and stereoselective formation of the desired compound from amongst the myriad of potential reaction products. In this regard, it has been the recent advances in catalyst design, coupled with the development of empirical models for predicting the outcome of cross-metathesis reactions (largely due to the pioneering work of the Grubbs group),[93] that have emboldened chemists with the courage to commit their valuable intermediates to these processes. In return, they have been rewarded with new synthetic avenues and opportunities that were unthinkable even just a few years ago.

In the context of total synthesis, the applications of the olefin cross-metathesis reaction can be divided, somewhat arbitrarily, into two main classes: 1) chain-elongation processes, and 2) fragment-coupling reactions (including dimerization processes). As one example of the latter, we highlight the efforts of the Nicolaou group towards overcoming emerging bacterial resistance to vancomycin, the antibiotic currently considered to be the last line of defense against methicillin-resistant *Staphylococcus aureus* (MRSA).[94] The strategy entailed the use of alkene cross-metathesis reactions to effect the dimerization of vancomycin-type monomers such as **74** (Scheme 16) to give compounds of type **76**.[95,96] Indeed, during the past decade, several other clinically employed compounds have been dimerized, based on the notion that their biological activity would be enhanced.[97] Among several of the particularly noteworthy features of the developed cross-metathesis protocol to reach these agents (e.g. **76**), as shown in Scheme 16, was the employment of a phase-transfer agent ($C_{15}H_{25}NMe_3Br$) to encapsulate the ruthenium catalyst, and hence enable it to carry out its function in aqueous media at 23 °C. Because these reaction parameters are essentially ambient conditions, it was then decided to extend this initial homodimerization approach to include the selective formation of heterodimers by adding combinations of different substrates of type **74** in the presence of vancomycin's biological target, a terminal L-Lys-D-Ala-D-Ala peptide subunit **75**. Since it had already been established that two monomers of vancomycin could bind simultaneously (and reversibly) to this target through separate hydrogen-bonding networks,[98] this design assumed that those monomers within the collection of examined substrates that bound most tightly to this peptide chain would be captured by cross-metathesis as the corresponding dimer. As such, this approach should lead to the formation of highly active antibacterial agents. Upon execution of this target-accelerated combinatorial strategy, also referred to as dynamic combinatorial screening,[99] non-statistical distributions of dimers were formed. In each case, the compound with the greatest potency (based on synthesizing and testing all potential dimers separately) was the predominant product in each round of compound formation. Significantly, several of the agents prepared in this fashion by cross-metathesis demonstrated not only enhanced activity against MRSA relative to vancomycin, but also potency against several vancomycin-resistant bacterial strains.

Another dimerization-based cross-metathesis approach was employed by the Corey group in their quest to determine the correct structure of the polycyclic oxasqualenoid glabrescol.[100] The team had originally prepared compound **77** (Scheme 17), corresponding to the structure first proposed for the natural product, through a beautifully orchestrated biomimetic polyepoxide-cyclization strategy to fashion all five tetrahydrofuran rings in a single step and in a stereospecific fashion.[101,102] However, much to their dismay, the spectroscopic data of their synthetic material did not match that reported for the natural product.[103] The team was, therefore, faced with the task of having to synthesize a number of other possible stereoisomers, which could correspond to either the C_s- or C_2-symmetric nature of the natural product, before they could clear the ambiguity regarding the actual structure of glabrescol. One of the targeted stereoisomers was compound **81**, which, following their general polycyclization strategy, they hypothesized could be derived from bisepoxide **79**, the symmetrical nature of which lends itself to its preparation through a dimerization protocol.



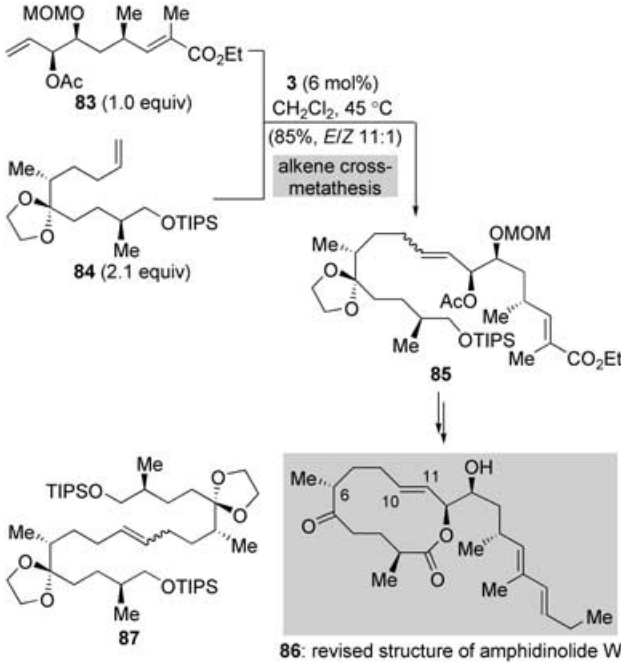
Scheme 16. Dynamic combinatorial synthesis: the use of cross-metathesis to effect selective formation of vancomycin dimers (**76**) under ambient-like conditions in the presence of its biological target, L-Lys-D-Ala-D-Ala (Nicolaou and co-workers, 2001).[95]



Scheme 17. Dimerization through cross-metathesis in the total synthesis of a glabrescol diastereomer (**81**) (Corey and Xiong, 2000).[100]

Indeed, the team found that readily available epoxide **78** underwent selective cross-metathesis upon treatment with initiator **2** (10 mol%) in CH_2Cl_2 at ambient temperature to afford the coupled product **79**. Pleasingly, only the terminal alkene units participated in the metathesis event, with no interference from the more sterically hindered trisubstituted olefins. Furthermore, the reaction was also superbly stereoselective, with the *E*-isomeric product being formed exclusively, although in this context the stereoselectivity was irrelevant as the newly formed double bond was immediately reduced in the next step. The resulting product **79** was then elaborated to give the desired pentacyclic diol **81**. Unfortunately, the new synthetic material the team now had in their hands still did not correspond to natural glabrescol, and it would be only after a great deal of further synthetic effort that the true structure of the natural product would be revealed as **82**.[104–106]

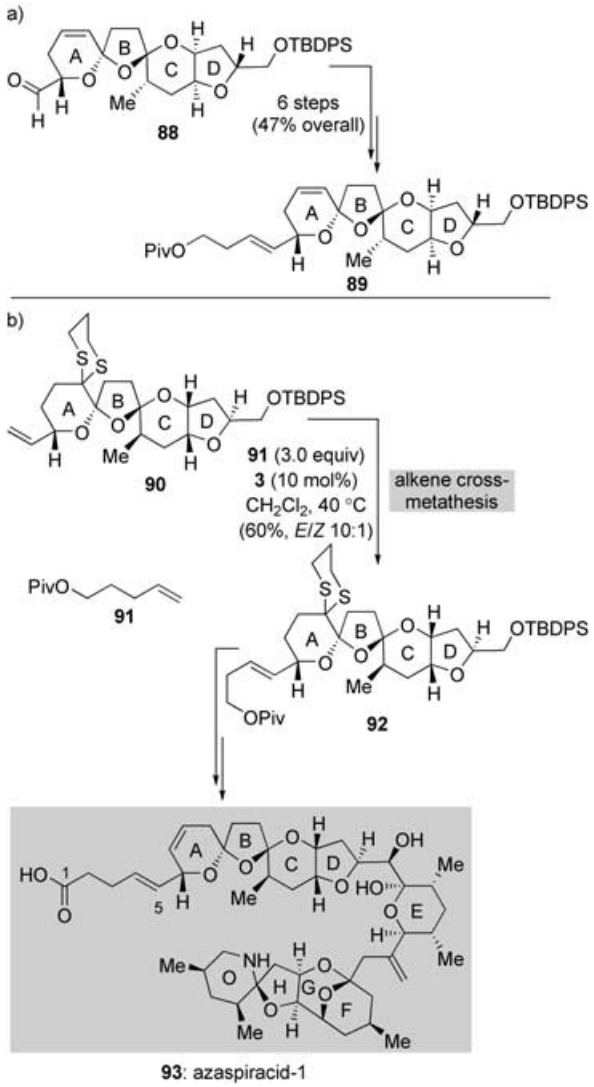
An elegant example of the coupling of two different fragments by means of alkene cross-metathesis can be found in the total synthesis and structure revision of amphidinolide W (**86**, Scheme 18) by the Ghosh group.[81a] The strategy adopted by the researchers for the formation of the macrocyclic ring system involved the coupling of the two advanced



Scheme 18. Fragment coupling through cross-metathesis in the total synthesis of the revised structure of amphidinolide W (**86**) (Ghosh and co-workers, 2004).[81a]

intermediates **83** and **84** through alkene cross-metathesis (with the concomitant installation of the C10–C11 olefin), followed by a late-stage macrolactonization. To their delight, the cross-metathesis between **83** and **84** proceeded smoothly over the course of 15 h upon the addition of catalyst **3** (6 mol%) to a refluxing solution of the two components in CH_2Cl_2, affording the desired product **85** in excellent yield (85%) and with good *E* selectivity (*E*/*Z* 11:1). An excess of alkene **84** was required, as this substrate underwent competitive homodimerization to give compound **87** (which was itself inert to secondary metathesis reactions). Furthermore, it was found that the specific employment of an acetate protecting group for the allylic secondary hydroxy group in coupling partner **83** was required for optimum results. With an efficient, modular approach to compound **85** now at their disposal, the researchers were able to advance this key intermediate over a number of steps to complete the total synthesis of the revised structure **86** of the targeted natural product.[107]

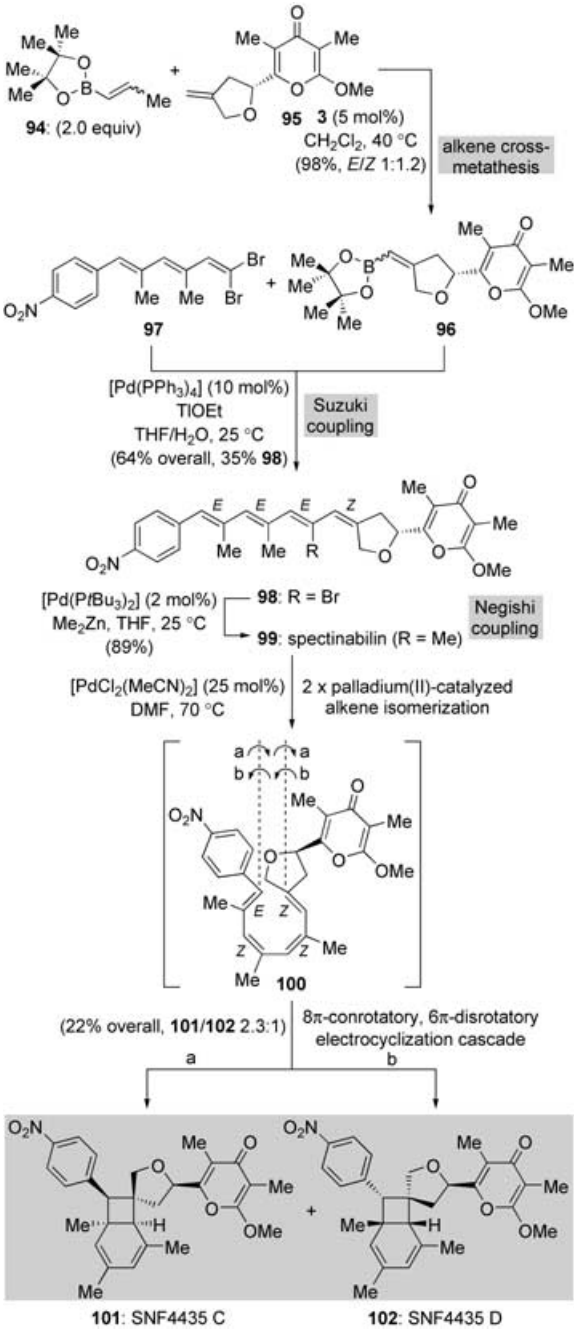
Alkene cross-metathesis was efficiently used as a means of chain elongation in the recent enantioselective synthesis of the revised structure of azaspiracid-1 (**93**, Scheme 19) by the Nicolaou group.[108] Previously, in the course of their synthesis of the originally proposed structure of this remarkable marine neurotoxin (which was subsequently shown to be incorrect), the team employed a six-step sequence to append the C1–C5 unsaturated side chain onto the ABCD-ring intermediate **88** (Scheme 19a).[109] While each individual step proceeded smoothly and in high yield, the somewhat laborious nature of this sequence prompted the team to consider other, more direct methods for the incorporation of this motif. The presence of the 1,2-disubstituted double bond in this side



Scheme 19. Introduction of the C1–C5 side-chain in the total synthesis of azaspiracid-1: a) six-step route in the synthesis of the originally proposed structure; b) single-step alkene cross-metathesis approach in the synthesis of the revised structure **93** (Nicolaou and co-workers, 2004).[108]

chain invites the possibility of its construction in a single step through alkene cross-metathesis, and indeed this was the method adopted in the final drive towards the revised structure of the natural product. Thus, exposure of a mixture of tetracyclic compound **90** and the readily available alkene **91** (used in excess) in refluxing CH_2Cl_2 to the second-generation catalyst **3** (10 mol%) resulted in the formation of the desired product **92** in 60% yield and with good stereoselectivity (*E*/*Z* 10:1, isomers readily separable by column chromatography; Scheme 19b). Most of the mass balance of this reaction consisted of unconverted starting material **90**, which could be recovered and resubjected to the reaction conditions. After three cycles, the total yield of **92** was 95%, which represented a considerable increase in both efficiency and elegance over the original six-step route.[110] Notably, the dithiane functionality did not interfere with the cross-metathesis by sequestering the catalyst **3**, further illustrating the remarkable functional-group tolerance of this ruthenium complex.

An exceedingly useful characteristic of the cross-metathesis protocol for chain elongation is that it can be employed for the concomitant generation of functionalized reagents that can be engaged in subsequent reactions to produce further molecular complexity. This is particularly beneficial when it provides access to reagents that could not be readily obtained by other methods. A stunning example of this concept, which furthermore demonstrates both brilliance in synthetic planning and the phenomenal enabling ability of modern transition-metal-mediated cross-coupling reactions, is the biomimetic synthesis of the immunosuppressant agents SNF4435 C (**101**) and SNF4435 D (**102**, Scheme 20) by Baldwin and co-workers.[111] The bicyclo[4.2.0]octadiene core structure of these architecturally unique natural products has been proposed to arise through a sequential 8π-conrotatory/6π-disrotatory electrocyclization cascade of the *Z*,*Z*,*Z*,*E* tetraene precursor **100**.[112] The viability of this hypothesis was experimentally verified by Parker and Lim who, in the preparation of tetraene **100** through a fragment-coupling Stille reaction, observed its rapid and spontaneous rearrangement to generate a mixture of **101** and **102** in a ratio closely matching that of the compounds found in Nature.[113] Furthermore, related electrocyclization cascades had been proposed as key steps in the biosynthesis of the endiandric acids by Black and co-workers[114] and subsequently demonstrated experimentally by the Nicolaou group[115] more than two decades earlier. However, Baldwin and co-workers noted the striking similarity between tetraene **100** and spectinabilin (**99**), the latter being a known natural product isolated from the same producing species (*Streptomyces spectabilis*) more than 25 years earlier by Rinehart and co-workers.[116] Indeed, the two compounds differ only in the geometry of the two central double bonds in their respective tetraene systems, thus leading the Baldwin group to the intriguing proposal that a key intermediate in the biogenesis of SNF4435 C (**101**) and SNF4435 D (**102**) is, in fact, spectinabilin (**99**), which undergoes an initial double alkene isomerization to give *Z*,*Z*,*Z*,*E* tetraene **100**, followed by the electrocyclization cascade.[117] From a synthetic point of view, this proposal is appealing because it should, in principle, be easier to construct a *Z*,*E*,*E*,*E* tetraene system (as in **99**) than the corresponding *Z*,*Z*,*Z*,*E* motif (as in **100**). The issue would then become whether the double isomerization of spectinabilin (**99**) could be effected selectively. Much to their delight, the team found that this biosynthetic proposal could, indeed, be reduced to practice, and the key steps in the synthesis are illustrated in Scheme 20. Thus, following a protocol developed by Grubbs and Morrill,[118] the cross-metathesis of vinyl boronate **94** with disubstituted alkene **95** generated the corresponding product **96** in excellent yield, albeit with moderate stereoselectivity (*E*/*Z* ≈ 1:1.2). This methodology offers a convenient approach for the preparation of synthetically useful vinyl boronate species, such as **96**, which would be inaccessible by more conventional means (e.g. hydroboration of alkynes).[119] The selective Suzuki coupling of boronate **96** (as a mixture of *E*/*Z* isomers) with the *E* vinyl bromide moiety in dibromide **97** occurred with retention of stereochemistry with respect to

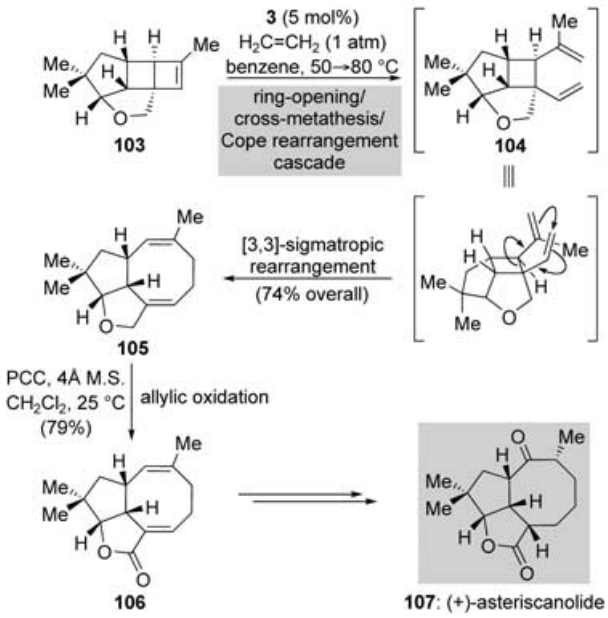


Scheme 20. Multiple use of transition-metal-catalyzed carbon–carbon bond-forming reactions in the total synthesis of SNF4435 C (**101**) and SNF4435 D (**102**) (Baldwin and co-workers, 2004).[111]

both coupling partners,[120] and was followed by separation of the resulting 1:1.2 mixture of stereoisomers to give the desired bromide **98** in 35% overall yield from **96**. A stereospecific Negishi coupling of bromide **98** with Me_2Zn, catalyzed by the commercially available 14-electron complex $[Pd(PtBu_3)_2]$,[121] then afforded spectinabilin (**99**). Finally, exposure of synthetic **99** to $[PdCl_2(MeCN)_2]$ (25 mol%) in DMF at 70°C initiated the novel isomerization/electrocyclization cascade, ultimately producing the target compounds **101** and **102** in a 2.3:1 ratio.[122] Although the overall yield for this cascade process was modest (22%), it nevertheless represents an important proof of principle. While the promotion of the initial double isomerization by a palladium(II) species can hardly be considered to be "biomimetic" in its own right, it is not unreasonable to speculate that Nature has her own complementary methods for effecting such a transformation. This remarkable total synthesis, in which all the key carbon–carbon bond-forming reactions employed transition-metal catalysis, stands as a powerful testament to the current state of the art of metathesis and cross-coupling reactions in contemporary organic synthesis.

2.3. Alkene Metathesis in Cascade Processes

The utility of alkene metathesis extends far beyond merely effecting individual ring-closing or cross-metathesis events, which necessarily generate only one new productive carbon–carbon linkage. The incorporation of metathesis steps into cascade processes has received a burgeoning level of attention in recent years, a trend that is likely to expand in the future, particularly in terms of combining metathesis with other reactions in the current synthetic repertoire. One such application is seen in the recent total synthesis of (+)-asteriscanolide (**107**, Scheme 21) by Limanto and Snapper,

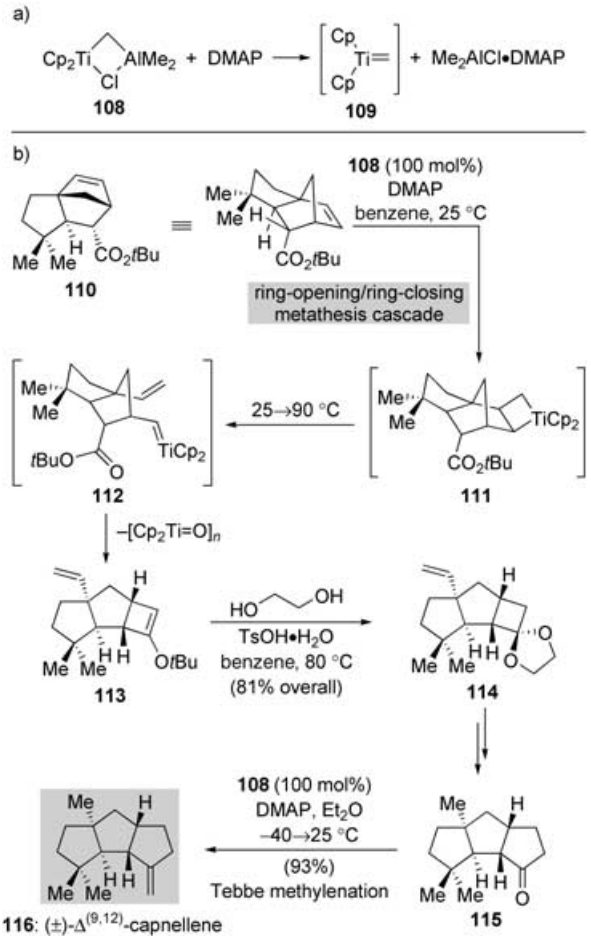


Scheme 21. A ring-opening/cross-metathesis/Cope rearrangement cascade in the enantioselective total synthesis of (+)-asteriscanolide (**107**) (Snapper and Limanto, 2000).[123]

which features the use of a novel ring-opening cross-metathesis/Cope rearrangement strategy to fashion the characteristic tricyclic core structure of the natural product.[123] The primary synthetic target was tricyclic lactone **106**, as this compound had previously been elaborated to the natural product by Wender and co-workers in their pioneering total synthesis of **107**.[124] Limanto and Snapper found that treatment of the highly strained cyclobutene **103** with catalyst **3** (5 mol%) in benzene under an ethylene atmosphere initially

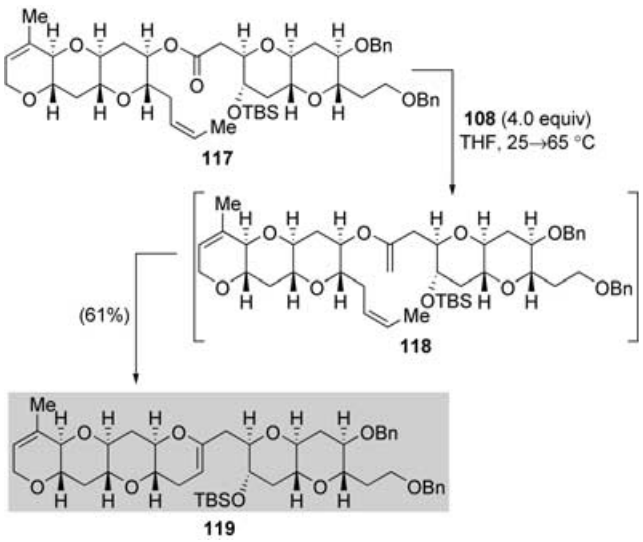
effected the selective ring-opening cross-metathesis to afford the presumed intermediate **104**, which under the reaction conditions underwent a [3,3]-sigmatropic rearrangement to yield tricyclic compound **105** in 74% overall yield. In this cleverly designed process, both the metathesis and Cope rearrangement steps enjoy the thermodynamic driving force provided by the relief of ring strain upon fragmentation of different four-membered rings. The uneventful allylic oxidation of product **105** then completed the concise synthesis of the desired lactone **106**, which was then converted into the natural product following the protocol of Wender and co-workers.[125] Cascade reactions that involve a metathesis step in combination with a number of other different transformations, including cycloadditions and Heck reactions,[126] have also been reported.

