Recent Advances in Alkene Metathesis for Natural Product Synthesis—Striking Achievements Resulting from Increased Sophistication in Catalyst Design and Synthesis Strategy


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Abstract. Every year, advances in the design of metathesis catalysts and insightful strategic applications of alkene metathesis work in concert to drive the field into new and exciting directions. From ring-closing to enyne and cross-metathesis, and from late-stage steps that directly furnish natural products to early transformations that supply starting materials, metathesis can play a role at every stage of a synthesis. This review will highlight some of the particularly innovative or surprising ways in which alkene metathesis has been implemented in natural product synthesis.

Outline

1. Introduction

The importance of alkene metathesis to synthetic chemistry cannot be overstated. The pioneering work by Chauvin, Grubbs, and Schrock on improving our mechanistic understanding of metathesis, on developing novel metathesis catalysts, and on developing metathesis applications garnered them the 2005 Nobel Prize in Chemistry.[1] For over two decades, organic chemists have harnessed the power of alkene metathesis in academic and industrial settings, and new applications continue to be reported on a regular basis. In the decade following Nicolaou's extensive review of the use of alkene metathesis in natural product synthesis,[2] the number of examples of such uses has grown at a dizzying rate. Books[3–7] and reviews[8–11] have been written to chronicle the breadth of applications of alkene metathesis. Herein, we aim to provide a structured look at a select group of alkene metathesis reactions that are employed in natural product synthesis. We discuss accomplishments from the past ten years that exemplify groundbreaking strategic applications of alkene metathesis and/or a particularly impressive reactivity or selectivity in metathesis processes. We have organized the discussion by transformation type: (i) ring-closing metathesis for normal- and medium-size rings, (ii) metathesis in the synthesis of macrocycles, (iii) tandem metatheses, (iv) ring-opening metathesis, and (v) cross-metathesis.

We note here that our purpose is only to demonstrate the power of metathesis for complex-molecule synthesis using select examples.

Furthermore, although closely related, alkyne metathesis[12] is not a prime focus of this article, and select examples are provided only to provide context. In this short review, only a small number of the myriad and incredibly versatile metathesis catalysts developed to date are showcased (**Figure 1**).

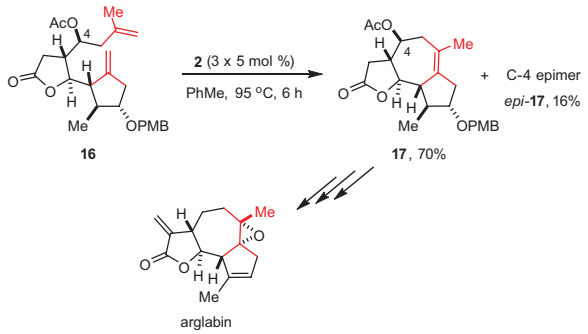
2. Ring-Closing Metathesis

By the mid-2000s, ring-closing metathesis (RCM) to form unstrained, normal-size rings was a well-established, reliable tool for synthesis. The examples below were selected because they have pushed forward the frontiers of what was thought possible in terms of reactivity and/or selectivity.

Reiser's group reported the first enantioselective synthesis of the complex sesquiterpenoid arglabin (**Scheme 1**).[13] A challenging RCM of two 1,1-disubstituted alkenes to forge a tetrasubstituted alkene within a 7-membered ring serves as a key step. A particularly direct, stereoselective synthesis of the RCM precursor, **16**, set the stage for this challenging ring closure. This metathesis required three separate charges (5 mol %) of the Grubbs second-generation catalyst[14] (**2**) and inert-gas sparging at 95 °C to successfully provide the tetrasubstituted alkene in **17**. Epoxidation of the tetrasubstituted alkene and installation of the requisite functional groups completed the synthesis of arglabin. At the time, and to this day, this RCM is striking for its efficient generation of a ring size that can often be slow to form, while simultaneously forging a tetrasubstituted alkene.

Stoltz's group was among the first to employ the RCM of alkenyl chlorides in natural product synthesis in the course of their innovative synthesis of elatol.[15] The authors built on Weinreb's earlier work which had demonstrated the general feasibility and utility of this type of RCM.[16] To access the salient chlorinated cyclohexene of elatol, the researchers utilized an RCM between two 1,1-disubstituted alkene groups in **18** (**Scheme 2**), one with two carbon substituents and one bearing an alkyl substituent and a chlorine atom. Substrate **18** underwent RCM in the presence of **3** to provide intermediate **19** containing a tetrasubstituted alkene. Following its introduction, catalyst **3** has become an important addition to the arsenal of available metathesis catalysts.[3,17]

In one of a few reported examples of stereochemical equilibration–RCM, Tang, Chen, Yang and co-workers reported the synthesis