Alternative strategies involve the design of substrates that can undergo consecutive metathesis reactions in a single step. A beautiful early example of this type of protocol can be found in the expeditious synthesis of (±)-$\Delta^{(9,12)}$-capnellene (**116**, Scheme 22) by the Grubbs group,[127] also highlighting one of the rare applications of the Tebbe reagent (**108**) in a metathesis-based context in total synthesis. First introduced by Tebbe and co-workers in 1978,[128] titanocene complex **108** undergoes reversible elimination of Me_2AlCl (the latter can then be sequestered by a mild base, in this case DMAP) to generate the reactive titanium methylene intermediate **109** (Scheme 22a). For preparative purposes, intermediate **109** can undergo two main types of reaction: 1) olefination of organic carbonyl-containing compounds (including esters and amides) to give Wittig-type methylenated products[129] and 2) reaction with alkenes to form metallacycles that can be used as catalysts in alkene metathesis.[130] From an historical perspective, the reported metathesis activity of carbene **109** predates the development of both the molybdenum- and ruthenium-based catalysts such as **1**, **2**, and **3**.[131] However, the reactivity profile of carbene **109** is such that it reacts with almost all other functional groups in preference to alkenes, accounting for why it is currently widely employed to methylenate carbonyl compounds, but is not a popular catalyst to initiate the metathesis of complex molecules. In the present case, however, the combination of steric hindrance around the *tert*-butyl ester carbonyl group and the increased reactivity of the strained norbornene-type alkene inverts the usual reactivity pattern such that titanium carbene **109** reacts preferentially with the latter motif present in bridged bicyclic compound **110**, at ambient temperature, to afford metallacyclobutane **111** (Scheme 22b). The remarkable regioselectivity of this step had been anticipated by the workers on the basis of model studies and is likely the result of steric effects. Upon heating the solution of this newly formed intermediate to 90 °C, a productive cycloreversion ensued to form the new titanium carbene species **112**, which in a display of its alternate mode of reactivity, reacted with the proximal carbonyl group to afford the observed product **113**. Owing to the sensitivity of the cyclobutene enol ether, this product was immediately protected and isolated as the corresponding ketal **114**, in 81% overall yield from **110**. Although necessarily stoichiometric in the titanium complex **108**, this reaction nevertheless effected the high-yielding conversion of a readily available starting material into an advanced intermediate, which required only a few more steps to reach the targeted compound **116**. Interestingly, the last of these steps called for the methylenation of ketone **115** to give the corresponding exocyclic olefin; again, the use of the Tebbe reagent resulted in an excellent yield.[132,133]



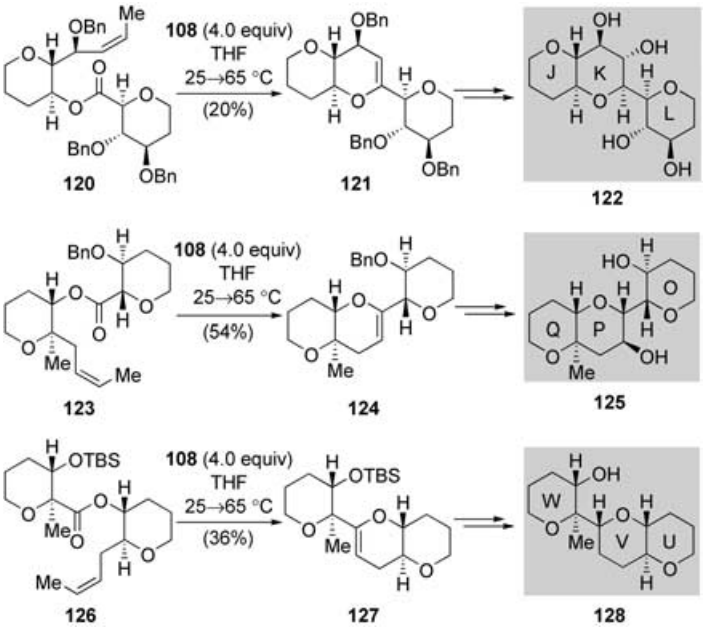
Scheme 22. Titanium methylidene reagents: a) generation from the Tebbe reagent (**108**), b) use in a ring-opening-/ring-closing-metathesis cascade in the total synthesis of (±)-$\Delta^{(9,12)}$-capnellene (**116**) (Grubbs and Stille, 1986).[127]

The Nicolaou group has developed a number of novel approaches to the synthesis of complex polyether frameworks through tandem metathesis reactions. One such protocol makes efficient use of the multifunctional reactivity of titanium carbene complexes as described above to effect tandem methylenation/alkene ring-closing metathesis, a representative example of which is illustrated in Scheme 23.[134] In this case, the sequence is believed to commence with the initial methylenation of the ester carbonyl group (i.e. **117**→**118**), based on the established general preference of this reagent to engage carbonyl functionalities before alkenes. With excess Tebbe reagent in solution, however, subsequent alkene metathesis between the newly generated alkene and its neighboring partner can ensue at elevated temperature (i.e. **118**→**119**). Since the initial disclosure of this transformation, the developed technology has been applied to several of the ring systems embedded within the structure of

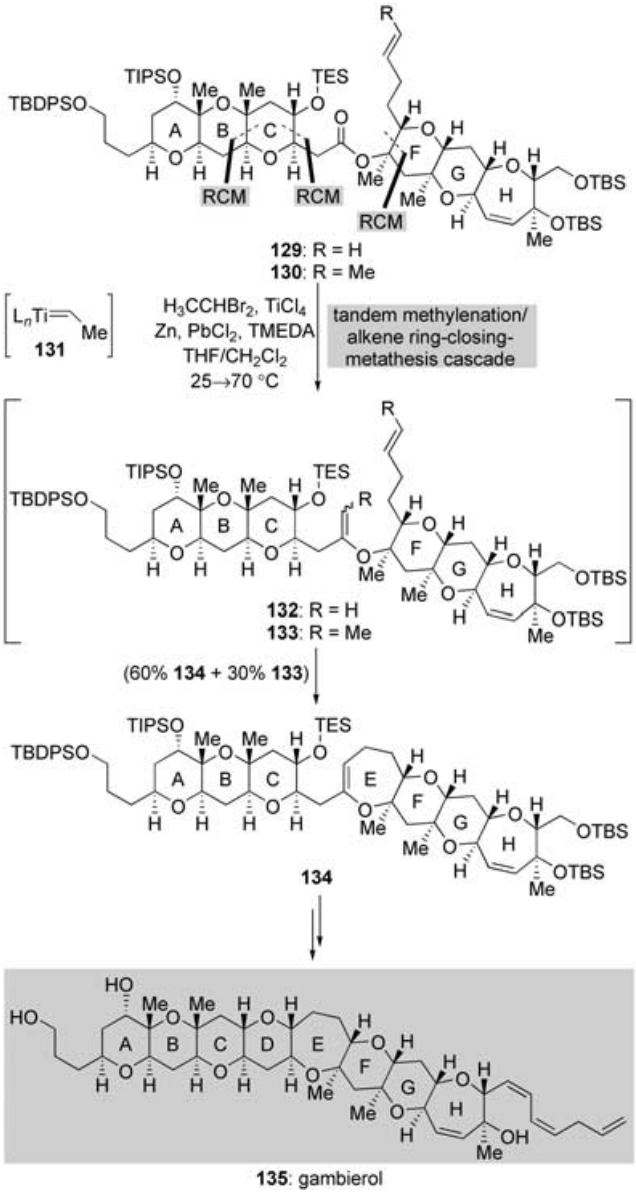


Scheme 23. The synthesis of complex polyether frameworks through tandem methylenation/ring-closing metathesis: proof-of-principle (Nicolaou and co-workers, 1996).[134]

the complex marine natural product maitotoxin (Scheme 24).[135] Rainier and co-workers subsequently made use of this type of tandem methylenation/ring-closing metathesis cascade sequence in their recent total synthesis of the polyether toxin gambierol (**135**, Scheme 25).[136] The convergent strategy adopted by these researchers initially called for the syntheses of separate ABC- and FGH-ring-containing fragments, followed by their union through an intermolecular esterification reaction. Ring-closing-metathesis reactions of enol ethers were instrumental in forging these subunits, used



Scheme 24. The synthesis of complex polyether frameworks through tandem methylenation/ring-closing metathesis: application to the JKL-, OPQ-, and UVW-ring systems of maitotoxin (Nicolaou and co-workers, 1996).[135] For the complete structure of maitotoxin, see reference [135].

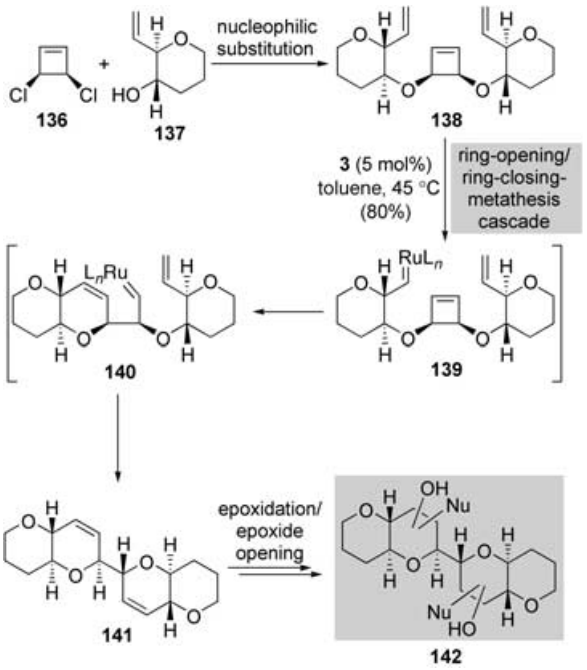


Scheme 25. The synthesis of complex polyether frameworks through tandem methylenation/ring-closing metathesis: application to the total synthesis of gambierol (**135**) (Rainier and co-workers, 2005).[136]

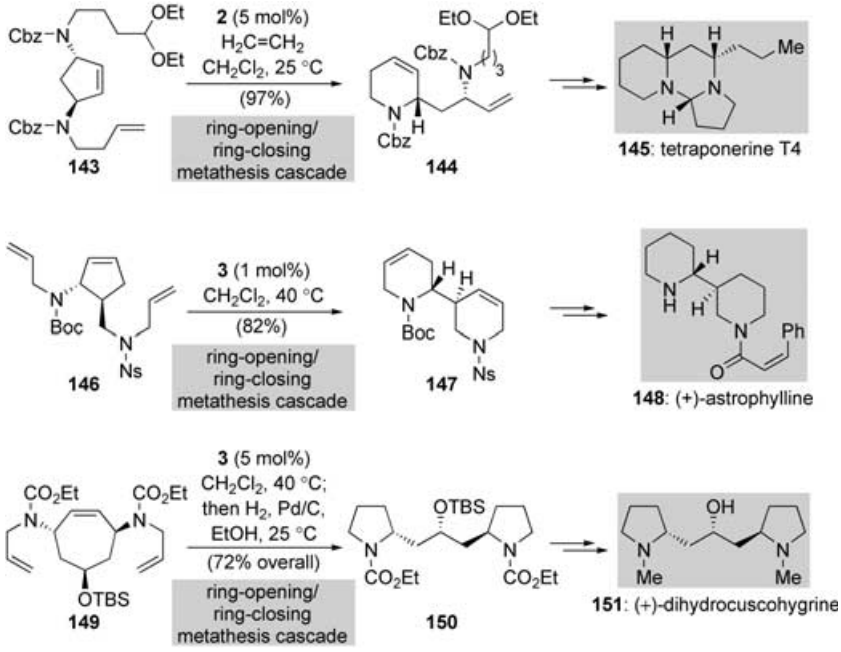
as they were to construct the B-, C-, and F-rings.[137] The fashioning of the F-ring by ring-closing metathesis was particularly noteworthy in light of the fact that it entailed the formation of a crowded tetrasubstituted alkene. Having arrived at the key hexacyclic intermediate **129**, the team had originally planned on closing the seven-membered E-ring to give compound **134** through a two-step process involving a Tebbe-type methylenation, which would generate enol ether **132**, followed by a separate ring-closing-metathesis event. Unfortunately, and to their dismay, they were unsuccessful in all their efforts at converting ester **129** into acyclic enol ether metathesis precursor **132** using the Takai–Utimoto titanium methylidene protocol.[138] Far from heralding the dismantlement of the synthetic

route, this misfortune inspired the team to investigate other methods for effecting the olefination of this ester carbonyl group. Eventually, and after much experimentation, they made the serendipitous and joyful discovery that subjecting ester **130**, which bore a different alkene-containing side-chain, to the modified Takai–Utimoto conditions shown (ostensibly to generate the corresponding substituted enol ether **133** through the intermediacy of the titanium alkylidene **131**) led to the formation of cyclic enol ether **134** in 60% yield! Furthermore, the expected product **133** was also isolated as a side product in 30% yield, and independently subjected to a ring-closing-metathesis reaction in the presence of the second-generation Grubbs catalyst **3**, also to afford cyclic product **134** in a yield of 60%. Having bypassed this synthetic roadblock in an unexpected manner, these researchers were then able to complete the total synthesis in only a few more steps.[139]

Another protocol developed by the Nicolaou group makes use of a cyclobutene scaffold as a template for tandem metathesis reactions. Thus, as is shown in Scheme 26, treatment of readily available cyclobutene-1,2-diol derivative **138** with the second-generation ruthenium catalyst **3** (5 mol%) in toluene at 45°C effected its smooth conversion into the corresponding tetracyclic compound **141**, with complete transfer of chirality from the original cyclobutene ring to the newly formed pyran systems.[140] Interestingly, and despite close precedent for analogous metathesis reactions with less-hindered substrates,[141] the first-generation catalyst **2** failed to induce the desired reaction in the present case. An alternative mechanism involving initiation at the cyclobutene alkene unit cannot be excluded. It should be recalled that all the steps in the catalytic cycle (and thus, in principle, the overall transformation) are reversible. However, there is a powerful thermodynamic driving force in this type of process that benefits from both entropic (release of ethylene) and enthalpic (release of ring strain) factors. The utility of this cascade process was extended beyond ring formation by the fact that the diolefinic product **141** could be subjected to epoxidation and subsequent stereospecific epoxide-opening reactions with a variety of nucleophiles. Such a route constitutes rapid and flexible access to complex molecular frameworks, which could easily be modified to produce tailor-made intermediates for total synthesis, or compound libraries for biological screening. These types of cascade processes, which involve sequential ring-opening and ring-closing metathesis reactions, have been termed "ring-rearrangement metatheses". Their use in target-oriented synthesis has been championed in particular by the Blechert group, who has applied them to the elegant syntheses of a variety of structurally diverse alkaloid natural products, including tetraponerine T4 (**145**, Scheme 27),[142] (+)-astrophylline (**148**),[143] and (+)-dihydrocuscohygrine (**151**).[144]

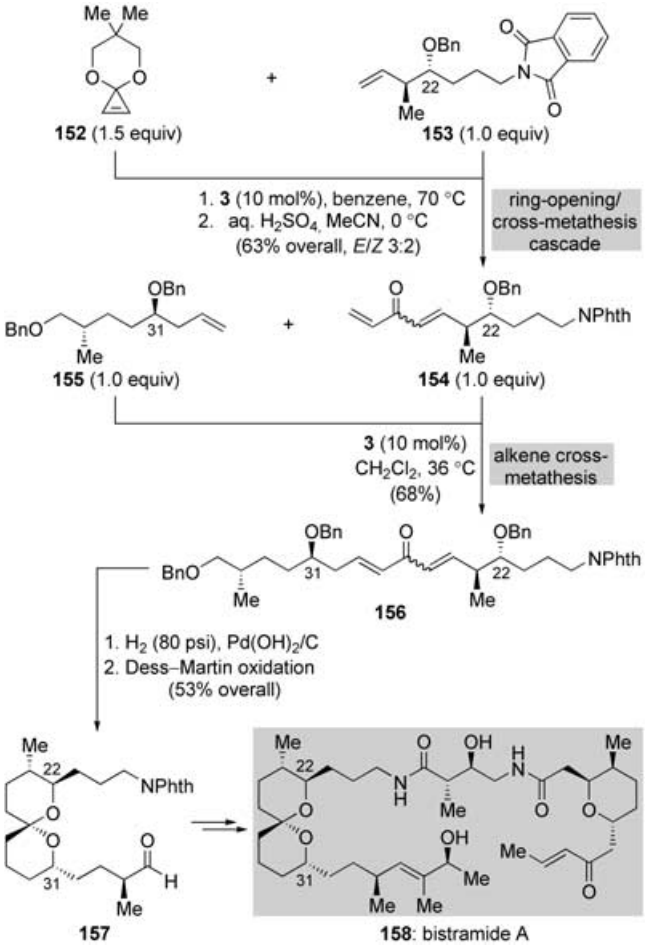


Scheme 26. A ring-opening-/ring-closing-metathesis cascade in the stereocontrolled synthesis of polyether frameworks (**142**) (Nicolaou and co-workers, 2001).[140]



Scheme 27. Ring-rearrangement metathesis reactions in the total syntheses of tetraponerine T4 (**145**), (+)-astrophylline (**148**), and (+)-dihydrocuscohygrine (**151**) (Blechert and co-workers, 2000, 2003, 2002).[142–144]

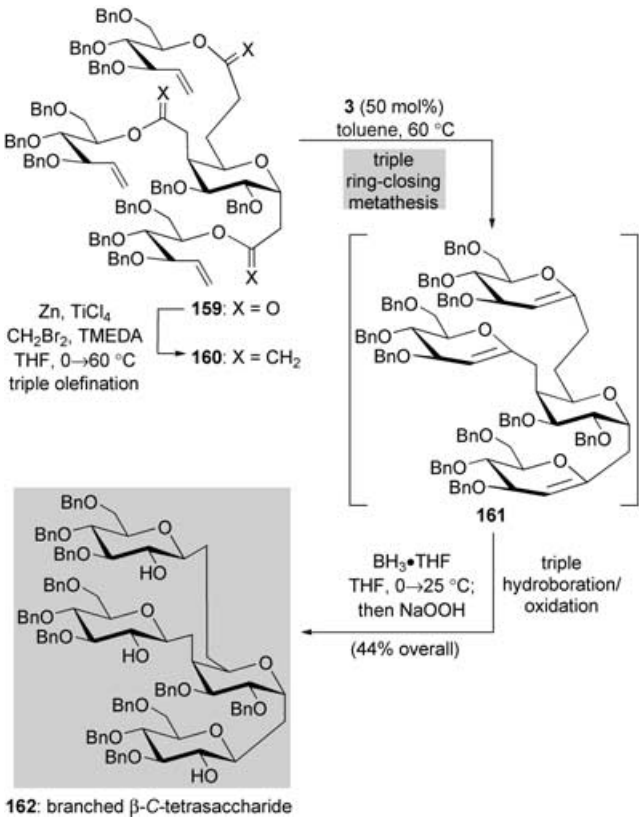
In a variation on this theme, a ring-opening/cross-metathesis cascade reaction featured prominently in the recent synthesis of the protein kinase C activator bistramide A (**158**,



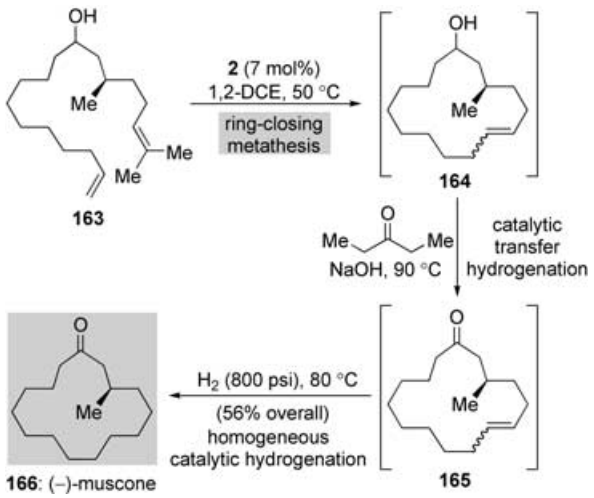
Scheme 28. Multiple use of alkene cross-metathesis reactions in the enantioselective total synthesis of bistramide A (**158**) (Kozmin and co-workers, 2004).[145]

Scheme 28) by Kozmin and co-workers.[145] The first key carbon–carbon bond-forming reaction in their inventive approach to the spiroketal domain of the targeted product involved the treatment of a mixture of terminal alkene **153** and a slight excess (1.5 equiv) of cyclopropene acetal **152** with second-generation ruthenium catalyst **3** (10 mol%) in benzene at 60 °C to afford, after acidic hydrolysis of the crude product mixture to effect the cleavage of the acetal protecting group, divinyl ketone **154**. The stereoselectivity of this reaction was poor, with the product being formed as a 3:2 mixture of *E*/*Z* isomers, but fortunately this was irrelevant in the context of this synthesis (see below). This ring-opening/cross-metathesis cascade follows the same principles as illustrated earlier in the synthesis of (+)-asteriscanolide **107** (see Scheme 21), except that in this case a substituted alkene is employed as the coupling partner instead of ethylene. As with the corresponding cyclobutenes, cyclopropenes make excellent participants in ring-opening-metathesis processes owing to the enormous relief of ring strain. It should be noted that, unlike the ring-opening/ring-closing metathesis cascade described in Scheme 26, this particular type of tandem process is atom economical (i.e. no ethylene is released), and thus largely driven by enthalpic factors, which must overcome the negative entropic factors (i.e. two molecules being combined into one). The α,β-unsaturated system generated within product **154** readily lends itself to further manipulation, and indeed the very next step involved an intermolecular fragment-coupling/cross-metathesis reaction between **154** and alkene **155**, again catalyzed by ruthenium complex **3**, to afford the expected product **156** in 68% yield. Interestingly, the corresponding acetal obtained before the acidic hydrolysis step proved to be inert towards subsequent metathesis, which may also go some way towards explaining the exclusive formation of the mono-cross-coupled product in the first metathesis step. Although the stereoselectivity of this process was again irrelevant, only a single geometrical isomer (*E*) was generated at the new linkage. Significantly, this cross-metathesis proceeded efficiently, employing only 1 equivalent of each coupling partner, whereas many cross-metatheses require one of the components to be used in an (often large) excess. High-pressure hydrogenation of the stereoisomeric mixture of **156** effected the cleavage of the three benzyl protecting groups, saturation of the two disubstituted alkenes and concomitant stereoselective spiroketalization in one pot. Subsequent Dess–Martin oxidation of the resulting primary alcohol afforded aldehyde **157**. The team thus had a remarkably concise and efficient route to the key spiroketal fragment **157** from which they were able to complete the total synthesis of (+)-bistramide (**158**) in due course.

An area of alkene-metathesis chemistry that has been investigated by a number of researchers involves the use of double, triple, or even quadruple ring-closing-metathesis reactions to generate a variety of bicyclic, tricyclic, and tetracyclic ring systems in a single step from an appropriately substituted acyclic precursor.[146] A highlight of this methodology is the novel approach to branched β-*C*-tetrasaccharides developed by the Postema group, an example of which is illustrated in Scheme 29.[147] Thus, triester **159** was, following the methylenation protocol developed by Takai and co-workers,[138] converted into the corresponding hexaene **160**, which was then exposed to catalyst **3** (50 mol%, added in five portions over 2.5 h) in toluene at 60 °C to effect the desired triple ring-closing metathesis to form tris-glycal **161**. This latter intermediate was not isolated, but directly subjected to a regio- and stereoselective triple hydroboration/oxidation procedure to afford tetrasaccharide **162** in 44% overall yield from triester **159**. Although the catalyst loading may seem relatively high in this case, this reflects the fact that not only do three metathesis reactions have to be catalyzed, but also that ring-closing metathesis of electron-rich enol ethers is known to be more difficult than that of simple alkyl-substituted diene systems.[148,149] Notably, no competing macrocyclization or oligomerization processes were observed during the metathesis step. Strictly speaking, the actual metathesis events cannot be classified as a cascade process, since the individual ring-closures occur independently of each other. Nevertheless, the overall conversion of **159** into **162** represents a highly efficient gain in molecular complexity, involving nine independent transformations (each occurring with an average yield of 91%) and the formation of three new rings and six new stereogenic centers without the need for the purification of any of the intermediates. Through the judi-



Scheme 29. A triple ring-closing-metathesis reaction in the synthesis of a novel branched β-*C*-tetrasaccharide (**162**) (Postema and Piper, 2004).[147]



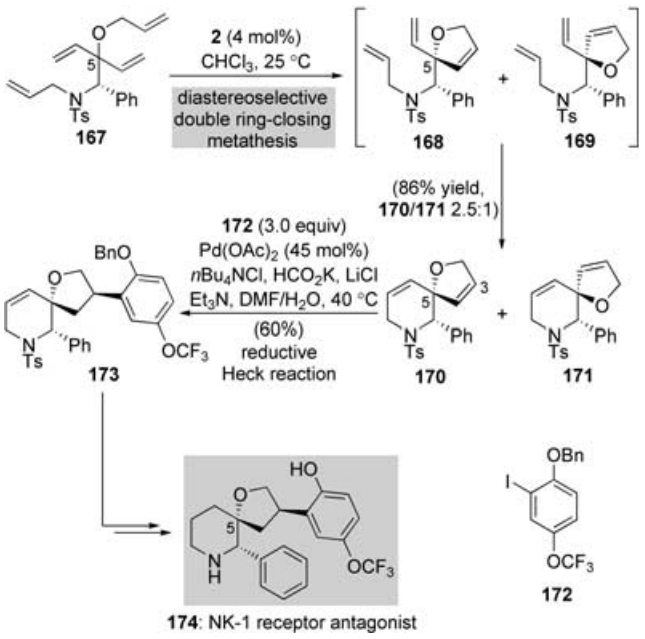
Scheme 30. "Tandem catalysis" in the enantioselective synthesis of (−)-muscone (**166**) (Grubbs and co-workers, 2001).[152]

cious positioning of alkene units within a precursor molecule, a diverse array of annulated, spirocyclic, and polycyclic ring systems can be fashioned by employing multiple ring-closing metathesis reactions.

Our final example in this section highlights the multifarious uses of ruthenium carbene systems such as **2** and **3**. In addition to being versatile catalysts for metathesis reactions, complexes **2** and **3** have been shown to function also as effective precatalysts for a variety of unrelated transformations, including hydrogenation, radical addition, and the vinylation of terminal alkynes.[150,151] This broad spectrum of activity has been employed by Grubbs and co-workers in a remarkable synthesis of the fragrant natural product (−)-muscone (**166**, Scheme 30), whereby sequential alkene ring-closing metathesis, hydrogen transfer, and hydrogenation reactions were mediated in a one-pot process by complexes derived from a single ruthenium carbene species, namely complex **2**.[152] As illustrated in Scheme 30, this sequence began with the treatment of diene **163**, bearing an unprotected secondary hydroxy group, with initiator **2** (7 mol%) in 1,2-dichloroethane at 50 °C, which effected the desired ring-closing-metathesis reaction to initially afford macrocyclic alkene **164** as a mixture of geometrical isomers. Subsequent addition of 3-pentanone and NaOH to this solution followed by heating to reflux then initiated the ruthenium-catalyzed transfer dehydrogenation of alcohol **164**, formally transferring "H_2" from this intermediate to the 3-pentanone (which is used in excess to drive this reversible reaction in the desired direction) to afford macrocyclic ketone **165**. At this point the reaction mixture was transferred to a Parr hydrogenation apparatus, pressurized with H_2 gas (800 psi), and heated to 80 °C. Under these conditions, the ruthenium complex(es) present is converted into ruthenium hydride species, which function effectively to hydrogenate the 1,2-disubstituted alkene chemoselectively in the presence of the ketone carbonyl group. Only once this stage was complete was the reaction mixture worked up and purified to give the targeted product **166** in an overall yield of 56% for the three steps.[153] This approach to "tandem catalysis"[152] offers great potential for the streamlining of synthetic processes and will undoubtedly find many more exciting applications in target-oriented synthesis once its fuller scope is convincingly demonstrated.[154]

2.4. Diastereoselective and Enantioselective Alkene Metathesis

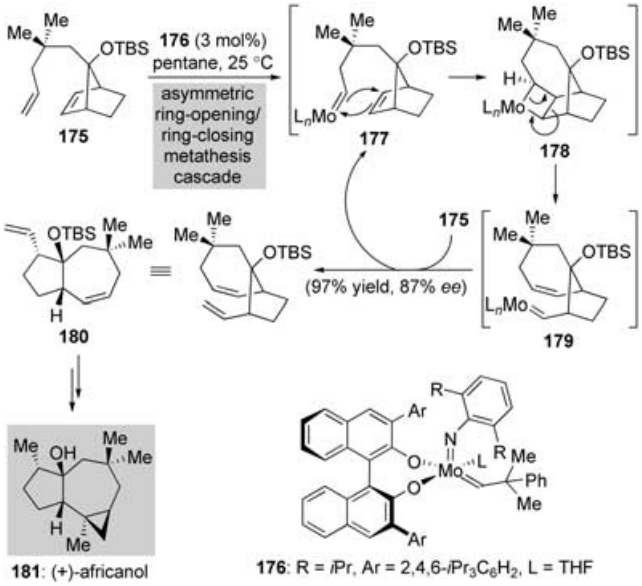
One of the frontiers of the alkene-metathesis reaction is its use in the generation of stereogenic centers within molecules. The two main methods that have been employed to achieve this process are: 1) diastereoselective ring-closing-metathesis reactions, with achiral metathesis catalysts, of systems containing pre-existing stereogenic centers and 2) enantioselective metathesis reactions of achiral substrates with chiral catalysts. An example of the former protocol is in the novel approach to the synthesis of selective NK-1 receptor antagonists (e.g. **174**, Scheme 31) developed by workers at Merck.[155,156] The spirocyclic core structure characteristic of this class of therapeutic agents had been previously synthesized in a stepwise manner, involving the fusion of the tetrahydrofuran ring onto a preexisting enantiomerically pure piperidine scaffold.[157] The Merck team was keen to investigate more direct and conceptually novel methods for the construction of this bicyclic template and found that this ring system could be formed in a single step from an acyclic precursor by using a diastereoselective double ring-closing-



Scheme 31. Diastereoselective double ring-closing metathesis and reductive Heck reactions in the synthesis of an NK-1 receptor antagonist **174** (Merck, 2001).[155]

metathesis reaction. Thus, as is shown in Scheme 31, treatment of the (*S*)-phenylglycine-derived tetraene **167** with the first-generation Grubbs catalyst **2** (4 mol%) in $CHCl_3$ at ambient temperature led to the formation of the two diastereoisomeric products **170** and **171** in a combined yield of 86% yield and with 70% diastereoselectivity. The major pathway for this reaction was believed to involve the initial formation of the five-membered ring to generate dihydrofuran intermediates **168** and **169**, which then undergo the second, slower ring closure. The diastereoselectivity of the overall process thus arises during the first stage, with the preferential cyclization of the *O*-allyl group onto one of the two diastereotopic C5 vinyl groups, dictated by the adjacent tertiary stereocenter. Following the separation of the major isomeric product **170** from the undesired component **171**, a remarkably chemo-, regio-, and stereoselective reductive Heck reaction was then employed to append the aromatic ring onto C3 of the dihydrofuran ring to give tricyclic compound **173**, which was converted, in two steps, into the final target structure **174**.

While undeniably elegant, there are a number of limitations associated with this type of diastereoselective metathesis process. Firstly, one or more stereogenic centers have to be incorporated into the precursor molecule at sites where they can influence the course of the reaction. More importantly, since the stereochemical course of the reaction is under substrate control, it is generally not possible to obtain selectively both possible diastereoisomeric products through modification of the reaction conditions. A more appealing approach in this regard would be to induce asymmetry in achiral molecules through the use of chiral metathesis catalysts since, in principle, one could obtain selectively either product stereoisomer through the use of the appropriate catalyst antipode. Collaborative efforts between the Schrock and Hoveyda groups have led to the development of such chiral molybdenum-based catalysts for catalytic asymmetric alkene metathesis. More recently, chiral ruthenium-based systems have been introduced by the Grubbs group;[158] however, to date, it is the corresponding molybdenum complexes that have been the most widely studied. Applications of this emerging methodology in total synthesis are still rare, and since catalytic asymmetric metathesis has recently been authoritatively reviewed,[159] the most recent example of this process in target-oriented synthesis may suffice to demonstrate its enormous potential. Thus, as illustrated in Scheme 32, Schrock, Hoveyda, and co-workers employed a



Scheme 32. An asymmetric ring-opening/ring-closing-metathesis cascade in the enantioselective synthesis of (+)-africanol (**181**) (Schrock, Hoveyda, and co-workers, 2004).[160]

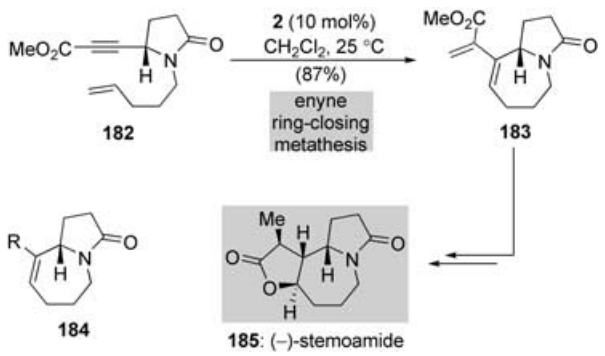
novel asymmetric ring-opening-/ring-closing-metathesis cascade reaction to furnish the bicyclic core structure and prove the stereochemical identity of the sesquiterpenoid (+)-africanol (**181**).[160] Treatment of readily available diene **175** with the chiral molybdenum carbene initiator **176** in pentane at ambient temperature effected its conversion, over the course of 6 h, into the rearranged bicyclic structure **180**, which was formed in nearly quantitative yield (97%) and with good enantioselectivity (87% *ee*). Notably, this reaction could be carried out under highly concentrated conditions, with sufficient pentane being added just to dissolve the chiral catalyst, yet homodimeric products were not observed. This metathesis cascade effects the enantioselective desymmetrization of a *meso* precursor substrate **175**, the most commonly employed mode of asymmetric alkene metathesis. This cascade sequence gave the team an extremely rapid and enantioselective access to an advanced intermediate **180**, which contained most of the key structural features present in the natural product **181**. Thus, with intermediate **180** in hand, these researchers were able to complete their elegant total synthesis in only a few more steps.

3. The Enyne-Metathesis Reaction

The enyne-metathesis reaction is an extremely useful method for the construction of 1,3-diene systems, often in a stereoselective manner, from simpler precursor molecules under mild conditions. The synthetic value of this reaction is enhanced by the fact that, in addition to being a means to an end in itself, the 1,3-diene systems thus formed are themselves versatile synthetic intermediates that can undergo further selective transformations (e.g. cycloaddition reactions). The intramolecular (ring-closing) enyne-metathesis reaction is a particularly powerful method for the construction of ring systems, both carbocyclic and heterocyclic and, indeed, it is in this context that the reaction has found the most use. Intermolecular (cross-metathesis) reactions have been employed much less frequently owing to the perceived difficulties in achieving at least reasonable levels of selectivity; however, even in this case there have been tremendous advances in recent years. The most widely used initiators for enyne metathesis are the ruthenium carbene based catalyst precursors, which have been "borrowed" from the alkene-metathesis realm, but which serve equally admirably in this context and exhibit the by now familiar levels of high activity and functional-group tolerance in these processes as well.[161] Here we highlight some of the most elegant and instructive applications of the enyne-metathesis reaction in total synthesis.

3.1. Enyne Ring-Closing Metathesis

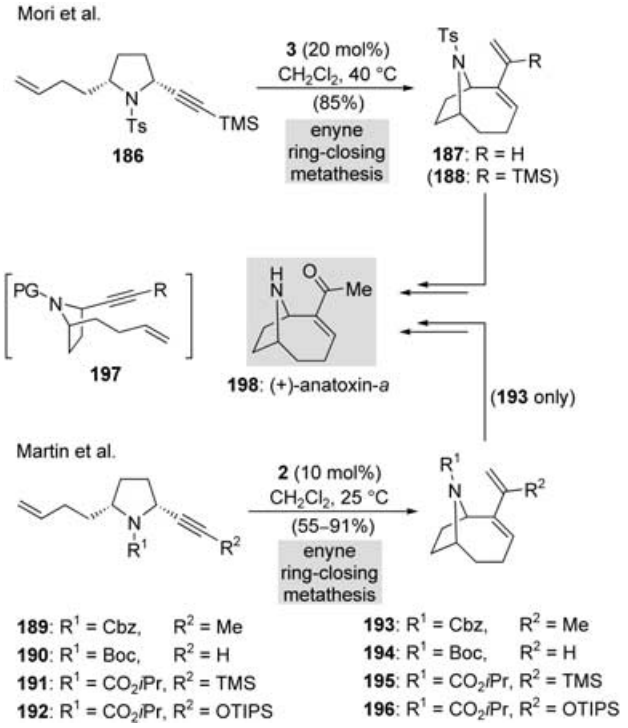
It was the Mori group who pioneered the use of ruthenium carbene complexes in enyne-metathesis chemistry, first demonstrating its applicability to the formation of five-, six-, and seven-membered nitrogen-containing heterocyclic rings in 1994.[162] Inspired by this achievement, it was not long before the same group also reported the first application of an enyne-metathesis reaction in a total synthesis, namely that of the tricyclic alkaloid (−)-stemoamide (**185**, Scheme 33) in 1996.[163] The team reasoned that, once a stereoselective route to bicyclic compound **183** had been secured, the resulting diene system would provide a convenient handle for the fusion of the third and final ring onto the structure,



Scheme 33. Enyne ring-closing metathesis in the enantioselective synthesis of (−)-stemoamide (**185**) (Mori and Kinoshita, 1996).[163]

thus completing the total synthesis. The immediate issue then became the construction of bicyclic intermediate **183**, and it was proposed that this compound could, in turn, arise from the enyne ring-closing metathesis of precursor **182**. To their delight, the researchers found that this transformation could be effected by treatment of a solution of precursor **182** in CH_2Cl_2 with the first-generation Grubbs catalyst **2** (4 mol%) at ambient temperature, to furnish bicyclic product **183** in 87% yield and without any erosion of stereochemical integrity at the sensitive propargylic position. This reaction is all the more noteworthy in light of the researchers' previous experience of enyne ring-closing-metathesis reactions of alkyne systems bearing carboalkoxy substituents, namely that, while the cyclization itself is accelerated by the presence of the ester substituent, the resulting sensitive cross-conjugated product typically undergoes extensive decomposition during purification and is only isolated in low yields.[162] To rationalize the apparent discrepancy in the excellent yield of compound **183**, it was proposed that the diene system is forced, by steric effects, to adopt a nonplanar conformation in which conjugation between the two alkene π systems is minimal, thus protecting the system from the destruction that otherwise might have been expected to occur. With intermediate **183** then in hand, only a few more steps were required to arrive at the targeted product **185**.[164] Interestingly, the formation of a trisubstituted alkene system such as **184** (Scheme 33) through simple alkene metathesis in the presence of the ruthenium carbene catalysts available at the time (e.g. **2**) would have been exceedingly difficult, if not impossible, yet this was readily accomplished by means of enyne metathesis.

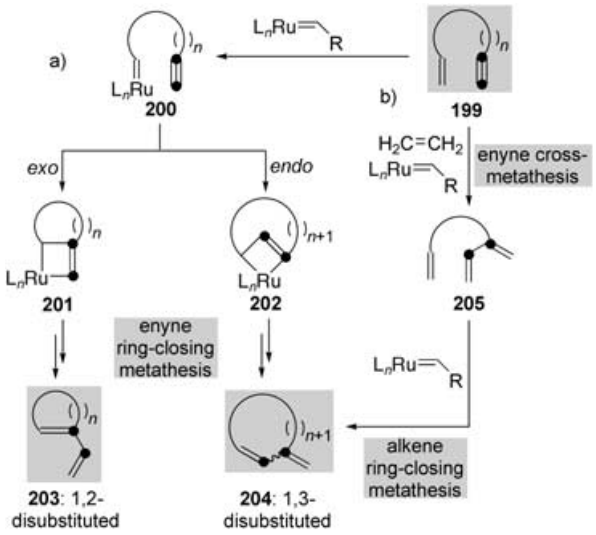
More recent applications of enyne metathesis in alkaloid total synthesis can be found in the concise routes to (+)-anatoxin-*a* (**198**, Scheme 34) developed independently and almost simultaneously by the groups of Martin[165] and Mori.[166] Despite its modest molecular weight, anatoxin-*a* has proven to be a particularly tempting target for synthetic chemists, due not only to its biological profile[167] but also to its unusual aza-bridged bicyclic structure, and has accordingly inspired a legion of elegant synthetic approaches.[168,169] The cornerstone of both groups' strategies was the employment of enyne ring-closing-metathesis reactions of readily available *cis*-2,5-disubstituted pyrrolidine precursors to assemble rapidly the bicyclic core framework, followed by the appropriate side-chain manipulation and amine-deprotection maneuvers required to complete the total synthesis. While the use of ring-closing olefin-metathesis reactions in the construction of bridged aza-bicyclic structures had been documented,[170] the formation of such systems through the corresponding enyne-metathesis processes represented uncharted terrain, which served to heighten the novelty associated with these proposed steps. In the event, both groups found that with the appropriate substrates the desired cyclizations could be effected with remarkable ease and efficiency. Martin and co-workers induced the cyclization of precursor **189** (R^1 = Cbz, R^2 = Me) by treatment with the second-generation Grubbs catalyst **3** (10 mol%) in CH_2Cl_2 at ambient temperature to afford bicyclic compound **193** in 87% yield. Selective oxidative cleavage of the less substituted double bond



Scheme 34. Enyne ring-closing-metathesis approaches to the total synthesis of (+)-anatoxin-*a* (**198**) (Martin and co-workers, 2004; Mori and co-workers, 2004).[165,166]

followed by removal of the Cbz group then yielded the target compound. The group had in fact previously shown that a variety of substituted alkynes, for example, **190**, **191**, and **192**, could undergo enyne ring-closing metathesis to generate the corresponding bicyclic systems **194**, **195**, and **196** in good yields. However, with the finishing line within tantalizing reach, the researchers were thwarted in their valiant efforts at converting any one of **194**, **195,** or **196** into the target compound **198**, and it was with only their fourth substrate **193** that the final synthetic hurdles could be surmounted. If nothing else, these tribulations illustrate the fact that synthetic routes almost invariably contain unexpected pitfalls, and that fortune favors the persistent! Mori and co-workers found that while the enyne metathesis of alkyne **186**, carried out in refluxing CH_2Cl_2 in the presence of catalyst **3** (20 mol%), did indeed yield the desired bicyclic skeleton, unexpected desilylation occurred during the reaction to generate diene **187** as the observed product. Much to the team's relief diene **187** could be elaborated also to give the coveted target compound, this time through a selective oxymercuration/alcohol oxidation sequence. The facile nature of these cyclization reactions in generating rather strained bicyclic systems provides further evidence for the beneficial effects of biasing substrates to adopt a conformation favorable to cyclization. In the present case, the potential $A^{1,3}$-strain between the N-protecting group and the *cis*-2,5-pyrrolidine ring substituents favors the diaxial conformer **197**.[171] Finally, it should be mentioned that the Aggarwal group has also utilized an analogous approach in their elegant synthesis of the related alkaloid (−)-ferruginine, employing an enyne ring-closing metathesis to construct the more constrained azabicyclo[3.2.1]octane core structure present in the natural product.[172]

The intramolecular enyne-metathesis reaction also offers a useful method for the synthesis of macrocyclic ring systems, albeit one much less utilized than the corresponding alkene ring-closing macrocyclizations. However, when applying enyne ring-closing metathesis reactions to the synthesis of large rings, a number of selectivity issues, absent in other metathesis processes, arise and need to be taken into careful consideration. These issues relate to the orientation of ring closure, and have been elegantly summarized by Lee and Hansen.[173] Thus, as shown in Scheme 35, the ruthenium