Scheme 1. Efficient Formation by RCM of a Cycloheptene with a Tetrasubstituted Double Bond in Reiser's Enantioselective Synthesis of Arglabin. *(Ref. 13)*

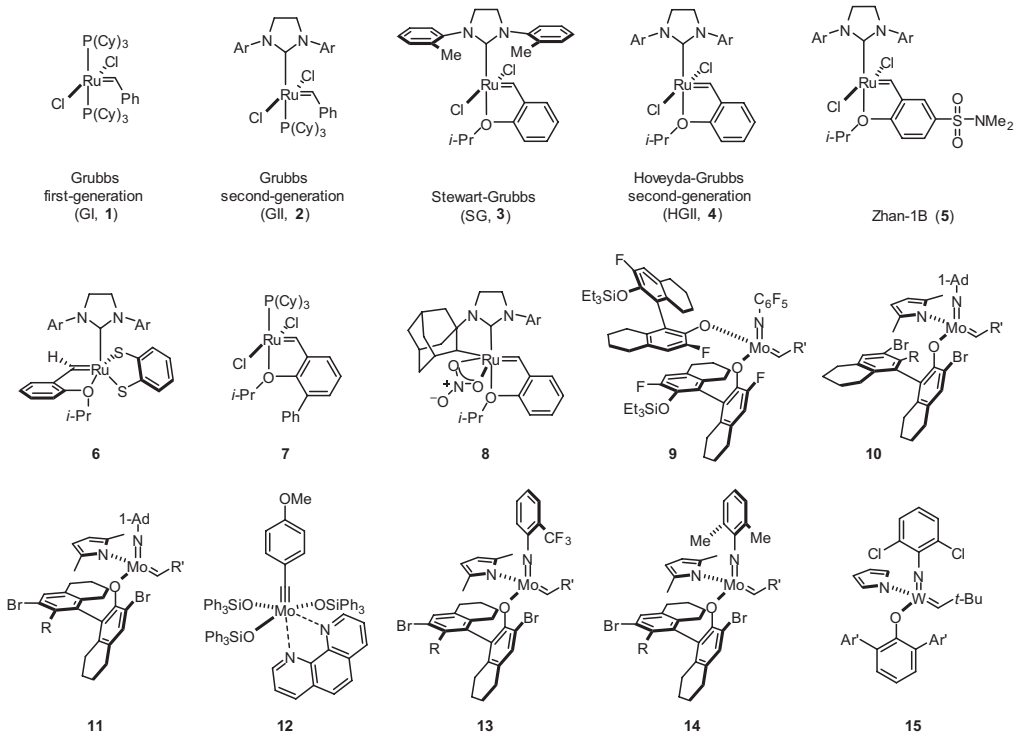
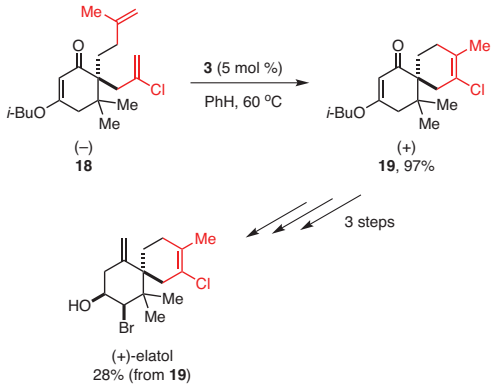


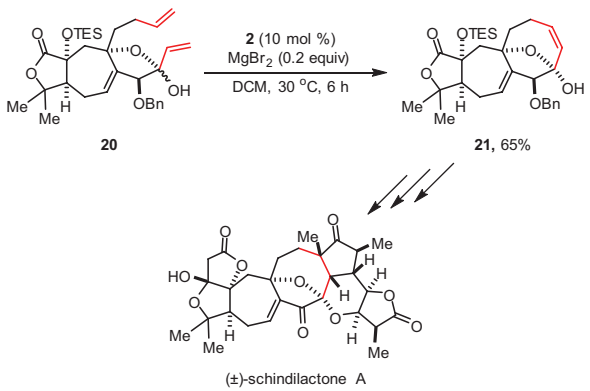
Figure 1. Structures of Metathesis Catalysts Featured in This Review.

of schindilactone A, in which that process provided the central oxabicyclo[4.2.1]nonane ring system of the target (**Scheme 3**).[18] In the presence of GII (**2**), the desired RCM gave **21**, with in situ epimerization producing a single diastereomer at the hemiketal carbon.[19] The resulting cyclooctene later participated in a Pauson–Khand reaction to annulate another one of the rings of the natural product. Other examples of stereochemical equilibration during RCM mostly involve epimerization of stereogenic centers adjacent to ketones.[20]