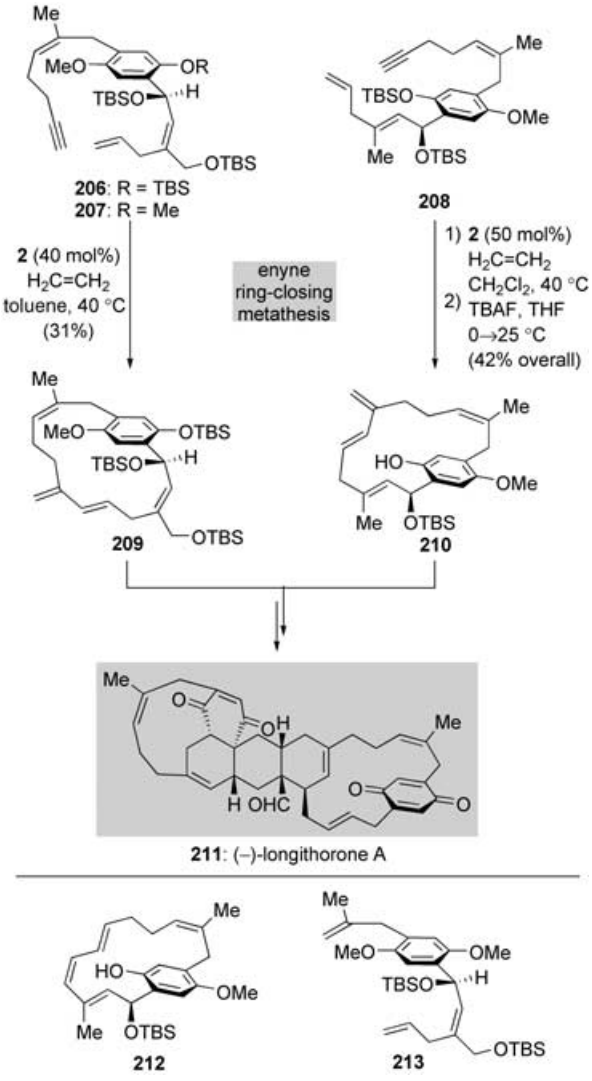


Scheme 35. Models for macrocyclization by enyne ring-closing metathesis: a) direct pathway; b) two-step enyne-cross-metathesis/alkene ring-closing-metathesis pathway (Lee and Hansen, 2003).[173]

carbene intermediate **200** generated from the starting enyne **199** can undergo two possible modes of ring closure, termed *exo* and *endo*, to generate the two different metallacyclobutene intermediates **201** and **202**, which subsequently yield the 1,2-disubstituted product **203** and 1,3-disubstituted product **204**, respectively. Furthermore, the *endo* mode of ring closure leads to products with an additional carbon atom within the ring relative to those derived from the *exo* mode. The mode of ring closure followed in any given case depends largely on the geometric constraints imposed by the tether linking the alkene and alkyne moieties. Thus, the formation of common- and medium-sized rings by enyne ring-closing metathesis is typically constrained to follow the *exo* path (as in the examples discussed above), whereas macrocyclizations generally follow the *endo* mode of ring closure owing to the increased flexibility of the tether. Another important factor to consider is that, following a seminal report by the Mori group,[174] enyne-metathesis macrocyclizations are generally conducted under an atmosphere of ethylene.[175] In these particular cases, the course of the macrocyclization is believed to be diverted away from that of a direct intramolecular

enyne-metathesis reaction, which would be expected to be inherently slow owing to the low effective concentration of the reacting termini. Instead, a two-step process has been proposed involving an initial rapid intermolecular enyne cross-metathesis of the terminal alkyne unit with ethylene (a known process, see below) to generate a 2-substituted butadiene **205**, which subsequently undergoes a conventional intramolecular alkene ring-closing-metathesis reaction. Given the sensitivity of the ruthenium metathesis catalysts to steric effects, the less hindered terminal double bond of the butadiene moiety would be expected to be engaged selectively in the macrocyclization event to yield the formal *endo* enyne-metathesis product **204**, and indeed this is observed experimentally.[176]

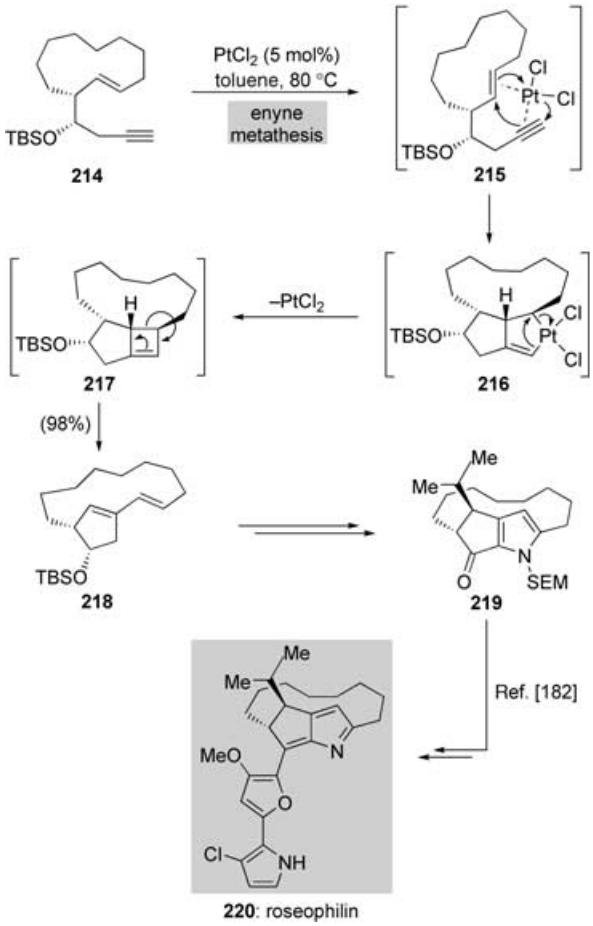
The regiochemical outcome of enyne-metathesis macrocyclizations certainly weighed heavily on the minds of Shair and co-workers as they embarked on their journey to complete the total synthesis of the marine natural product (−)-longithorone A (**211**, Scheme 36).[177] Inspired by the insightful biogenetic hypothesis of the Schmitz group,[178] the Shair team proposed to employ a beautifully choreographed sequence of inter- and intramolecular Diels–Alder reactions to assemble much of the imposing polycyclic architecture of this remarkable natural product. This then led them to conceive of macrocyclic compounds **209** and **210** as key synthetic intermediates, corresponding to the "left" and "right" halves of the natural product, respectively. On first inspection, the stereocontrolled synthesis of these "simpler" intermediates would still appear to be far from trivial. However, recognizing the characteristic 1,3-disubstituted butadiene system embedded within both compounds **209** and **210**, the team began to contemplate the exciting possibility of constructing both intermediates through enyne ring-closing-metathesis reactions of the respective precursors **206** and **208**. From the discussion above (see Scheme 35), one would be forgiven for thinking that this was a fairly routine assumption, but at the time enyne metathesis had never been applied to the synthesis of macrocycles, only to smaller rings, which had always resulted in the formation of the corresponding 1,2-disubstituted cyclic products. Eager to answer the question of 1,2- versus 1,3-disubstitution selectivity in enyne-metathesis macrocyclizations, the group performed some simple model studies, which showed for the first time that the desired 1,3-disubstituted diene systems could be obtained preferentially, if not exclusively, in the formation of larger rings. Emboldened by this breakthrough, the group set to work on the real system and arrived at intermediates **206** and **208** in short order. At this point, it will be noted that both **206** and **208** bear seemingly extraneous functionality, in the shape of benzylic hydroxy group derivatives, which is not present in the target product **211**. These substituents were, in fact, key to the planning of the macrocyclization reactions, as it was anticipated that these groups would gear the ring closures to produce selectively only the desired atropisomers of the cyclized products. Specifically, the potential steric interactions between the benzylic TBS ether groups and the phenolic hydroxy derivatives would, ideally, dictate that macrocyclization of compounds **206** and **208** occur selectively through the lower-energy conformers shown, thus generating the desired atropisomeric products.[179] In practice, the cyclization of enyne **208**, induced by treatment with catalyst **2** (50 mol%) in refluxing CH_2Cl_2 under ethylene atmosphere, proceeded with both excellent atropselectivity and *E*/*Z* selectivity to afford, after treatment of the crude product mixture with TBAF to effect the selective desilylation of the phenolic hydroxy group, the desired paracyclophane **210** in 42% overall yield. A significant by-product formed in this reaction was the unusual paracyclophane **212** in which a methylene group was lost during the macrocyclization.[180] In contrast, the macrocyclization of enyne **206** was both less atropselective (3:1) and less selective in the control of the endocyclic olefin geometry (*E*/*Z* 4.5:1); nevertheless, the desired product **209** could be produced reliably in yields averaging 31%. In the absence of an ethylene atmosphere, macrocyclization did not occur with either **206** or **208**; thus, it seems likely that both reactions proceed through the two-step process alluded to earlier. Interestingly, when the cyclization of precursor **207** was attempted in the presence of the more



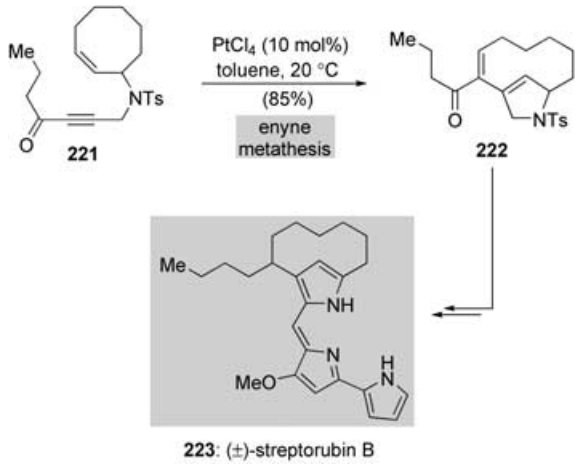
Scheme 36. Enyne ring-closing-metathesis macrocyclizations in the enantioselective total synthesis of (−)-longithorone A (**211**) (Shair and co-workers, 2002).[177]

reactive ruthenium initiator **3**, the unexpected product **213** was obtained in which the alkyne-bearing side chain had been truncated, presumably resulting from the increased activity of this catalyst towards trisubstituted olefins. Having secured both the key intermediates **209** and **210**, the Shair group was then able to complete the total synthesis in only a few more steps. Significantly, the 1,3-diene systems formed in both intermediates **209** and **210** ultimately participated in the crucial biomimetic Diels–Alder reactions. This meritorious total synthesis is noteworthy not only for its pioneering applications of enyne metathesis in macrocyclizations, but also in that it sets a new "gold standard" for enyne-metathesis chemistry in general.

An important feature of the enyne-metathesis reaction is that, unlike the other metathesis processes we have discussed so far, the overall process can be mediated by catalysts other than metal carbene containing species, and in these cases the reaction can proceed by (one or more) entirely different mechanisms. An illustrative example can be found in the formal total synthesis of roseophilin (**220**, Scheme 37) by Trost and Doherty.[181,182] The treatment of enantiomerically pure enyne **214** with $PtCl_2$ (5 mol%) in toluene at 80°C initiated a sequence of events involving the formal cleavage of one and the formation of two carbon–carbon double bonds, expansion of a macrocyclic ring by two carbon atoms, and the installation of a bridgehead alkene moiety, ultimately leading to the formation of the bicyclic product **218** as a single stereoisomer in a remarkable yield of 98%! The 1,3-diene system in compound **218** then provided a handle for its elaboration into tricyclic compound **219**, an intermediate in the Fürstner group's pioneering total synthesis of roseophilin (**220**),[183] and thus the completion of the formal synthesis of the natural product. The mechanism proposed for this transformation invokes a platinum(II)⇄platinum(IV) manifold, involving the initial formation of the metallacyclopentene intermediate **216**, followed by reductive elimination to generate cyclobutene **217**, which under the conditions of the reaction undergoes conrotatory electrocyclic ring-opening (driven by the release of ring strain) to yield the observed product **218**. It has been shown that a wide range of electrophilic species, ranging from other transition-metal complexes (e.g. $[\{RuCl_2(CO)_3\}_2]$, $[IrCl(CO)_3]_n$, and various palladacycles) to simple Lewis and Brønsted acids that cannot undergo redox equilibria (e.g. $BF_3{\cdot}OEt_2$, $AlCl_3$, and HBF_4) are also effective catalysts for this type of transformation. In these cases, alternative mechanistic pathways have been proposed involving formal cationic intermediates.[184] These types of transformations have been termed "skeletal reorganizations" to differentiate them from the metal carbene mediated processes; however, they all fall under the banner of enyne metathesis since the net outcome is the same.[185] Semantics aside, these reactions offer a remarkably simple, atom-economical, and user-friendly method for generating molecular complexity by employing the most basic of catalyst systems. Another example of this type of enyne metathesis is in the synthesis of streptorubin B (**223**, Scheme 38) by the



Scheme 37. $PtCl_2$-catalyzed enyne metathesis in the formal synthesis of roseophilin (**220**) (Trost and Doherty, 2000).[181]

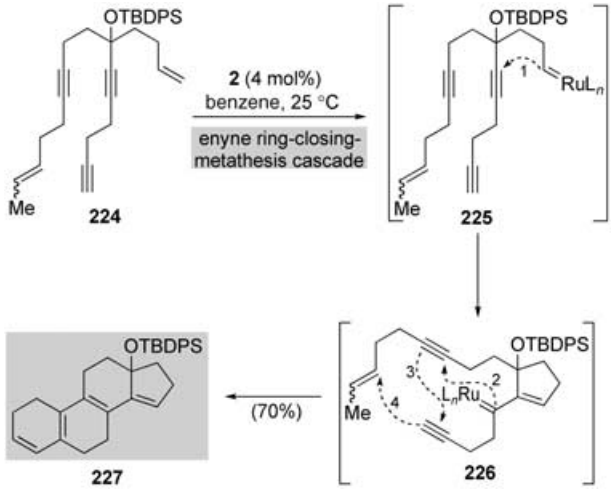


Scheme 38. $PtCl_4$-catalyzed enyne metathesis in the total synthesis of (±)-streptorubin B (**223**) (Fürstner and co-workers, 1998).[183a]

Fürstner group, in which the metathesis of enyne **221**, mediated by a catalytic amount of $PtCl_4$ (10 mol%), generated bicyclic pyrrolophane **222** in 85% yield.[183a] The same transformation could also be effected with $BF_3{\cdot}OEt_2$ or HBF_4 as catalysts, although the yield of the product was somewhat lower in these cases (64% and 57%, respectively).

3.2. Enyne Metathesis in Cascade Processes

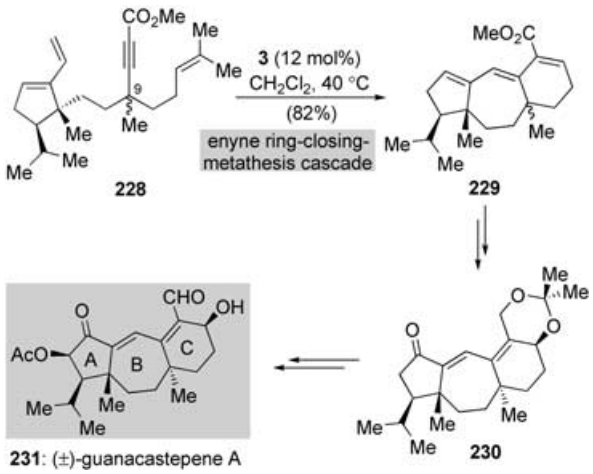
One of the most exciting and powerful applications of the enyne-metathesis reaction is its use in cascade processes to generate complex polycyclic structures from simpler precursor substrates. An enyne ring-closing-metathesis reaction initially generates a new metal carbene that can potentially be intercepted by another appropriately located olefin within the same molecule, resulting in a second intramolecular metathesis event to form another ring and a new metal carbene species, and so on. The first examples of tandem enyne metathesis were reported by Grubbs and co-workers,[186] with the same group subsequently reporting the instructive example highlighted in Scheme 39.[187] Thus, exposure of acyclic



Scheme 39. Use of a domino enyne ring-closing-metathesis sequence for the construction of a steroid-type polycycle **227** (Grubbs and co-workers, 1996).[187]

compound **224** to ruthenium catalyst **2** (4 mol%) in benzene at ambient temperature triggered a cascade sequence resulting in the regiocontrolled formation of four new carbon–carbon bonds and four new rings to afford the steroid-type compound **227** in 70% yield. The initiation of this highly orchestrated process presumably occurred with the insertion of the ruthenium alkylidene into the most (kinetically) reactive terminal alkene of the starting material **224** to generate **225**. The latter carbene species underwent enyne ring-closing metathesis with the proximal triple bond to generate the subsequent intermediate **226**, a substrate poised to react, in order, with the next three sites of unsaturation. Hence, each alkyne unit serves as a metathesis relay point, thus allowing the propagation of the polycyclization cascade until the terminating alkene ring-closing-metathesis event. Through the judicious positioning of unsaturation within an acyclic precursor molecule, one can envisage any possible number of multiple ring-forming processes.

The Hanna group made gainful use of this type of tandem ring-closing process in their recent formal synthesis of guanacastepene A (**231**, Scheme 40).[188] The first total synthesis of this novel tricyclic diterpene had been reported in 2002 by the Danishefsky group,[189] with a subsequent formal



Scheme 40. An enyne ring-closing-metathesis cascade in the formal synthesis of (±)-guanacastepene (**231**) (Hanna and co-workers, 2004).[188]

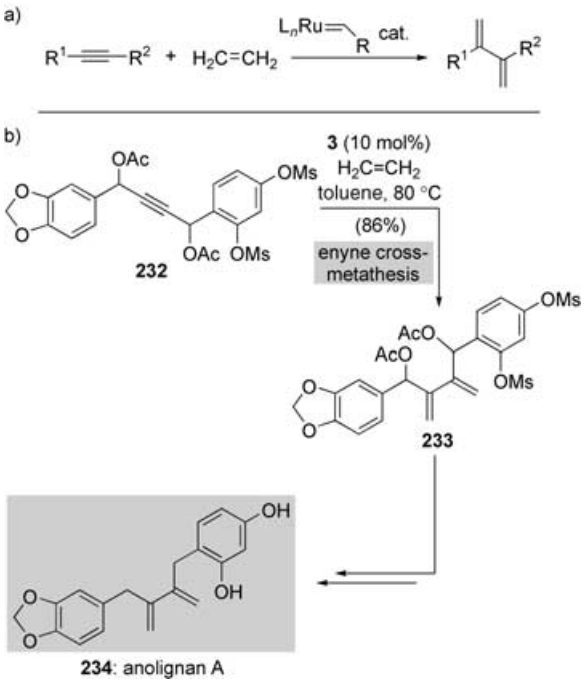
synthesis being reported by Snider and co-workers a year later.[190] Both of these two elegant syntheses adopted a stepwise approach to the construction of the tricyclic core structure, first fusing the seven-membered ring onto a pre-existing cyclopentane derivative, then at a later point installing the final six-membered ring (i.e. A→AB→ABC). In an unprecedented approach to this terpene skeleton, Hanna and co-workers surmised that it would be possible to generate the characteristic tricyclic ring system of guanacastepene A (**231**) in a single step from an appropriate monocyclic A-ring precursor through a tandem enyne ring-closing-metathesis reaction (i.e. A→ABC). Indeed, it was found that readily available ester **228** (as a 1:1 mixture of epimers at the C9 stereocenter) underwent the desired cyclization cascade upon treatment with the second-generation Grubbs catalyst (12 mol%) in refluxing CH_2Cl_2 to afford exclusively tricyclic compound **229** in 82% yield. The particular use of catalyst **3** was essential to the success of this transformation, as previous studies by the group had indicated that the less active ruthenium-based catalyst **2** was ineffective at promoting similar reactions.[191] The selectivity of this cascade process is quite remarkable, and is again due to the fact that the reaction had been "programmed" to initiate at a specific point in the precursor molecule **228**, namely the least hindered (and hence most kinetically reactive) terminal alkene, thus ensuring the correct regiochemical outcome. Equally important is the fact that the triene functionality concomitantly installed in the formation of intermediate **229** proved to be amenable enough to allow its elaboration to give ketone **230**, a late-stage intermediate in the Danishefsky team's original total synthesis of guanacastepene A (**231**), thus completing the formal synthesis of the natural product.[192]

3.3. Enyne Cross-Metathesis

In comparison to the generally reliable, high-yielding, and selective intramolecular processes, intermolecular enyne metathesis (enyne cross-metathesis) has seen little use in

the synthesis of complex molecules, despite its appealing potential for the formation of synthetically useful acyclic 1,3-diene systems in fragment-coupling processes.[193] The biggest problem in effecting intermolecular metathesis between an alkene and an alkyne is selectivity. Not only can three different types of intermolecular metatheses (alkene, alkyne, and enyne) potentially occur in these reactions, but the formation of stereoisomeric *E*/*Z* mixtures in the desired cross-metathesis diene product can also be a major problem. Currently, the success or failure of any given intermolecular enyne-metathesis reaction appears to be very substrate-dependent, and there is as yet no "working model" that can be used to predict the outcome of these reactions reliably.

The most common application of intermolecular enyne metathesis employs ethylene as the alkene component, and this provides a particularly convenient method for the production of 2,3-disubstituted butadiene systems (or 2-substituted butadienes in the case of terminal alkynes), an important and synthetically useful structural motif (Scheme 41 a). This protocol was introduced by the Mori group,



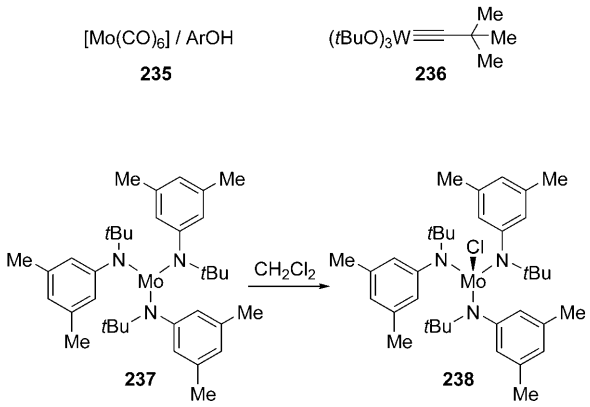
Scheme 41. Enyne cross-metathesis: a) generalized scheme; b) application to the total synthesis of anolignan A (**234**) (Mori and co-workers, 2002).[194a]

who subsequently applied it to an expedient synthesis of anolignan A (**234**, Scheme 41 b).[194] Thus, the cross-metathesis of internal alkyne **232** was induced by treatment with initiator **3** (10 mol%) in toluene at 80 °C under ethylene at atmospheric pressure to furnish butadiene **233** with the required regiochemistry and in 86% yield. A few more routine steps then completed the total synthesis. These cross-metathesis conditions were found to be more effective than those in the presence of the first-generation ruthenium catalyst **2** (10 mol%, CH_2Cl_2, 25 °C), which gave **233** in lower yield (65%). Indeed, heteroatom substitution at the propargylic position(s) of the alkyne coupling partner is(are) generally required to attain at least satisfactory yields when using catalyst **2** in this type of cross-metathesis, whereas the more active catalyst **3** is effective with a much wider range of terminal and internal alkynes.[195] Atmospheric pressure of ethylene is usually sufficient for these reactions, although the Diver group reported that certain sluggish cases can be accelerated by employing ethylene at elevated pressures.[196]

The first enyne-cross-metathesis reactions of substituted alkenes to afford acyclic 1,3-disubstituted butadiene systems were reported by the Blechert group in 1997.[197] The potential utility of these processes has since caught the attention of many researchers, who have developed their own improvements and applications,[198] including elegant cascade reactions.[199] Nevertheless, the first application of an enyne-cross-metathesis reaction with an alkene other than ethylene in a total synthesis remains an unfulfilled, yet eagerly anticipated, event[200] representing as it does one of the frontiers of enyne-metathesis chemistry.

4. The Alkyne-Metathesis Reaction

Despite the mechanistic parallels between alkyne metathesis and its more ubiquitous alkene-based sibling, the familiar carbene-type catalysts used most routinely in alkene metathesis (e.g. **1**, **2**, and **3**) do not catalyze the corresponding alkyne-metathesis reactions. Instead, this field has its own selected assortment of transition-metal-based catalyst systems, of which the most commonly employed three are illustrated in Scheme 42. The first of these is the classic



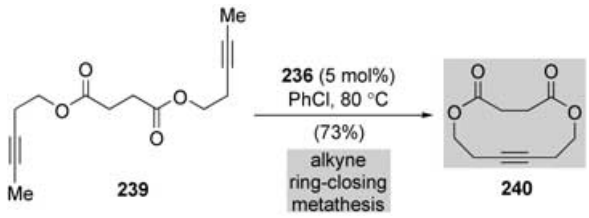
Scheme 42. Commonly used alkyne-metathesis initiators.

Mortreux system **235**[25] (later refined by Bunz and co-workers)[201] based on a mixture of $Mo(CO)_6$ and any one of a number of phenolic additives (e.g. 4-chlorophenol), which generates one or more not as yet well-defined catalytically active species in situ. The simplicity and user-friendly nature of this catalyst system is offset somewhat by its rather limited tolerance of polar functional groups and the elevated temperatures (ca. 140–150 °C) required to initiate and maintain

catalytic activity. A major breakthrough in rational catalyst design for alkyne metathesis came with the development of well-defined tungsten alkylidyne complexes by the Schrock group, of which catalyst **236** is the most widely used.[202] Recently, the Fürstner group introduced the monochloro molybdenum complex **238** as a powerful precatalyst for alkyne metathesis; **238** is conveniently formed in situ by the activation of the corresponding trisamido complex **237** with CH_2Cl_2 as a chlorine source.[203–205] The tungsten and molybdenum complexes **236** and **238** complement each other nicely in terms of scope, activity, and functional-group tolerance, and typically perform more efficiently in advanced settings than do the Mortreux catalysts **235**.

4.1. Alkyne Ring-Closing Metathesis

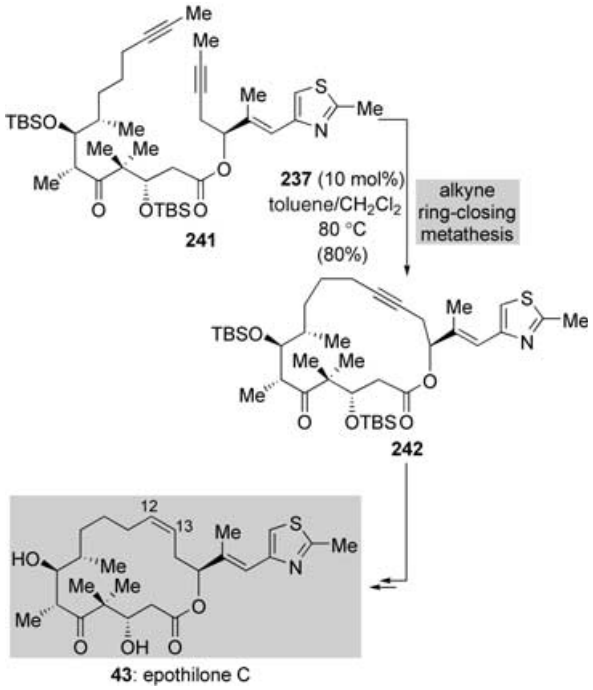
In the 20 or so years following its discovery, alkyne metathesis had found only sporadic and limited application in organic synthesis.[206] However, a groundbreaking report by the Fürstner group in 1998 detailing the first examples of alkyne ring-closing metathesis,[207,208] of which one is illustrated in Scheme 43, heralded a new era for this process. It is



Scheme 43. One of the first applications of alkyne ring-closing metathesis (Fürstner and Seidel, 1998).[207]

an indication of the rapid blossoming of the field that, even only a few years later, these first examples now appear extremely modest; nonetheless they remain highly instructive. Thus, the treatment of diyne **239** with a catalytic amount of the Schrock tungsten initiator **236** (5 mol%) in chlorobenzene at 80 °C led to smooth cyclization to generate the corresponding 12-membered cycloalkyne **240** in 73% yield. Several features of this reaction deserve further comment. First, terminal alkynes make poor substrates for alkyne-metathesis reactions as they deactivate the catalysts and are prone to polymerization. Thus, methyl-substituted alkynes are routinely employed, since not only are they sufficiently reactive, but the by-product (2-butyne), which has to be sacrificed, is volatile and easily removed. Secondly, systems smaller than 12-membered rings have not yet been formed in synthetically useful yields by alkyne ring-closing metathesis,[209] as a result of the geometric constraints of the alkyne unit and the resulting product strain; thus this process is restricted to macrocyclization reactions. Finally, an interesting and useful empirical observation is that alkyne ring-closing-metathesis reactions generally proceed even faster than those of the corresponding alkene ring-closing-metathesis macrocyclizations.

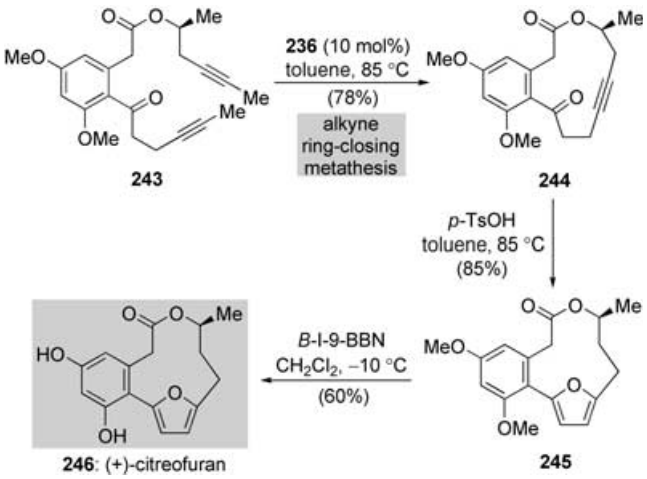
However, the real utility of alkyne ring-closing metathesis stems from the subsequent selective manipulations that are possible with the alkyne system thus formed. In particular, the combination of alkyne ring-closing metathesis followed by stereoselective partial reduction of the triple bond offers an efficient, though indirect, method for the preparation of macrocyclic alkenes of well-defined *E* or *Z* stereochemistry. As we have seen, alkene ring-closing-metathesis macrocyclization reactions are often plagued by the formation of geometrical isomers, with the product distribution often not being predictable and varying dramatically with seemingly subtle changes in precursor structure. This can often have disastrous consequences in terms of product isolation and yield, particularly if it occurs at a late stage in a multistep synthetic route. A case in point is the various approaches to the total synthesis of epothilone C **43** (see Scheme 10). Indeed, it is interesting to note that while three of the earliest total syntheses (those of the Nicolaou,[68] Danishefsky,[69] and Schinzer groups[71]) all employed successful, yet relatively nonstereoselective, alkene ring-closing-metathesis reactions to fashion the C12–C13 double bond; subsequent approaches have largely shied away from this protocol, employing instead more conventional olefination methods, which in this context allowed greater control of alkene stereochemistry.[210] Upon revisiting this problem, the Fürstner group postulated that the stereoselective formation of the coveted natural C12–C13 *Z* isomer of epothilone C could indeed be achieved by metathesis technology through the alkyne ring-closing metathesis of diyne **241** followed by hydrogenation in the presence of the Lindlar catalyst (Scheme 44). This system thus proved to be a significant testing ground for their nascent method. The team found that the desired macrocyclization could be effected in a pleasing 80% yield by treatment of substrate **241** with the



Scheme 44. Alkyne ring-closing metathesis in the total synthesis of epothilone C (**43**) (Fürstner and co-workers, 2001).[211]

trisamido molybdenum catalyst precursor **237** (10 mol%) in a toluene/CH_2Cl_2 solvent mixture at 80 °C for 8 h.[211] Only two more steps, one of which involved the chemo- and stereoselective semi-hydrogenation of the triple bond under Lindlar conditions, were then required to unveil the target compound **43**.[203b] Notably, the catalyst system rigorously distinguishes between the (reactive) alkyne moieties and the preexisting double bond present in the precursor **241**; indeed, a useful feature of alkyne metathesis is that alkene systems are generally inert toward the catalysts. The particular choice of catalyst system in this case was important, owing to its tolerance of both the sulfur and basic nitrogen atoms of the thiazole ring, the presence of which would have been deleterious to the use of the Schrock catalyst **236**.

The Fürstner group has applied this alkyne ring-closing metathesis/Lindlar reduction protocol in the stereocontrolled synthesis of a number of other macrocyclic natural products,[212] thus demonstrating the versatility, broad applicability, and mildness of this method. It is important to also recall the recent development of novel mild procedures for the conversion of alkynes into the corresponding *E*-alkene systems.[213,214] However, given the synthetic versatility of the alkyne group, it is only appropriate that other ways to elaborate the cycloalkynes formed by alkyne ring-closing metathesis besides simple hydrogenation procedures have begun to be investigated. The first foray into this territory was recently documented in the enantioselective synthesis of (+)-citreofuran (**246**, Scheme 45). Although not readily apparent

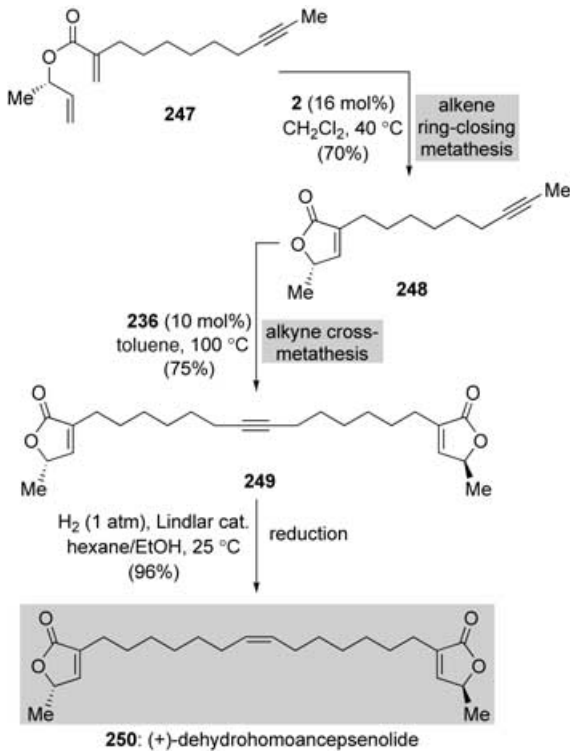


Scheme 45. Alkyne ring-closing metathesis in the enantioselective synthesis of (+)-citreofuran (**246**) (Fürstner and co-workers, 2003).[215]

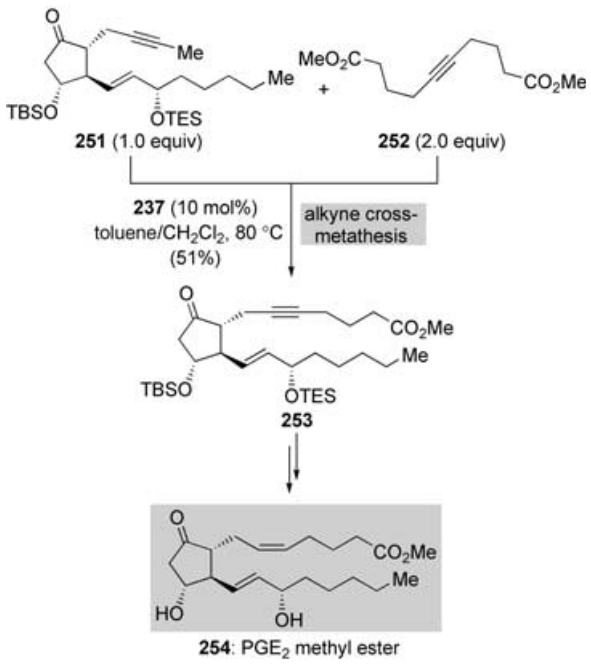
from a cursory inspection of the molecular structure of **246**, an alkyne-metathesis reaction was used to forge the macrocyclic ring system and to provide a handle for the construction of the furan ring.[215] Thus, as shown in Scheme 45, the readily prepared diyne **243** underwent smooth macrocyclization within 1 hour upon the addition of tungsten alkylidyne catalyst **236** (10 mol%) to a solution of the substrate in toluene at 85 °C to afford the 12-membered bicyclic product **244** in 78% yield. The relative ease of this cyclization is likely to be due, in part, to the presence of the preexisting aromatic ring, which restricts the conformational degrees of freedom available to the starting material **243**. Concomitantly, all the elements required for the formation of the furan ring had been installed during the cyclization. Hence, exposure of cycloalkyne **244** to acidic conditions rendered the somewhat strained triple bond susceptible to nucleophilic attack by the neighboring ketone group, thus initiating a transannular cycloaromatization event that led to the formation of tricyclic compound **245**.[216] With the complete skeleton of the target compound thus formed, the uneventful liberation of the phenolic hydroxy groups was all that was required to complete this concise total synthesis.[217] Notably, there is a particular strategic advantage associated with this order of ring construction (i.e. macrocycle then furan), namely that while the tricyclic framework of the natural product is in fact somewhat strained, the bulk of this strain energy is introduced during the kinetically favorable formation of a five-membered ring. In the alternative scenario (i.e. furan then macrocycle), the extra enthalpic energy barrier would have to be overcome during the macrocyclization event, which is inherently less favorable owing to entropic factors.[218]

4.2. Alkyne Cross-Metathesis

Alkyne cross-metathesis also holds great potential for selective and efficient carbon–carbon bond formation. To date, the major use of alkyne cross-metathesis has been in acyclic diyne metathesis (ADIMET) polymerization reactions, particularly in the preparation of poly(*p*-phenyleneethynylene) (PPE) type conjugated organic polymers which have a number of potentially useful applications.[219] Recently, however, the first applications in natural products synthesis have emerged. As with the corresponding alkene cross-metathesis reactions, for the purposes of categorization it is convenient to divide alkyne cross-metathesis into two broad classes: dimerization reactions and chain elongation processes. An example of the former process, which also nicely illustrates the current state of the art of metathesis catalyst design, is found in the concise approach to (+)-dehydrohomoancepsenolide (**250**, Scheme 46) reported by Fürstner and Dierkes.[220] Given the C_2 symmetry of the deceptively simple looking structure of the target compound, a reasonable retrosynthetic scission would appear to involve the breaking of the central *Z*-configured alkene, which would be fashioned in a stereoselective manner through the alkyne cross-metathesis of butenolide **248** followed by hydrogenation in the presence of the Lindlar catalyst. The key step in the formation of butenolide **248** was itself proposed to involve a metathesis event, namely the alkene ring-closing-metathesis reaction of enoate **247**. Indeed, it was found that this initial transformation could be effected by treatment of enoate **247** with the first-generation Grubbs catalyst **2** (16 mol%) in CH_2Cl_2 at reflux for 24 h. This reaction was superbly chemoselective and no competing enyne-metathesis side reactions were observed, which was due only to the modulated reactivity of the catalyst employed as the more active second-generation catalyst **3** failed to distinguish rigorously between the alkyne and alkene moieties of the precursor **247**. Furthermore, no co-catalytic



Scheme 46. Sequential alkene ring-closing-metathesis and alkyne-cross-metathesis reactions in the total synthesis of (+)-dehydrohomoancepsenolide (**250**) (Fürstner and Dierkes, 2000).[220]



Scheme 47. Alkyne cross-metathesis in the enantioselective synthesis of PGE_2 methyl ester (**254**) (Fürstner and co-workers, 2000).[222]

$Ti(OiPr)_4$ was required in this reaction, which is often not the case in ring-closing-metathesis reactions of similar substrates with the first-generation catalyst **2**.[221] Treatment of butenolide **248** with the Schrock catalyst **236** (10 mol%) in toluene at 100 °C effected its successful dimerization to give alkyne **249** in 75% yield, and a subsequent Lindlar hydrogenation completed the expedient total synthesis. The chemoselectivity was inverted in the second metathesis step; the catalyst employed this time selectively activated the triple bond at the expense of the alkene group. The lasting impact of this synthesis is its demonstration of the selectivity for different types of unsaturation within the same molecule that is now possible with the metathesis catalysts currently available.

The first examples of alkyne metathesis to effect chain elongation were also documented by the Fürstner group in their recent incursion into the field of prostaglandin synthesis.[222] As shown in Scheme 47, these researchers found that the selective cross-metathesis of cyclopentanone **251** (prepared through a three-component coupling reaction)[223] with an excess of symmetrical alkyne **252** could be achieved in the presence of complex **237** and CH_2Cl_2 (which serves as the activating agent) in toluene at 80 °C to provide the desired product **253** in 51% yield. No unwelcome side products derived through homodimerization of the starting material **251** were observed in this reaction, possibly as a result of steric effects. This transformation attests to both the excellent reactivity profile of the catalyst system, which again selectively engaged the alkyne units in the presence of both the alkene and the polar, coordinating ketone and ester groups, and the overall mildness of the method, leaving as it did the rather fragile β-hydroxyketone motif on the cyclopentane ring unscathed. While the synthetic potential of alkyne metathesis is undeniable, it will only be through its application in a wider variety of settings that a clearer picture of the generality and predictability of this process will emerge.[224]

5. Summary and Outlook

The emergence of metathesis reactions in chemical synthesis over the last few years has been rather dramatic. It has been delightful to review the field and highlight some of its most exciting applications in total synthesis. Indeed, the speed and imagination with which synthetic chemists have adopted the olefin-metathesis reaction and its siblings, the enyne- and alkyne-metathesis reactions, have been both remarkable and highly productive. Despite this progress, however, limitations do remain with these reactions. These shortcomings include the rather poor ability to predict and control the *E*/*Z* ratio of olefin products (except for small and common rings) and the rather large catalyst loading often necessary for reaction completion. Furthermore, more-efficient and practical chiral catalysts are needed to enable asymmetric processes.

Unquestionably, the early and stunning successes of these reactions will be followed by improvements in catalyst design that will overcome at least some of the above-mentioned problems and lead to even more spectacular applications. Furthermore, although the novelty of these reactions may wear off as time goes by, their power as tools in the minds and hands of creative synthetic chemists will always remain sharp as they attempt to solve more complex puzzles, whether posed by natural or designed molecules. It is also evident that

metathesis reactions are beginning to rival the venerable and more-established palladium-catalyzed cross-coupling reactions[4] as means to construct carbon–carbon bonds and as enablers of total synthesis. Equally crystal clear is the fact that together these discoveries have revolutionized the way synthetic chemists go about their business these days.

Abbreviations

Ac	acetyl
B-I-9-BBN	9-iodo-9-borabicyclo[3.3.1]nonane
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Cbz	benzyloxycarbonyl
Cp	cyclopentadienyl
Cy	cyclohexyl
1,2-DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMAP	4-dimethylaminopyridine
DME	ethylene glycol dimethyl ether
DMF	*N*,*N*-dimethylformamide
HPLC	high-pressure liquid chromatography
Mes	2,4,6-trimethylphenyl
MOM	methoxymethyl
Ms	methanesulfonyl
M.S.	molecular sieves
NAP	2-naphthylmethyl
Ns	4-nitrobenzenesulfonyl
*p*BrBz	4-bromobenzoyl
PCC	pyridinium chlorochromate
Phth	phthalimido
Piv	pivaloyl
PMB	4-methoxybenzyl
SEM	2-(trimethylsilyl)ethoxycarbonyl
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TMS	trimethylsilyl
Ts	4-toluenesulfonyl

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A General Model for Selectivity in Olefin Cross Metathesis

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Abstract: In recent years, olefin cross metathesis (CM) has emerged as a powerful and convenient synthetic technique in organic chemistry; however, as a general synthetic method, CM has been limited by the lack of predictability in product selectivity and stereoselectivity. Investigations into olefin cross metathesis with several classes of olefins, including substituted and functionalized styrenes, secondary allylic alcohols, tertiary allylic alcohols, and olefins with α-quaternary centers, have led to a general model useful for the prediction of product selectivity and stereoselectivity in cross metathesis. As a general ranking of olefin reactivity in CM, olefins can be categorized by their relative abilities to undergo homodimerization via cross metathesis and the susceptibility of their homodimers toward secondary metathesis reactions. When an olefin of high reactivity is reacted with an olefin of lower reactivity (sterically bulky, electron-deficient, etc.), selective cross metathesis can be achieved using feedstock stoichiometries as low as 1:1. By employing a metathesis catalyst with the appropriate activity, selective cross metathesis reactions can be achieved with a wide variety of electron-rich, electron-deficient, and sterically bulky olefins. Application of this model has allowed for the prediction and development of selective cross metathesis reactions, culminating in unprecedented three-component intermolecular cross metathesis reactions.

Introduction

Olefin cross metathesis (CM) is a convenient route to functionalized and higher olefins from simple alkene precursors. Cross metathesis has recently gained prominence due to the availability of catalysts with varied activities, such as **1**,[1] **2**,[2] and **3**[3] (Figure 1). These catalysts have expanded the variety of functional groups amenable to CM and have demonstrated the ability to prepare highly substituted olefins by CM, often in a stereoselective manner. The installation of structural elements within complex natural products and the synthesis of reagents for further synthetic transformations can now be accomplished by CM using active and functional group tolerant metathesis catalysts. However, cross metathesis remains an underrepresented area of olefin metathesis when compared to ring-opening metathesis polymerizations (ROMP)[4] and ring-closing metathesis (RCM).[5] This has been predominantly a result of several factors: first, low catalyst activity to effect a reaction without a strong enthalpic driving force (such as ring-strain release in ROMP) or the entropic advantage of intramolecular reactions (such as RCM), second, low product selectivity for the CM product, and, third, poor stereoselectivity in the newly formed olefin. While the development of increasingly active catalysts has resolved many of these concerns, the inability to accurately predict selectivity of cross metathesis reactions remains a pertinent issue for the practical application of cross metathesis.

By placing sterically large and electron-withdrawing groups near the reacting olefin, we expected to be able to improve CM product selectivity and stereoselectivity. As a result of our investigations with catalysts **1** and **2**, a significant number of new substrates classes that participate in selective olefin cross metathesis reactions have been discovered.[6] While a descriptive model of selective CM processes had not yet been disclosed,[7] we observed that several different types of olefins could be properly matched to provide highly selective CM reactions.

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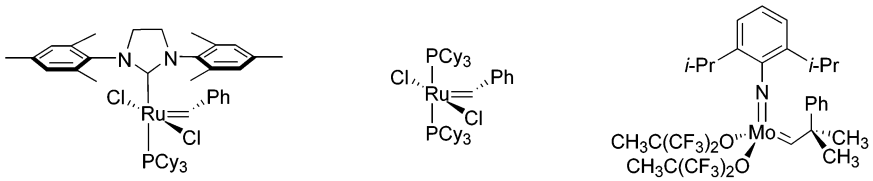


1 **2** **3**

Figure 1. Commonly used olefin metathesis catalysts.

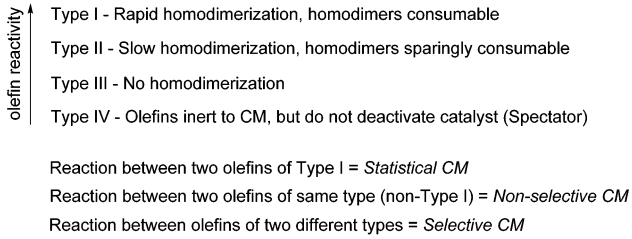


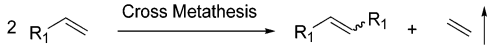
Figure 2. Olefin categorization and rules for selectivity.

These trends from our CM results, in addition to the trends derived from the rapidly expanding body of CM literature, provide the foundation for an empirical model for product selective CM. In this article, we will present a general model based on the categorization of olefin reactivity which can be used to predict both selective and nonselective cross metathesis reactions for a number of commercially available metathesis catalysts with varying activities.