In their synthesis of sculponeatin N, a bioactive diterpene, Thomson and co-workers accomplished the equivalent of a butadiene–cyclopentenone Diels–Alder cycloaddition by a sequence featuring an unusual equilibrating diastereoselective RCM reaction (**Scheme 4**).[21] When **24** could not be made by the more straightforward Diels–Alder approach, sequential alkene installation converted the spiro-cyclopentenone precursor to the triene-containing RCM substrate **22**. Subjecting triene **22** to metathesis conditions with GII (**2**) afforded the desired cis-fused cyclohexene-containing **24**. The authors commented that spirocyclopentene **23** could be isolated by stopping the reaction early; however, the trans-fused cyclohexene was never observed. This particularly creative workaround to the unsuccessful cycloaddition also sets a key quaternary stereogenic center of the target.



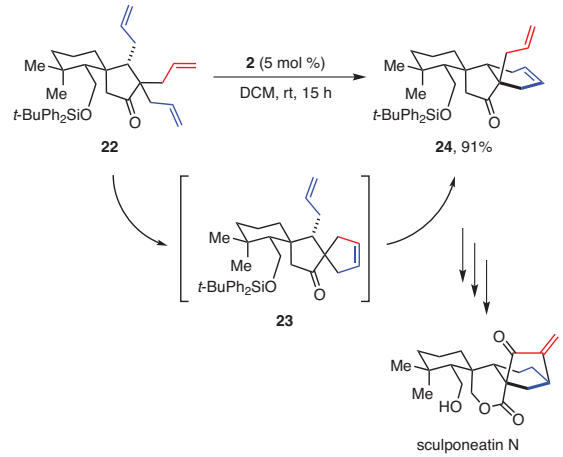
Scheme 2. First Application of the RCM of Alkenyl Chlorides in Natural Product Synthesis as Demonstrated in Stoltz's Asymmetric Total Synthesis of (+)-Elatol. *(Ref. 15)*



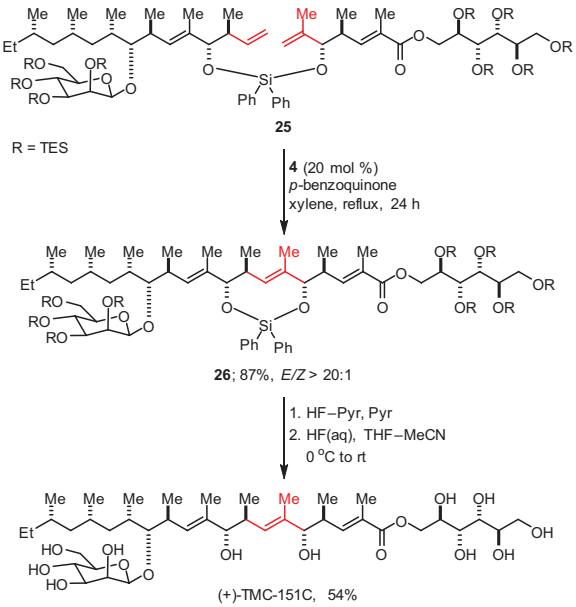
Scheme 3. Yang's Diastereoselective Synthesis of the Fully Functionalized CDE Ring System in (±)-Schindilactone A by RCM. *(Ref. 18)*

3. Tethered Ring-Closing Metathesis

Temporary tethers are enormously useful for increasing the rates of slow bimolecular reactions, and are advantageous with respect to both chemo- and stereoselectivity. In Kobayashi's total synthesis of (+)-TMC-151C, a silicon-tethered RCM reaction convergently assembled the polyketide natural product from two fragments of similar complexity in a reaction that would have been virtually impossible to achieve in a bimolecular setting (**Scheme 5**).[22] Further, the tether served to reinforce the selectivity of the alkene geometry in forming the trisubstituted alkene. The RCM reaction of **25** was effected with the Hoveyda–Grubbs second-generation catalyst (**4**),[23] and global desilylation of **26** afforded (+)-TMC-151C directly.



Scheme 4. Diastereoselective RCM as a Butadiene–Cyclopentenone Diels–Alder Equivalent in Thomson's Total Synthesis of Sculponeatin N. *(Ref. 21)*



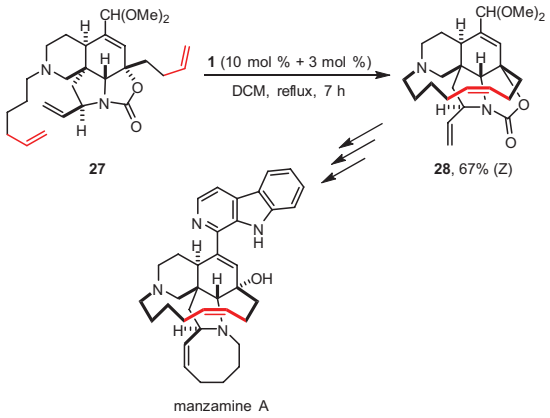
Scheme 5. Silicon-Tethered RCM in Kobayashi's Convergent Total Synthesis of (+)-TMC-151C. *(Ref. 22)*