Olefin Reactivity and Product Selectivity in Cross Metathesis. Given the various possible alkylidene intermediates and the numerous primary and secondary metathesis pathways involved in a cross metathesis reaction, it is difficult to accurately predict how the complex interplay of steric and electronic factors will determine the ability of various sets of olefins to participate in selective CM reactions. Due to the multitude of factors influencing olefin reactivity in cross metathesis, a more straightforward, empirical ordering or categorization of olefin reactivity is required. The most convenient way to rank olefin reactivity is to examine their ability to homodimerize (Scheme 1). However, instead of simply looking at the *absolute* ability of an olefin to undergo homodimerization, we looked at its ability to undergo homodimerization *relative* to other olefins and describe olefins on a gradient scale of their propensity to undergo homodimerization, and importantly, the subsequent reactivity of their homodimers. This analysis leads to a general model that comprises four distinct olefin types which can be used to predict both selective and nonselective CM reactions (Figure 2).

Type I olefins are categorized as those able to undergo a rapid homodimerization and whose homodimers can participate in CM as well as their terminal olefin counterpart. Type II olefins homodimerize slowly, and unlike Type I olefins, their homodimers can only be sparingly consumed in subsequent metathesis reactions. Type III olefins are essentially unable to be homodimerized by the catalyst but are still able to undergo CM with Type I and Type II olefins. Type IV olefins are not able to participate in CM with a particular catalyst but do not inhibit catalyst activity toward other olefins. Outside these categories are olefins that deactivate the catalyst. In general, a reactivity gradient exists from most active type (Type I olefin) to least active Type (Type IV), with sterically unhindered, electron-rich olefins categorized as Type I and increasingly

Scheme 1. Homodimerization in Cross Metathesis



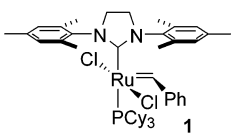
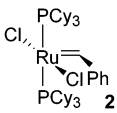
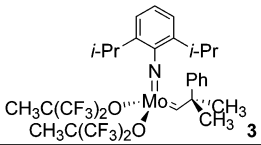
sterically hindered and/or electron-deficient olefins falling into Types II through IV.

Olefin Categorization for Metathesis Catalysts of Various Activities. Table 1 categorizes all reported CM substrates for catalysts **1**, **2**, and **3** and provides chemists with two basic functions. First, it provides a starting reference point for the design of potentially selective CM reactions. Second, for those working to develop more active metathesis catalysts, it provides a challenging set of olefins that are not active with current catalysts in CM (i.e., Type IV olefins). Up to this point, methodology developed in the area of olefin metathesis has been marked by repeated use of the most active catalyst available. While simple modification of the steric or electronic properties of an olefin (i.e., by choice of protecting groups) is often sufficient to change the reactivity of an olefin and result in a selective reaction, CM selectivity may also be achieved by simply choosing a catalyst with differing activity, as will be shown specifically in the case of styrene CM. Since these catalysts are commercially available, it is straightforward to employ the most selective catalyst. As new types of olefins are used in CM, assigning them an appropriate olefin type will allow them to be used more effectively in selective CM.

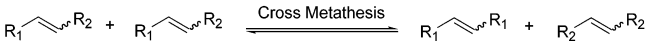
An olefin's general reactivity (as shown in Figure 2) with a given catalyst determines the role of secondary metathesis, that is, subsequent reactions of a product olefin with the propagating catalyst. Predicting the ability (or inability) of the catalyst to perform secondary metathesis on a newly formed CM olefin is important for the development of selective CM reactions. Efficient secondary metathesis occurs when all components in the reaction are readily accessible to the metal alkylidene complex, including homodimers and the CM product. The key to CM reaction selectivity is minimizing the number of undesirable CM side products (such as the homodimers of the starting olefins) either by avoiding their initial formation or by ensuring that they are fully consumed in secondary metathesis events. It is also important that the desired cross product not be redistributed into a statistical product mixture by these same secondary metathesis events.

Throughout this paper, examples of both selective and nonselective CM reactions with combinations of olefins from various types (categorized in Table 1) will be presented to illustrate how the general model shown in Figure 2 accounts for CM selectivity with a wide variety of substrates and how it can be used to predict selectivity in new CM reactions. Specific attention will be paid to how the manipulation of the rates of homodimerization and the role of secondary metathesis in CM through the modification of the steric and electronic properties

Table 1. Olefin Categories for Selective Cross Metathesis

Olefin type	 1	 2	 3
Type I (fast homodimerization)	terminal olefins,[6] 1° allylic alcohols, esters,[6h,20] allyl boronate esters,[6f] allyl halides,[6f,6i] styrenes (no large ortho substit.),[6c,d,f,i] allyl phosphonates,[6d] allyl silanes,[25] allyl phosphine oxides,[6h] allyl sulfides,[6h] protected allyl amines[6h]	terminal olefins,[8] allyl silanes,[14,18,19] 1° allylic alcohols, ethers, esters,[8,19,21] allyl boronate esters,[10f] allyl halides[17]	terminal olefins,[11a,b,12,14] allyl silanes[11b]
Type II (slow homodimerization)	styrenes (large ortho substit.),[6d,f] acrylates,[6b,i] acrylamides,[6c] acrylic acid,[6c] acrolein,[6b,24] vinyl ketones,[6b] unprotected 3° allylic alcohols,[6f,h] vinyl epoxides,[6b] 2° allylic alcohols, perfluorinated alkane olefins[6b,23]	styrene,[16] 2° allylic alcohols, vinyl dioxolanes,[8] vinyl boronates[8]	styrene,[11a,11b] allyl stannanes[15]
Type III (no homodimerization)	1,1-disubstituted olefins,[6a,g] non-bulky trisub. olefins,[6a,g] vinyl phosphonates,[6d] phenyl vinyl sulfone,[22] 4° allylic carbons (all alkyl substituents), 3° allylic alcohols (protected)	vinyl siloxanes[16]	3° allyl amines,[14] acrylonitrile[12]
Type IV (spectators to CM)	vinyl nitro olefins, trisubstituted allyl alcohols (protected)	1,1-disubstituted olefins,[8] disub. α,β-unsaturated carbonyls, 4° allylic carbon-containing olefins,[8] perfluorinated alkane olefins,[8] 3° allyl amines (protected)[14]	1,1-disubstituted olefins[11a]

Scheme 2. Equilibration of Cross Products



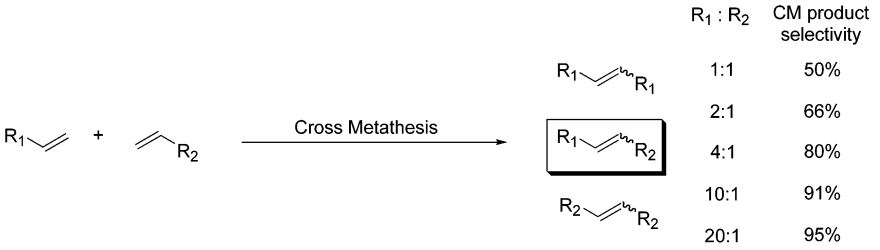
of an olefin or the appropriate choice of catalyst can lead to selectivity in cross metathesis.

Nonselective Cross Metathesis with Two Type I Olefins. When two Type I olefins are used in a CM reaction, the rates of homodimerization are similar and the reactivities of the homodimers and cross products toward secondary metathesis events are high. In these reactions, the desired cross product will be equilibrated with the various homodimers through secondary metathesis reactions (Scheme 2). This will result in a statistical product mixture. For these reactions, one must use nearly 10 equiv of one CM partner to provide 90% of the CM product (Scheme 3). More generally, when two olefins of the same type are combined, nonselective product mixtures are usually obtained. For example, two Type II olefins (such as methyl vinyl ketone and methyl acrylate) can react with each other but will generally undergo nonselective CM, albeit with reduced yields due to the lower overall olefin reactivity.[6e]

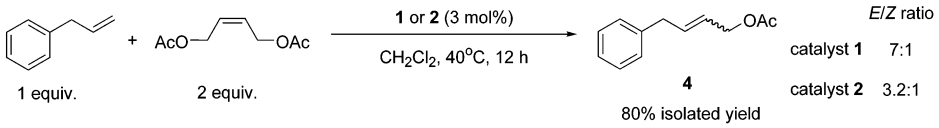
A good example of nonselective CM is the reaction of allylic alcohols using either catalyst **1** or **2** (Scheme 4). The CM reaction between allylbenzene and an allylic alcohol equivalent affords the CM product **4** in 80% isolated yield with either catalyst **1** or **2**, with good to moderate stereoselectivity. Since both reaction partners are Type I olefins, four allyl acetate equivalents are required to provide an 80% yield of the CM product. However, the reaction with catalyst **1** yields a much higher amount of the more thermodynamically favorable trans isomer, presumably due to secondary metathesis on the CM product formed in the reaction. Therefore, the increased trans ratio is simply an effect of the higher activity of catalyst **1** toward the product than catalyst **2**. This brings up the complicated and multifaceted role of secondary metathesis. As will be shown in subsequent sections, in some instances, we observe good product selectivity due to the stability of the cross product toward redistribution by secondary metathesis but poor stereoselectivity due to the inability of the cross product to readily undergo cis/trans isomerization via these same secondary metathesis processes.

Selective Cross Metathesis. To avoid the statistical product distributions produced by these inefficient reactions, one can design selective CM reactions using olefins from two different types, whose rates of dimerization are significantly different and/or slower than CM product formation. The first approach toward selective CM involves the reaction of a Type I olefin with a less reactive Type II or Type III olefin that undergoes homodimerization at a significantly lower rate, if at all. In this reaction, although the Type I olefin may initially homodimerize, the product distribution is driven toward the desired cross product as ethylene is driven from the system (preventing the regeneration of terminal olefins) and the Type I homodimer readily undergoes secondary metathesis with the Type II/III olefin (Scheme 5). This desired cross product will not be

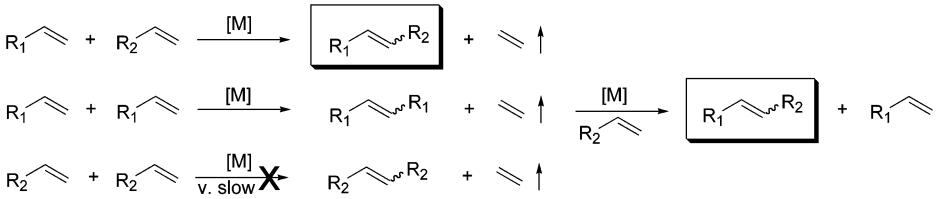
Scheme 3. Statistical Distribution of CM Products



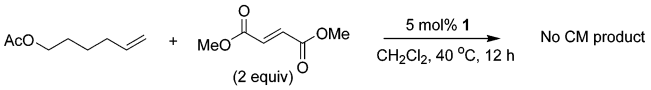
Scheme 4. Nonselective Olefin Cross Metathesis



Scheme 5. Primary Reactions in Cross Metathesis of Type I with Type II/III



Scheme 6. Cross Metathesis of Type I Olefin with Methyl Fumarate



equilibrated to a statistical product mixture due to the inability of the catalyst to efficiently convert the cross product to other products (i.e., the homodimer of the Type II/Type III olefin) via secondary metathesis.

Selective Cross Metathesis of Type I with Type II Olefins. For example, reactions between Type I terminal olefins and Type II olefins such as α,β-unsaturated carbonyl olefins, including acrylates, acrylamides, acrylic acid, and vinyl ketones result in highly selective CM reactions with high stereoselectivity (E/Z > 20:1).[6b,c] In this case, methyl acrylate is a Type II olefin because it undergoes homodimerization to a small extent under the reaction conditions, allowing for selective reactions with Type I olefins.[6b] To illustrate the low reactivity of the homodimers of these Type II olefins, when methyl fumarate, the trans homodimer of methyl acrylate, is resubjected to catalyst **1** and 5-hexenyl acetate, no CM product is observed (Scheme 6). This is similar to our previously reported results using the homodimer of 2-vinyl-1,3-dioxolane with catalyst **2**.[8]

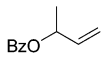
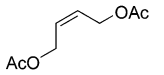
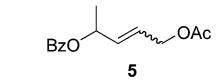
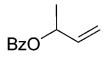
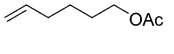
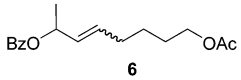
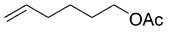
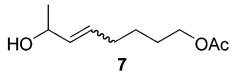
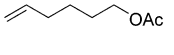
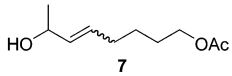
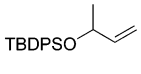
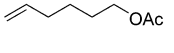
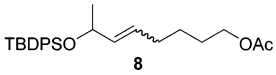
Secondary allylic alcohols are another class of Type II olefins which can be utilized in CM with moderate to high cross product yields and good stereoselectivity[8] without using large stoichiometric excesses of one reagent (Table 2). It is interesting that the addition of a methyl group at the allylic position leads to much greater trans selectivity, compared to the 7:1 E/Z ratio obtained with a primary allylic alcohol. Similar results were also obtained using catalyst **2**.[8] Interestingly, most of the trans selectivity obtained in entry 1 is retained when a simple α-olefin is used in the reaction (entry 2). We decided to also investigate if protecting groups were required to provide stereoselectivity in this system, similar to our previous work with catalyst **2**.[8] We hypothesized that increasing steric bulk through the addition of protecting groups would decrease CM reactivity but would increase the trans selectivity. Interestingly, although the reactivity trends were as expected, the product stereoselectivity trends were opposite to our hypothesis. Greater selectivity was observed with the unprotected alcohol (entry 3) than with a bulky protecting group, such as a *tert*-butyldiphenylsilyl ether (Entry 5). It is not clear why a smaller protecting group (entry 2 vs entry 5) allows for greater trans selectivity but may in part be due to greater steric accessibility of the cross product with the smaller protecting group to isomerization via secondary metathesis.

Selective Cross Metathesis of Type I with Type III Olefins. During the course of our earlier studies with catalyst **2**, we found that olefins with fully substituted allylic carbons/quaternary centers did not participate in CM.[8] They did not eliminate activity of the catalyst but simply did not participate in the reaction (Type IV). However, due to the greater activity of catalyst **1**, CM reactions of quaternary allylic olefins with α-olefins are now possible with excellent stereoselectivity due to their great steric bulk (Table 3). These reactions are useful because they are able to install highly substituted carbons in a stereodefined manner.

We were pleased to discover that these reactions are the first example of exclusive trans olefin selectivity in CM based solely on the sterics of alkyl substituents. For example, an unprotected tertiary alcohol (entry 1) provides an excellent yield of the CM product with only the trans isomer observed by ^{1}H NMR. Alkyl substituents have also been explored in the reaction and work quite nicely with catalyst **1** with a variety of terminal olefins (entries 2 and 3). There are several key differences observed when comparing the selectivity of tertiary allylic substrates in CM (Table 2) with quaternary allylic substrates (Table 3). While the steric bulk of tertiary allylic substrates leads to the initial

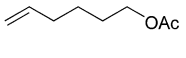
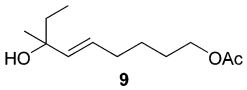
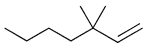
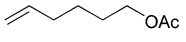
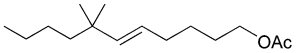
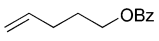
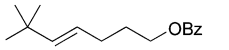
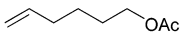
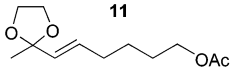
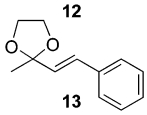
(8) Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58.

Table 2. Secondary Allylic Alcohol Cross Metathesis

Entry	2° Allylic Alc.	Cross Partner (Equiv)	Product	Iso. Yield (%)	E/Z ratio[a]
1		 (1.8)	 **5**	38	18:1
2		 (2.0)	 **6**	82	10:1
3		 (2.0)	 **7**	92	13:1
4		 (1.0)	 **7**	50 62[b]	14:1 14:1
5		 (0.5)	 **8**	53	6.7:1

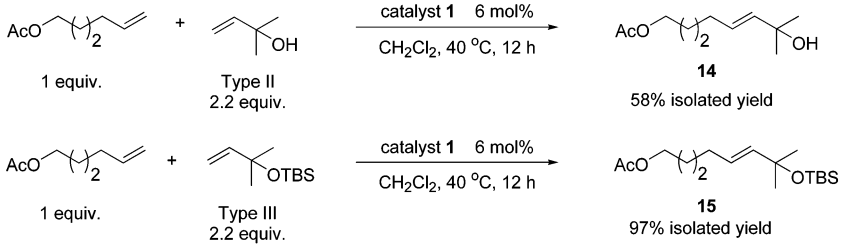
[a] Determined by ^{1}H NMR. [b] Reaction performed at 23 °C.

Table 3. Quaternary Allylic Olefin Cross Metathesis[a]

Entry	4° Allylic Olefin	Equiv.	CM Partner	Product	Isolated Yield[b] (%)
1		2.0		 **9**	93
2		2.0		 **10**	90
3		excess		 **11**	99
4		1.0		 **12**	91
5		2.0		 **13**	70

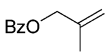
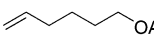
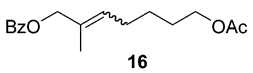
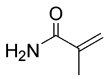
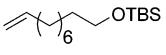
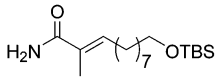
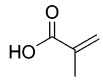
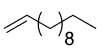
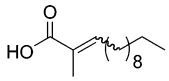
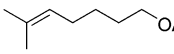
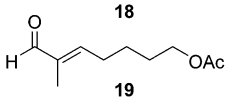
[a] 3−5 mol % of catalyst **1** used, CH_2Cl_2, 40 °C, 12 h. [b] Only *E* isomer observed by ^{1}H NMR.

Scheme 7. Altering Cross Metathesis Selectivity Using Steric Effect



formation of moderately trans product distribution, it also hinders secondary metathesis with the result being moderate trans selectivity. However, the greater steric bulk of the quaternary allylic substrates presumably leads to the initial formation of an exclusively trans product distribution which is unchanged by secondary metathesis events. In addition, the homodimerization of the quaternary allylic olefins is negligible in many cases, allowing for greater CM product selectivity. For example, with 2-methyl-2-vinyl-1,3-dioxolane (Table 3, entries 4 and 5), there was no observation of the dimer of the cyclic ketal, characteristic of a Type III olefin. However, when the tertiary alcohol in entry 1 was used in the CM at 40 °C, there was a background dimerization of the tertiary alcohol. When a similar tertiary alcohol was used, a reduced yield of CM product was observed (Scheme 7). In addition, the independent dimerization of this tertiary allylic alcohol can be performed in excellent yields. However, if this isolated dimer is subsequently reacted with a terminal olefin, no CM product is observed. This indicates that once the dimer is formed, it does not undergo secondary metathesis presumably due to steric bulk. In addition, we found homodimers of olefins with tertiary allylic carbons were not accessible for secondary metathesis either. As a result of these observations, unprotected tertiary allylic alcohols can be considered to be Type II olefins. Interestingly, this undesired dimerization could be suppressed to a large extent by increasing steric bulk via the addition of a silyl protecting group, effectively

Table 4. Cross Metathesis of 1,1-Disubstituted Olefins

Entry	1,1-disub.	CM partner (equiv.)	Product	Isolated Yield (%)	*E/Z* ratio[a]
1		 (2.0)	 **16**	80	4:1
2		 (1.2)	 **17**	71	>20:1
3		 (1.1)	 **18**	23	4:1
4		 (1.0)	 **19**	97	>20:1

[a] Determined by ^{1}H NMR, confirmed by ^{1}H NMR NOE experiments.

changing the substrate to a Type III olefin (Scheme 7). This simple substrate modification results in increased CM selectivity by suppressing the unwanted homodimerization side reaction. These reactions represent the control of product and stereoselectivity in CM based purely on steric considerations, which may be manipulated through the judicious choice of protecting groups.

Other examples of CM with Type III olefins, such as 1,1-disubstituted olefins, using catalyst **1** are shown in Table 4.[6a,b] Even functionalized 1,1-disubstituted olefins are excellent substrates for CM which can give high stereoselectivity (Table 4, entries 2 and 4). Highly active catalyst **1** has also been shown to perform secondary metathesis on trisubstituted prenyl olefins[6g] (Entry 4) allowing for a regio- and stereoselective formal allylic oxidation of one of the terminal methyl groups. The reason methacrylic acid (entry 3) gives relatively poor yield and *E*/*Z* ratio is unclear. The results in Table 4 demonstrate the ability to use olefins with functionalities of several different oxidation states in the CM reactions.

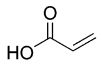
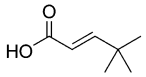
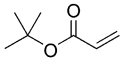
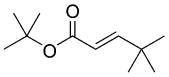
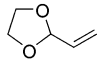
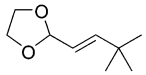
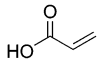
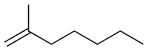
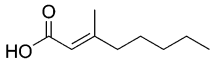
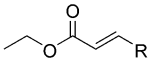
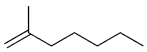
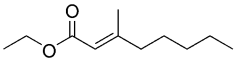
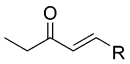
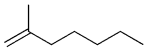
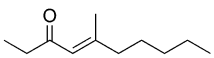
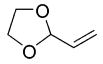
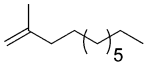
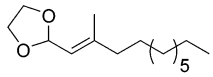
Selective Cross Metathesis of Type II with Type III Olefins. A second approach to selective CM processes utilizes two olefins which *both* dimerize at much slower rates than the formation of productive cross-metathesis product. The inability of Type III olefins to homodimerize allows them to also undergo selective reactions with Type II CM partners. In these reactions, formation of cross product dominates if the rates of homodimerization of Type II olefins and secondary metathesis of the CM products are very slow. For example, most 1,1-disubstituted olefins will readily perform selective CM with terminal (Type I) olefins as well as acrylates[6e] (Type II) and acrolein acetals[6a] (Type II) but will not homodimerize. However, given the low reactivity of some Type III olefins, reduced CM yields may be obtained. Also, since the undesired dimers of Type II olefins are essentially inactive for further CM (unlike Type I dimers), stoichiometric excesses of the less reactive Type III olefin may be required to produce high yields of cross product, such as the CM of acrylates carried out in neat isobutylene.[6g]

In a similar manner, cross metathesis was carried out in neat 3,3-dimethyl-1-butene to drive the CM between the Type III olefin and various Type II olefins (Table 5, entries 1−3). Entries 5 and 6 illustrate the importance of the relative rates of dimerization of the Type II olefins. Even with 4 equiv of 2-methyl-1-heptene (Type III), the rates of dimerization of ethyl acrylate (Type II) and ethyl vinyl ketone (Type II) compete with the CM formation, resulting in a considerable amount of homodimer side products. However, by capping with a β-methyl group, the dimerization is suppressed and higher selectivity toward CM product is obtained. Another strategy is to utilize slow addition of the Type II olefin in order to maintain a low concentration of the more reactive Type II olefin, thereby, minimizing the amount of dimerization (Table 5, entry 7).

Cross Metathesis with Olefins that Bridge Type Categories. While protection of tertiary allylic alcohols has been shown to change their CM behavior leading to enhanced CM selectivity, other olefins, such as styrenes, bridge the broad type categories outlined previously. The CM behavior of styrenes depends strongly on their substitution patterns, providing far more flexibility in terms of functionalization/substitution and catalyst choice in order to achieve selective reactions. Styrenes represent one of the classes of olefins used widely in CM with ill-defined catalyst systems,[9] as well as **2**[10] and **3**,[11] because of high trans selectivity in the CM product. In all these cases, the dimerization of styrene to stilbene was reported to be slow, allowing for moderate to good selectivities in CM (Type II). However, catalyst **1** showed a significantly different reactivity and prompted further investigation into this family of CM substrates. For example, with 2.5 mol % of catalyst **1**, the dimerization of styrene to *E*-stilbene was achieved in 94% isolated yield. Consequently, the CM reaction of styrene with a terminal olefin employing catalyst **1** produces a statistical product distribution (Table 6, entry 1) and is different from the results using catalyst **3**, as reported by Crowe and Zhang (entry 2).[11] To confirm that homodimerized styrene can undergo efficient secondary metathesis during CM with catalyst **1**, *E*-stilbene was successfully used as a styrene surrogate in CM with an allylic acetate equivalent (Entry 7). The reaction produced a statistical ratio of CM products. This is unprec-

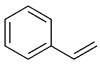
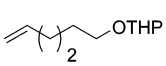
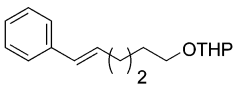
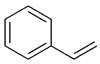
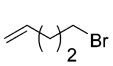
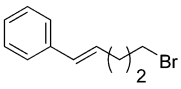
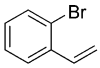
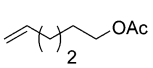
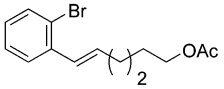
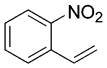
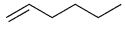
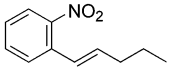
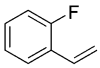
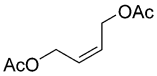
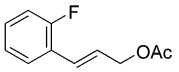
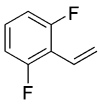
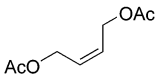
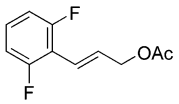
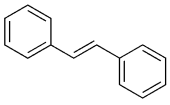
(9) Warwel, S.; Winkelmuller, W. *J. Mol. Catal.* **1985**, *28*, 247.
(10) (a) Feher, F. J.; Soulivong, D.; Eklund, A. G.; Wyndham, K. D. *Chem. Commun.* **1997**, 1186. (b) Biagini, S. C. G.; Gibson, S. E.; Keen, S. P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2485. (c) Huwe, C. M.; Woltering, T. J.; Jiricek, J.; Weitz-Schmidt, G.; Wong, C.-H. *Bioorg. Med. Chem.* **1999**, 773. (d) Seshadri, H.; Lovely, C. J. *Org. Lett.* **2000**, *2*, 327. (e) Eichelberger, U.; Mansourova, M.; Henning, L.; Findeisen, M.; Giesa, S.; Muller, D.; Welzel, P. *Tetrahedron* **2001**, *57*, 9737. (f) Yammamoto, Y.; Takahashi, M.; Miyaura, N. *Synlett* **2002**, 128.
(11) (a) Crowe, W. E.; Zhang, Z. J. *J. Am. Chem. Soc.* **1993**, *115*, 10998. (b) Crowe, W. E.; Goldberg, D. R.; Zhang, Z. J. *Tetrahedron Lett.* **1996**, *37*, 2117.

Table 5. Cross Metathesis between Type II and Type III Olefins

Entry	Type II	Type III (Equiv)		Product	Isolated Yield (%)
1			(neat)		73
2			(neat)		73
3			(neat)		75
4			(4.0)		83[a]
5			(4.0)		55[a] R=H 83[a] R=Me
6			(4.0)		26[a] R=H 68[a] R=Me
7			(1.0)		67[b]

[a] $E/Z = 2$ determined by ^{1}H NMR, confirmed by ^{1}H NOE experiments. [b] Vinyldioxolane (3 equiv) added slowly in four equal parts over a 6 h period. $E/Z = 3$ determined by ^{1}H NMR, confirmed ^{1}H NOE experiments.

Table 6. Cross Metathesis of Styrenes with Terminal Olefins

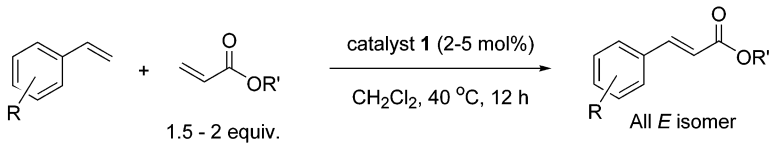
Entry	Catalyst	Aromatic Olefin	Cross-Partner	Aromatic : CM Partner	Product[a]	Isolated Yield (%)
1	**1**			1 : 1 4 : 1		47 71
2	**3**			2 : 1		90
3	**1**			1 : 1 3 : 1		80 98
4	**3**			2 : 1		48
5	**1**			1 : 2		98
6	**1**			1 : 2		50
7	**1**			1 : 1.2		51

[a] Only *E* isomer observed by ^{1}H NMR.

edented since catalysts **2** and **3**, as well as ill-defined catalysts, are not able to efficiently use stilbene as a CM partner, providing another example of the unique reactivity of catalyst **1**. These results clearly indicate that styrene is a Type I olefin for the more active catalyst **1**; however, for catalyst **3** employed by Crowe and Zhang, styrene is a Type II olefin. Styrene CM clearly demonstrates how matching the olefin with an appropriate catalyst (shown in Table 1) can be equally as important as matching olefins in order to achieve selective CM.

In addition to the possibility of using a less active catalyst to

Table 7. Styrene Cross Metathesis with Acrylate Esters



Entry	R	R'	Isolated Yield (%)[a]
1	H	CH_3	92
2	2,4-Dimethyl	CH_2CH_3	87
3	2,4,6-Trimethyl	CH_2CH_3	5[b]
4	2-CF_3	CH_2CH_3	44
5	3,4-Dimethoxy	*n*-Butyl	89
6	4-NO_2	CH_3	89
7	4-CHO	CH_2CH_3	83
8	2-F	CH_2CH_3	72
9	2-Cl	CH_2CH_3	62
10	2-Br	CH_2CH_3	49
11	2,6-Difluoro	CH_2CH_3	15[b]

[a] Only *E* isomer observed by ^{1}H NMR. [b] Determined by ^{1}H NMR.

achieve selectivity, alterations in styrene structure allow for selective CM reactions with terminal olefins using catalyst **1**, by changing styrene from a Type I olefin to a Type II or Type III olefin. For example, the use of 2-bromostyrene as the CM partner leads to selective formation of the CM product (entry 3). By simply using an excess of this substituted styrene, we achieved near quantitative conversion of hexenyl acetate. In the case of 2-bromostyrene, both the steric bulk of the bromine atom and its electron-withdrawing character contribute to make it a Type II olefin. Crowe and Zhang also were able to incorporate *ortho*-substituted styrenes in CM with catalyst **3** but found that their reactivity is low with terminal olefins (entry 4).[11] This may be due to low catalyst activity toward electronic-deficient styrene substrates, since the accompanying terminal olefin was dimerized efficiently. Due to the higher reactivity of **1**, we only observed reduced activity when *multiple* electron-withdrawing substituents were present. For example, 2,6-difluorobenzene was subjected to CM conditions, and only moderate yields of CM product were isolated (entry 6).

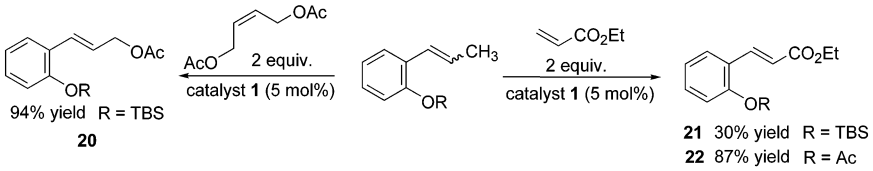
With the differences in reactivity observed with substituted styrenes, we began to investigate CM of styrenes with a variety of non-Type I olefins. We had previously disclosed that a variety of Type II olefins such as α,β-unsaturated esters, amides, ketones, and acids are excellent CM partners with terminal olefins.[6b,c] In addition, it has been demonstrated by Crowe and Goldberg that CM of π-conjugated olefins, such as acrylonitriles, was not compatible with CM with styrenes using catalyst **3** because they possessed similar electronic properties. They suggested that CM required matching of a more nucleophilic, electron-rich olefin with either styrene or acrylonitrile.[12] However, in contrast to Crowe's work with catalyst **3**, we found that styrenes are excellent CM partners with electron-deficient α,β-unsaturated carbonyls, such as acrylates using catalyst **1** (Table 7). This CM complements Wittig or Horner−Wadsworth−Emmons chemistry since unprotected benzaldehydes work well (entry 7). Similar results were also obtained using acrylamides and vinyl phosphonates as the "enone" component.[6c,d,i]

We discovered that the reactivity trends of styrenes were different in these CM reactions when compared to terminal olefin CM in Table 6. While Type I styrenes (Table 7, entries 1 and 6) were excellent CM partners with acrylates, it was observed that *ortho*-substituted styrenes that did not dimerize readily (Type II or Type III olefins) were also not good CM partners with acrylates (entries 3−4, 9−11). Simple *ortho*-alkyl groups did not reduce the reaction yield with acrylates (entry 2); however, when electron-withdrawing functionalities (entry 4) or significant steric bulk (entry 3) was added to the *ortho* position, CM yields fell dramatically due to the low reactivity of both cross partners with the catalyst. Therefore, for proper CM selectivity, the two olefins in CM need to have a difference in rate of reaction with the metal alkylidene complex (e.g., the olefins must be of different types and, preferably, one should be able to readily react with the catalyst to make an active alkylidene).

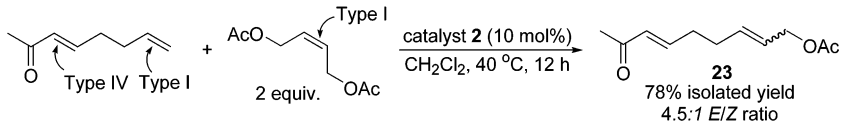
As additional evidence for alteration in styrene reactivity based on substitution patterns, we investigated *ortho*-phenol styrene derivatives. These are interesting substrates for catalytic reactions, since several *ortho*-phenol derivatives form stable benzylidene complexes.[13] However, instead of inhibiting catalyst activity, a variety of protected phenols are active for catalytic CM (Scheme 8). We found that small protecting groups, such as acetate, allowed for excellent CM with acrylates (Type I +

(12) Crowe, W. E.; Goldberg, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 5162.

Scheme 8. *ortho*-Phenol Cross Metathesis

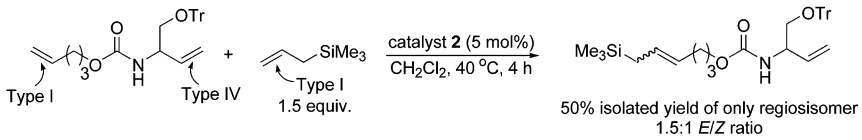


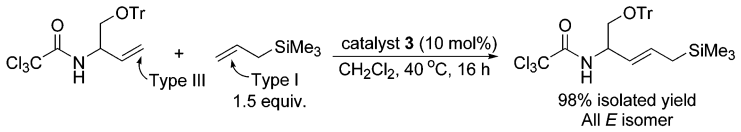
Scheme 9. Chemoselective CM Based on Olefin Categorization



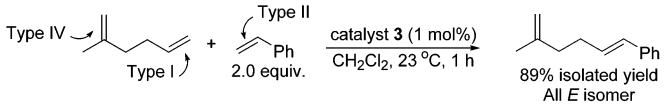
Scheme 10. Chemoselective Cross Metathesis Using Catalysts 2 and 3

(A) *Blechert, et al.*





(B) *Crowe and Zhang*



Type II, respectively). The balance of the material in this reaction was recovered as the stilbene dimer. This protection pattern is similar to other unhindered styrenes in Table 4. However, when a larger protecting group is employing, such as *tert*-butyldimethylsilyl, CM of the hindered styrene with acrylate (Type III + Type II, respectively) gives poor yields. In contrast, the reaction provides a very good yield with allyl acetate equivalents (Type III + Type I, respectively). In this case, this substrate reacts like Type III due to steric bulk and is very selective in CM with Type I α-olefins. Collectively, the disclosed work in styrene CM provided an important contribution to the development of the categorization model described in this paper. Both the steric and/or electronic effects of substituents on the styrene, as well as the catalyst choice, can be manipulated to achieve CM selectivity.

Regioselective and Chemoselective Cross Metathesis. The model outlined so far provides a foundation for predicting product selectivity in CM, but it also can be applied to the prediction of chemoselective CM, which is critical for differentiating olefins in the synthesis of complex molecules. The CM of a Type I or Type II olefin in the presence of a Type IV olefin is a good example of this type of chemoselectivity. For example, using catalyst **2**, a disubstituted α,β-unsaturated carbonyl containing olefin (Type IV) is not affected, allowing for selective reactions between a Type I olefin dimer and a Type I olefin (Scheme 9).

Importantly, the CM model outlined in Figure 2 also is consistent with results previously reported by other groups. For example, Blechert, et al. used steric constraints and heteroatom functionality to demonstrate that a highly substituted allylamine (Type IV for catalyst **2**) could be benign to CM in the presence of two Type I olefins (Scheme 10).[14] Interestingly, in the same report by Blechert, catalyst **3** was used to effect a highly selective CM reaction of that protected allylamine (Type III for catalyst **3**) with allylsilanes (Type I) in excellent yield (Scheme 10). In addition, this is one of the first examples of using steric bulk at the allylic carbon to obtain high olefin stereoselectivity and is comparable to the results we observed in Tables 1 and 2 with catalyst **1**.

Similarly, Crowe and Zhang performed a selective CM between a Type I terminal olefin and styrene (Type II for catalyst **3**) in the presence of a 1,1-disubstituted olefin (Type IV).[11a] As demonstrated previously in our lab,[6a,g] with the more active catalyst **1**, 1,1-disubstituted olefins are a Type III olefin

(13) (a) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168. (b) Wakamatsu, H.; Blechert, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2403.

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(18) Faure, S.; Piva-Le Blanc, S.; Piva, O. *Tetrahedron Lett.* **1999**, *40*, 6001.
(19) Langer, P.; Holtz, E. *Synlett* **2001**, 110.
(20) Zhang, L.; Herndon, J. W. *Tetrahedron Lett.* **2002**, *43*, 4471.
(21) Maishal, T. K.; Sinha-Mahapatra, D. K.; Paramjape, K.; Sarkar, A. *Tetrahedron Lett.* **2002**, *43*, 2263.
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(23) Imhof, S.; Randl, S.; Blechert, S. *Chem. Commun.* **2001**, 1692.
(24) BouzBouz, S.; Cossy, J. *Org. Lett.* **2001**, *3*, 1451.
(25) BouzBouz, S.; De Lemos, E.; Cossy, J. *Adv. Synth. Catal.* **2002**, *344*, 627.

Scheme 11. Three Component Olefin Cross Metathesis

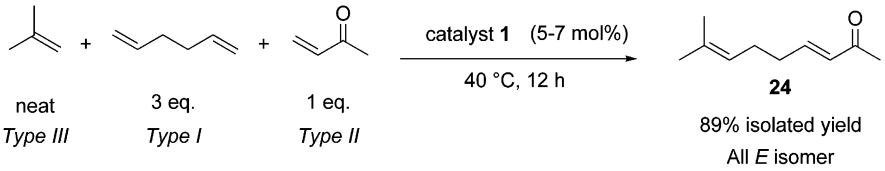
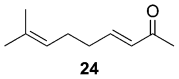
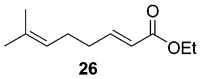
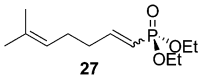
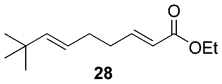
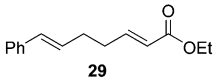
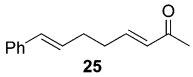


Table 8. Three Component Olefin Cross Metathesis[a]

Entry	Method[d]	CM partner Y	CM partner Z	Ratio (Diene:Y:Z)	Product	Isolated Yield (%)
1	A			3:neat:1	 **24**	89
2	A			3:neat:1	 **26**	60
3	A			3:neat:1	 **27**	57[b]
4	A			1:neat:1	 **28**	67[c]
5	B			1:3:1	 **29**	34
6	B			2:3:1	 **25**	47

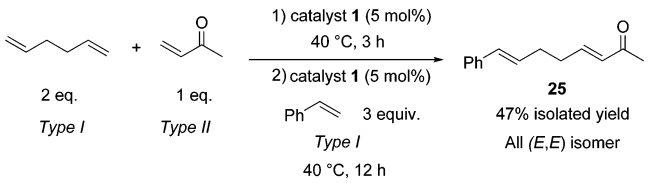
[a] Using 5−7 mol % of **1** in 0.1−0.2 M refluxing CH_2Cl_2, 12 h. [b] E/Z = 8:1 by ^1H NMR. [c] Reaction at 23 °C. [d] Method A = added all components at one time. Method B = added component Z and then added component Y after 4 h.

that is active for CM to form trisubstituted olefins. This shows that while more active catalysts have a larger set of CM active olefins (Type I, II, III), it is useful to identify Type IV olefins for less active catalysts, to help elucidate possible chemoselective CM reactions (Scheme 10). While electronic and steric parameters of olefins account as key contributing factors in ways olefins are classified, other factors are often implied in determining selectivity, including chelating ability of certain functional groups to metal catalysts. For example, the effects of carbonyl groups, such as acetate protecting groups, and allylic heteroatoms have been implied to alter reactivity in CM. It is for these reasons that a comprehensive empirical model is necessary that can simplistically account for all of these observations in the CM methodology literature.

Three-Component Cross Metathesis Reactions. In addition to describing selectivity in the simple homologation of two olefins in a CM reaction, the olefin classification in Table 1 also provides an opportunity to develop new reactions, such as multicomponent processes. While a three-component reaction has always been theoretically possible, the large mixture of compounds that would form via nonselective processes has made this a challenging method to develop. However, with the current model of selective CM described here, two important concepts have been learned. First, under selective CM conditions, secondary metathesis of the resulting olefins can be significantly slower than productive CM. Second, by using two olefins that do not perform CM with each other or do so only very slowly, then a third diene-containing olefin can be functionalized at both olefinic sites to provide an unsymmetrical product (Scheme 11).

In such a reaction, olefins of three different types may be converted predominantly into one product as a single stereoisomer. This reaction is successful because the Type III and Type II olefins react at a much slower rate with each other than their respective reactions with the Type I olefin. In addition, the product olefin from the diene-methyl vinyl ketone CM does not readily undergo secondary metathesis reactions with isobutylene, allowing for a selective reaction.

Scheme 12. One-Pot Three Component Olefin Cross Metathesis



The formation of a kinetic CM product also allows for chemoselective coupling, where a one-pot sequential CM reaction can occur (Scheme 12). For example, if two CM partners that can react with each other are used in a three-component reaction, such as styrene and methyl vinyl ketone, then a sequential addition strategy is necessary to avoid the unwanted side reaction between these components. Using these two types of three-component CM reactions, a variety of asymmetrically substituted dienes have been prepared (Table 8). These reactions illustrate the use of olefin categorization to effectively predict proper three-component reactivity. In theory, any combination of a Type I diene with a Type II and a Type III olefin would provide a three-component product (Method A, entries 1−4). As mentioned previously, if two Type I olefins need to be coupled, then this coupling must be performed after coupling of the Type II olefin (Method B, entries 5 and 6). The reactions add a new level of complexity to olefin metathesis

reactions and are possible due to development of a better understanding of CM reactivity patterns.

Conclusions

In conclusion, a general empirical model for olefin reactivity in cross metathesis has been developed for the prediction of CM selectivity, in terms of olefin product selectivity, regioselectivity, and chemoselectivity. A general ranking of olefin reactivity in CM is achieved by categorizing olefins by their relative ability to undergo homodimerization via cross metathesis and the susceptibility of their homodimers toward secondary metathesis reactions. Product selectivity can be achieved by suppressing the rate of homodimerization of one component and controlling the rate of secondary metathesis on the desired cross product. These rates can be controlled through the choice of olefins with significantly different activities, which can be modified by altering their steric and electronic properties through substituents, functionalities, or protecting groups. In addition, an appropriate choice of olefin metathesis catalyst is critical for product selectivity, regioselectivity, or chemoselectivity. This empirical approach toward understanding cross metathesis selectivity by categorizing the reactivity provides a convenient starting point for the prediction and design of new, selective CM reactions, such as multicomponent CM processes.

Experimental Section

General Information. Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Flash column chromatography was performed using silica gel 60 (230−400 mesh) from EM Science. All other chemicals were purchased from the Aldrich or TCI America and used as delivered unless noted otherwise. CH_2Cl_2 was purified by passage through a solvent column prior to use. Catalyst **1** and **2** were stored and manipulated on the bench. NMR spectra were recorded on a Varian Mercury 300 MHz NMR.

Representative Procedure. Olefin A (1.0 mmol) and Olefin B (1.0 mmol) were added via syringe to a stirring solution of **2** (0.05 mmol, 5.0 mol %) in CH_2Cl_2 (2.5 mL). The flask was fitted with a condenser and refluxed under nitrogen for 12 h. The reaction mixture was then reduced in volume to 0.5 mL and purified directly on a silica gel column (2 × 10 cm), eluting with hexane:ethyl acetate (500 mL).

Representative Procedure Using One Olefin as Solvent. Olefin A (0.28 mmol) was added via syringe to a stirring solution of **1** (18 mg, 0.021 mmol, 7.6 mol %) in 3,3-dimethylbutene (1.5 mL, excess) under a nitrogen atmosphere. The flask was stirred under a continuous flow of nitrogen for 12 h at room temperature (23 °C). The reaction mixture was then reduced in volume to 0.5 mL and purified directly on a silica gel column (2 × 10 cm), eluting with hexane:ethyl acetate to provide cross product.

Compound 4. *cis*-2-Butene-1,4-diacetate (160 μL, 1.0 mmol) and allylbenzene (55 μL, 0.50 mmol) were added simultaneously via syringe to a stirring solution of **2** (11 mg, 0.014 mmol, 2.7 mol %) in CH_2Cl_2 (2.5 mL). The flask was fitted with a condenser and refluxed under nitrogen for 12 h. The reaction mixture was then reduced in volume to 0.5 mL and purified directly on a silica gel column (2 × 10 cm), eluting with 9:1 hexane:ethyl acetate (500 mL). Pale oil was obtained (76 mg, 80% yield, *trans*/*cis* as determined by integration of peaks at 4.73 and 4.55 ppm). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.34−7.17 (5H, m), 5.92 (1H, m), 5.65 (1H, m), 4.55 (2H, app d), 3.41 (2H, d, J = 3.3 Hz), 2.06 (3H, unresolved s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 171.4, 135.1, 134.0, 129.2, 129.1, 126.8, 125.8, 65.5, 60.8, 39.2, 21.6. R_f = 0.53 (9:1 hexane:ethyl acetate); HRMS (EI) calcd for $C_{12}H_{14}O_2$ $[M - H]^+$ 189.0916, found 189.0916.

Compound 5. *cis*-2-Butene-1,4-diacetate (160 μL, 0.9 mmol) and 2-benzyloxy-3-butene (90 μL, 0.51 mmol) were added simultaneously via syringe to a stirring solution of **1** (11 mg, 0.015 mmol, 2.8 mol %) in CH_2Cl_2 (2.5 mL). The flask was fitted with a condenser and refluxed under nitrogen for 12 h. The reaction mixture was then reduced in volume to 0.5 mL and purified directly on a silica gel column (2 × 10 cm), eluting with 9:1 hexane:ethyl acetate (500 mL). Pale oil was obtained (48 mg, 0.19 mmol, 38% yield). Spectra was compared to reported compound; see Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A. *J. Am. Chem. Soc.* **2000**, *122*, 58. R_f = 0.36 (9:1 hexane:ethyl acetate).

Compound 24. To an oven dried, 100 mL Fischer−Porter bottle with Teflon stir bar, ruthenium metathesis catalyst **1** (14 mg, 0.017 mmol, 7.0 mol %) was added. The bottle was capped with a rubber septum and flushed with dry nitrogen and cooled to −78 °C. 1,5-Hexadiene (85 μL, 0.72 mmol) and methyl vinyl ketone (20 μL, 0.24 mmol) were injected into the bottle. Once the substrates were frozen, a pressure regulator was attached to the bottle. The bottle was evacuated and backfilled with dry nitrogen 3 times. Subsequently, isobutylene (10 mL) was condensed into the bottle. The bottle was backfilled to ∼2 psi with nitrogen, sealed, and allowed to slowly warm to room temperature, at which time it was transferred to an oil bath at 40 °C. After stirring for 12 h, the bottle was removed from the oil bath and allowed to cool to room temperature. The isobutylene was slowly vented off at room temperature until the pressure apparatus could be safely disassembled. The reaction mixture was then reduced in volume to 0.5 mL and purified directly on a silica gel column (2 × 10 cm), eluting with 10:1 hexane:ethyl acetate. Clear oil was obtained (32 mg, 0.21 mmol, 89% yield). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.78 (1H, dt, J = 15.9, 6.6 Hz), 6.07 (1H, dt, J = 15.9, 1.5 Hz), 5.12−5.06 (1H, m), 2.26−2.14 (7H, m), 1.69 (3H, s), 1.60 (3H, s). R_f = 0.53 (9:1 hexane:ethyl acetate). Spectra matches that of a previous characterization; see Coxon, J. M.; Garland, R. P.; Hartshorn, M. P. *Aust. J. Chem.* **1972**, *25*, 353.

Compound 25. 1,5-Hexadiene (70 μL, 0.59 mmol) and methyl vinyl ketone (25 μL, 0.30 mmol) were added simultaneously via syringe to a stirring solution of **1** (18 mg, 0.021 mmol, 7.1 mol %) in CH_2Cl_2 (2.0 mL) under a nitrogen atmosphere. The flask was fitted with a reflux condenser stirred at 40 °C with a continuous flow of nitrogen for 3 h. At that point, a solution of styrene (25 mL, 0.30 mmol) and catalyst **1** (16 mg, 0.019 mmol, 6.2 mol %) in CH_2Cl_2 was cannula transferred. The reaction mixture was stirred at 40 °C for an additional 8 h. The resulting solution was then reduced in volume to 0.5 mL and purified directly on a silica gel column (2 × 10 cm), eluting with 15:1 hexane:ethyl acetate to provide cross product (R_f = 0.33 in 9:1 hexane:ethyl acetate) as a clear oil (28 mg, 0.14 mmol, 47% yield). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): d 7.35−7.21 (5H, m), 6.87−6.79 (1H, m), 6.42 (1H, d, J = 15.9 Hz), 6.27−6.10 (2H, m), 2.41 (4H, app s), 2.26 (3H, s). Spectra match those of a previously characterized compound; see Johns, A.; Murphy, J. A.; Sherburn, M. S. *Tetrahedron* **1989**, *45*, 7835.

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Supporting Information Available: Experimental procedures and nuclear magnetic resonance and mass spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JA0214882

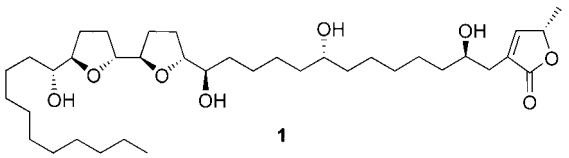
Natural Products Synthesis

The Total Synthesis of the Annonaceous Acetogenin 10-Hydroxyasimicin**

*Gillian L. Nattrass, Elena Díez, Matthew M. McLachlan, Darren J. Dixon, and Steven V. Ley**

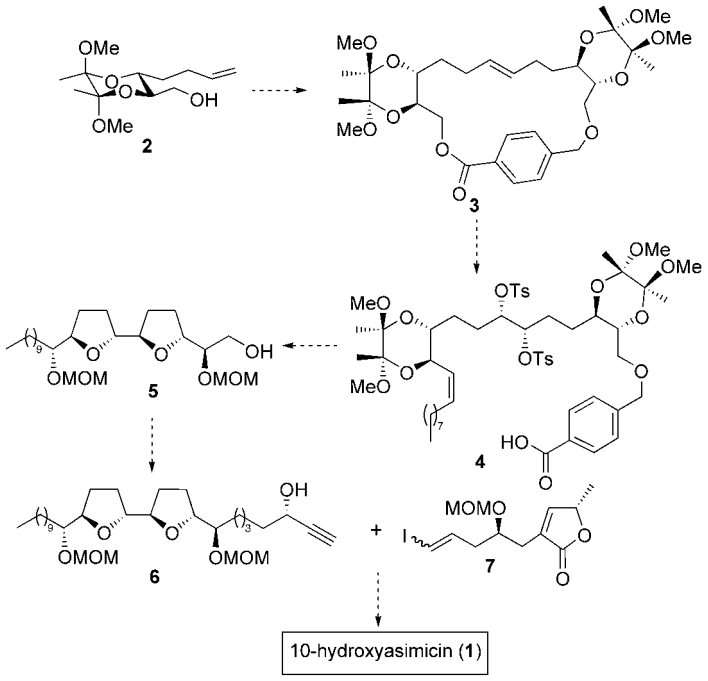
The annonaceous acetogenins comprise a class of almost 400 natural products that exhibit a remarkably broad spectrum of biological activity. They function as insecticides, fungicides, herbicides, and, perhaps most importantly, in vivo antitumor agents and have been shown to overcome resistance in multidrug-resistant tumors.[1] Structurally, the acetogenins are characterized by a long lipophilic tail, a central polyoxygenated core, and a terminal α,β-unsaturated γ-lactone. The structural diversity in this family arises principally from variations in the stereochemistry and connectivity of the polyoxygenated central core, which can consist of one or more tetrahydrofuranyl (THF) rings or, occasionally, a tetrahydropyranyl (THP) ring with various patterns of hydroxylation. These variations and the stereochemical consequences give rise to an impressive molecular diversity within the family. Owing to their biological activity and limited availability from natural sources, these compounds have attracted worldwide attention and have become the targets for total synthesis for a number of research groups,[2–9] including our own.[10] The majority of publications to date have focused on the synthesis of individual members of the family that suit a particular reaction type or stereochemical outcome. Motivated by the bioactivity of the annonaceous acetogenins, we embarked on a project to develop a more general route that utilizes an orthogonal and modular templating approach to provide access to many members in the series. Herein we describe the first successful synthesis of 10-hydroxyasimicin (**1**),[11] which contains a bis-THF motif in the central core.

The crucial component in the synthesis of any of these natural products is the stereoselective preparation of the polyoxygenated central fragment. 10-Hydroxyasimicin bears adjacent bis-THF rings flanked by two hydroxy groups with a *threo,trans,threo,trans,threo* stereochemistry. Our synthetic strategy to this oxygenated arrangements (Scheme 1) hinged upon the design of a



1

tether that could temporarily link two BDA-protected alkenol building blocks **2** (BDA = 2,3-butanediacetal) of, in principle, any desired stereochemical arrangement.[12] The tether could then induce stereocontrol during the critical ring-closing metathesis (RCM) to give compound **3**.[13] Subsequent Sharpless asymmetric dihydroxylation and chemoselective cleavage of the tether would afford **4**.[14] Intramolecular displacement by the unmasked hydroxy groups of the desymmetrized bistosylate **4** would yield the bis-THF unit **5**. Late-stage Sonogashira coupling of the terminal alkyne **6** and the butenolide **7** (constructed through a hetero-Diels–Alder (HDA) reaction to install the 1,5-stereochemical relationship and mask the butenolide double bond simultaneously, as reported in our synthesis of muricatetrocin C)[10] would



Scheme 1. Proposed synthetic route to 10-hydroxyasimicin (**1**). Ts = *p*-toluenesulfonyl, MOM = methoxymethyl.

complete the carbon skeleton. Finally, selective hydrogenation and global deprotection would furnish the natural product **1** (Scheme 1).

Synthesis of fragment **2** began from (*S*,*S*)-dimethyl-D-tartrate, which was readily converted into the monoprotected diol **8** in three steps according to a previously established procedure (Scheme 2).[12] Subsequent tosylation of **8** and treatment of the corresponding tosyl derivative with allylmagnesium bromide in the presence of CuBr afforded **2** in multigram quantities after deprotection with TBAF.

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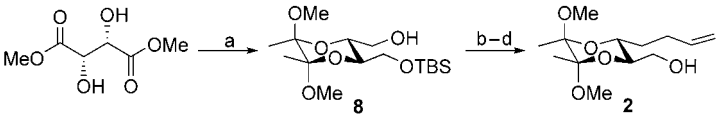


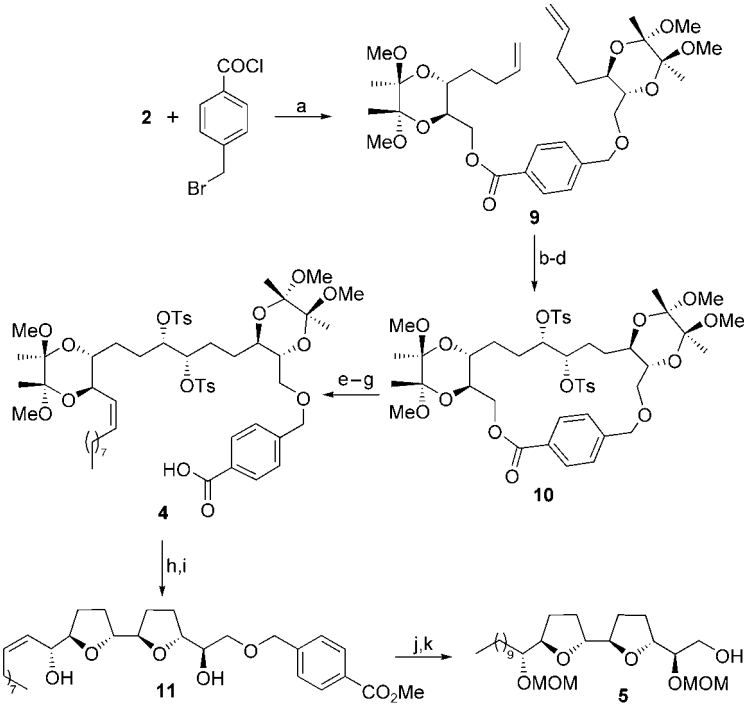
Scheme 2. Synthesis of alkenol **2**. a) Reference [12]; b) NEt_3, TsCl, DMAP, CH_2Cl_2, 1.5 h, room temperature, 99%; c) allylMgBr, CuBr, Et_2O, 8 h, 0°C, 84%; d) TBAF, THF, 5 h, 0°C, 100%. DMAP = 4-(dimethylamino)pyridine, TBAF = tetrabutylammonium fluoride.

The next step in the synthesis involved the development of a suitable template to link the two alkenol molecules together in order to proceed with an intramolecular metathesis reaction. As mentioned earlier, we required a tethering unit that could adjust the conformation of the macrocycle to control the stereoselectivity during the RCM reaction.[13] The chosen tethering template should behave as a "molecular workbench" and help orientate the olefin so that one face is preferentially available for attack during a *syn*-stereoselective dihydroxylation reaction.[14] Furthermore, the tether would play the role of a protecting group upon cleavage of the macrocycle to enable desymmetrization of the core. Hence the unit had to be dissymmetric to allow orthogonal cleavage upon completion of the dihydroxylation. On top of this, a dissymmetric tethering unit would enable us to attach different BDA-protected alkenol units sequentially to produce acetogenins with alternative stereochemistries at the core.[15] To put these concepts into effect, a differentiated arene with orthogonal substituents was chosen, as we could fine-tune the macrocycle ring size simply by varying the substitution pattern of the aryl system. 4-Bromomethylbenzoyl chloride was found to give the best results and was used in all subsequent investigations.[16]

Coupling of alkenol **2** with 4-bromomethylbenzoyl chloride in the presence of KHMDS gave the doubly loaded *para*-linked diene **9** in 69% yield. Subsequent treatment of **9** with a second-generation Grubbs catalyst[17] in dichloromethane at reflux delivered the intramolecular metathesis product in excellent yield, exclusively as the *E* adduct. Sharpless asymmetric dihydroxylation of the olefin with AD-mix-α afforded the diol in a diastereomeric ratio of 16:1 favoring the desired *S*,*S* product (Scheme 3).[18] Treatment of the diol with TsCl in pyridine afforded the ditosylated compound **10** in 90% yield.

The macrocycle was opened by treatment of **10** with sodium methoxide in methanol at room temperature to afford the primary alcohol.[19] Swern oxidation and a subsequent Wittig reaction installed the nine-membered carbon side-chain terminus as the *Z* olefin **4**. Removal of the BDA groups followed by an intramolecular Williamson cyclization with potassium carbonate as the base led to the formation of the bis-THF core **11** in 80% yield over the two steps. Finally, protection of the free secondary alcohols with MOMCl, followed by parallel reduction of the double bond and debenzylation under transfer-hydrogenation conditions completed the synthesis of fragment **5** (Scheme 3).

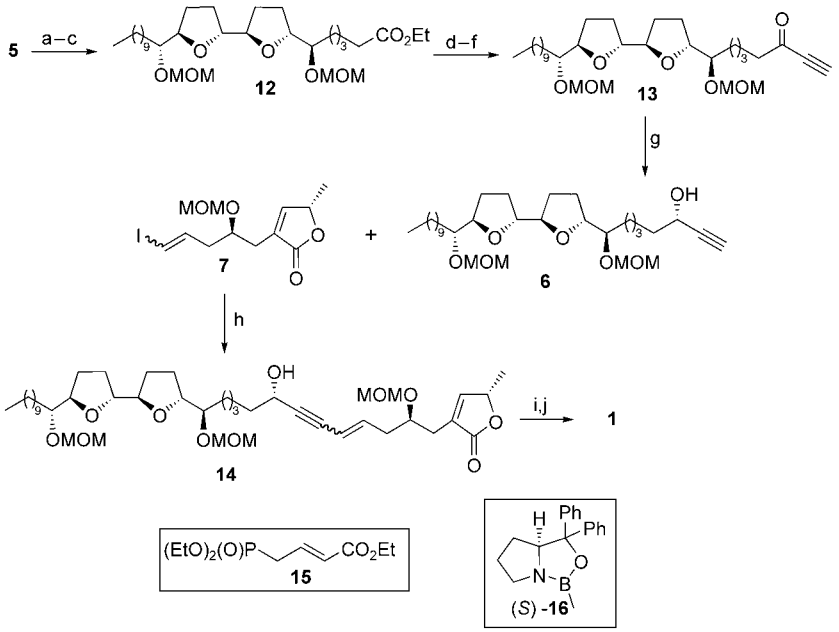
Fragment **5** was further elaborated by Dess–Martin oxidation, followed by Horner–Wadsworth–Emmons olefination with phosphonate **15**, which afforded an *E*,*E* diene exclusively.[20] Exhaustive reduction of the *E*,*E* diene with the Pearlman catalyst then afforded saturated ester **12** in 94% yield (Scheme 4). To generate the last stereocenter, further chain extension to propargylic ketone **13** was required. To this end ketone **13** was obtained by conversion of the saturated ester into the Weinreb amide,[21] which was then



Scheme 3. Synthesis of bis-THF framework **5**. a) KHMDS, THF, 5 h, −78→0°C, 69%; b) second-generation Grubbs catalyst, CH_2Cl_2, 1 h, reflux, 99%; c) AD-mix-α, $MeSO_2NH_2$, $NaHCO_3$, *t*BuOH/H_2O (1/1), 96 h, 0°C→RT, 96% (*S*,*S*/*R*,*R* 16:1); d) TsCl, pyridine, 20 h, 0°C→RT, 90%; e) NaOMe, MeOH, 44 h, room temperature, 93%; f) DMSO, $(COCl)_2$, CH_2Cl_2, −78°C; NEt_3, −78°C→RT, 98%; g) $CH_3(CH_2)_8PPh_3Br$, *n*BuLi, THF, 7 h, −78→0°C, 69%; h) TFA/H_2O (2:1), 5 min (repeat twice), room temperature; i) K_2CO_3, MeOH, 3.5 h, reflux, 80% over two steps; j) MOMCl, Hünig base, DMAP, CH_2Cl_2, 18 h, 0°C→RT, 78%; k) Pd/C, $HCO_2^-NH_4^+$, MeOH, 2 h, reflux, 79%. HMDS = hexamethyldisilazide, DMSO = dimethyl sulfoxide, TFA = trifluoroacetic acid.

treated with the lithium derivative of trimethylsilylacetylene followed by desilylation with TBAF to give **13** in 60% yield over the two steps.[22] Diastereoselective oxazaborolidine-catalyzed (CBS)[23] reduction gave **6** in 78% yield, with an excellent ratio favoring the desired isomer (44:1).

With the synthesis of fragment **6** completed, we now turned our attention to the synthesis of butenolide **7** in preparation for the final coupling reaction. Diene **17** was synthesized in seven steps from 1,4-butanediol according to a previously established procedure (Scheme 5).[10] As in our synthesis of muricatetrocin C, the 1,5-stereochemical relationship in the butenolide moiety was installed through the HDA reaction with nitrosobenzene at 0°C which afforded an inseparable 7:3 mixture of regioisomers favoring the desired adduct **18**.[24] The N–O bond was cleaved by using freshly

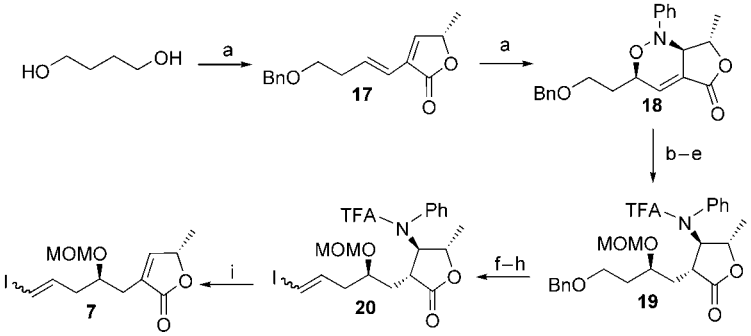


Scheme 4. Synthesis of 10-hydroxyasimicin (**1**). a) DMP, $NaHCO_3$, CH_2Cl_2, 1 h, 0 °C→RT, 95 %; b) **15**, NaHMDS, THF, 18 h, −78 °C→RT, 81 %; c) $Pd(OH)_2/C$, H_2, THF, 1 h, room temperature, 94 %; d) Me(MeO)NH·HCl, *i*PrMgCl, THF, 1.5 h, −10 °C, 82 %; e) trimethylsilylacetylene, *n*BuLi, THF, 1 h, −78→0 °C; f) TBAF, THF, 20 min, −20 °C, 60 % over two steps; g) (*S*)-**16**, $BH_3{\cdot}Me_2S$, THF, 1 h, −35 °C, 78 % (*S*/*R* 44:1); h) $[Pd(PPh_3)_2Cl_2]$, CuI, NEt_3, 45 min, room temperature, 86 %; i) $[Rh(PPh_3)_3Cl]$, H_2, benzene/EtOH (1:1), 23 h, room temperature, 74 %; j) $BF_3{\cdot}OEt_2$, Me_2S, 20 min, room temperature, 68 %. DMP = Dess–Martin periodinane.

prepared $[Mo(CO)_3(MeCN)_3]$ in the presence of water at room temperature.[25] Protection of the resultant secondary hydroxy group as a MOM ether enabled the separation of the regio- and stereoisomers through flash-column chromatography, thus avoiding the need for the laborious preparative HPLC separation required in the previous synthesis of muricatetrocin C. Subsequent hydrogenation over catalytic palladium and protection of the amine as the trifluoroacetamide afforded compound **19**. Debenzylation with the Pearlman catalyst afforded the free alcohol. Oxidation of the released primary alcohol with TPAP,[26] followed by one-carbon homologation, according to the Takai procedure,[27] provided the vinyl iodide **20** as a mixture of isomers (3.7:1 ratio favoring the *E* geometry) in 59 % yield over two steps. Subsequent elimination of the trifluoroacetamide group in the presence of DBU in acetonitrile at 0 °C afforded fragment **7** without epimerization of the butenolide methyl substituent (Scheme 5).

Sonogashira cross-coupling of vinyl iodide **7** with the propargylic alcohol **6** proceeded smoothly to produce the skeleton **14** in 86 % yield (Scheme 4).[28] The enyne functional group was reduced selectively over the butenolide double bond by using the Wilkinson catalyst to afford the protected acetogenin in 74 % yield. Final global deprotection with $BF_3{\cdot}Et_2O$ in methyl sulfide afforded **1** as a colorless wax in 68 % yield. The spectroscopic data for synthetic **1** (^{1}H NMR, ^{13}C NMR, IR, MS, and specific rotation)[29] were in excellent agreement with those reported for naturally occurring 10-hydroxyasimicin (**1**).[11]

In conclusion, the successful synthesis of 10-hydroxyasimicin (**1**) demonstrates the potential of the template approach to the oxygenated core of the acetogenins in an efficient and easily adapted manner. This route provides an efficient method for the construction of the bis-THF moiety incorporating a tether that enhances the stereochemical outcome of the RCM step and enables desymmetrization of the central fragment for further chain extension. The TBS-protected diol building block **8**, arising from (*R*,*R*,*S*,*S*)-2,3-BDA-protected (*S*,*S*)-dimethyl-D-tartrate, and the highly diastereoselective HDA approach to the butenolide unit are usefully employed in this new synthesis of an acetogenin natural product. Further applications of these general approaches will be employed in the preparation of other members of the acetogenin series in due course.



Scheme 5. Synthesis of butenolide **7**. a) Reference [10]; b) $[Mo(CO)_6]$, MeCN, 4 h, reflux; then **18**, H_2O, 15 min, room temperature; c) MOMCl, Hünig base, DMAP, CH_2Cl_2, 16 h, 0 °C→RT, 20 % over three steps, including HDA; d) Pd/C, H_2, THF, 2 h, room temperature, 100 %; e) TFAA, Hünig base, CH_2Cl_2, 30 min, 0 °C, 74 %; f) $Pd(OH)_2/C$, H_2, MeOH, 30 min, room temperature, 99 %; g) TPAP, NMO, NEt_3, CH_2Cl_2, 2 h, room temperature, 84 %; h) $CrCl_2$, CHI_3, THF, 17 h, 0 °C→RT, 70 % (*E*/*Z* 3.7:1); i) DBU, CH_3CN, 6 h, −15→−5 °C (60 %). TFAA = trifluoroacetic anhydride, TPAP = tetrapropylammonium perruthenate, DBU = 1,8-diazobicyclo[5.4.0]undec-7-ene.

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