4. Macrocycles

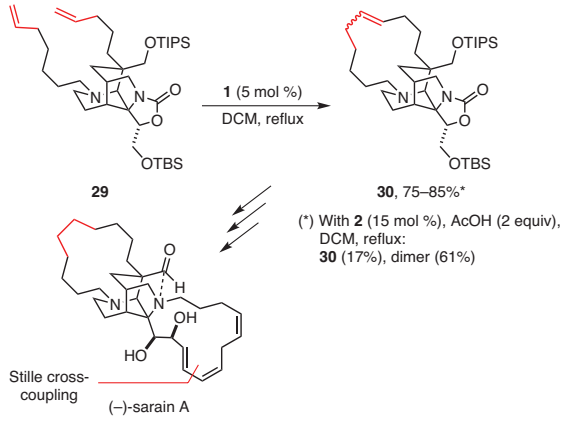
4.1. Macrocyclic Ring Closure by Metathesis

4.1.1. The Alkylpiperidine Alkaloids

A number of structurally related alkaloids, including the manzamines,[24a] sarains,[24b] haliclonacyclamines,[24c] and haliclonins,[24d] belong to the family of alkylpiperidine natural products. In addition to an alkylpiperidine subunit, these secondary metabolites usually contain one or more macrocycles. The synthesis of the macrocycle(s) of the various alkylpiperidines has been accomplished by ring-closing alkene or alkyne metathesis numerous times, by employing various strategies aimed at accomplishing the transformation selectively for the challenging *Z*-configured alkene present in many of the natural products. In 1999, Martin and co-workers were the first to utilize a macrocyclizing RCM reaction in the synthesis of an alkylpiperidine natural product (**Scheme 6**).[25] Since then, few have achieved the same level of substrate-controlled *Z*-selectivity Martin's group observed for the conversion of **27** to **28**, without the use of modern *Z*-selective metathesis catalysts. In the past decade, a number of syntheses of alkylpiperidine natural products relying on RCM reactions for macrocyclic ring-closure have been reported.



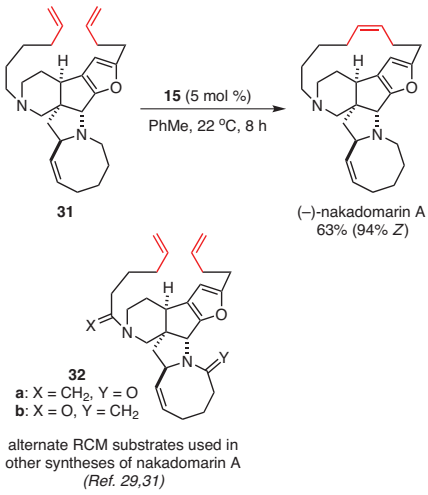
Scheme 6. Macrocycle Ring Closure by Metathesis, as Illustrated in Martin's Total Synthesis of Manzamine A, an Alkylpiperidine Alkaloid. *(Ref. 25)*



Scheme 7. Macrocycle Ring Closure by Metathesis in Overman's Total Synthesis of (–)-Sarain A. *(Ref. 26)*

Overman's group reported the first total synthesis of the incredibly complex alkaloid sarain A, which exhibits antibacterial, insecticidal, and antitumor activities. In this work, the saturated 13-membered-ring of the natural product was formed via RCM and subsequent hydrogenation (**Scheme 7**),[26] while the second, 14-membered ring of sarain A containing the skipped-triene was ultimately constructed by a Stille cross-coupling, and not by metathesis. In the RCM step to generate the saturated macrocycle, the use of catalyst **2** with **29** led to significant quantities of dimeric byproducts, in addition to some of the desired macrocyclization product, **30**. Switching to the less active, first-generation Grubbs catalyst (**1**)[27] diminished the amount of dimer formed and, after optimization, a 75–85% yield of the macrocyclization product, **30**, was obtained. It was postulated that the use of the more active catalyst **2** gave a thermodynamic ratio of products, as supported by subjection of either the isolated macrocycle or dimer to the same reaction conditions, which yielded in each case a similar mixture of macrocycle and dimer. The less active **1**, however, may have been unable to initiate metathesis on the resultant internal alkene, making the RCM step effectively irreversible, and providing only the desired RCM product.

Nishida's first-generation synthesis of nakadomarin A[28] was published in 2003, and, since then, many other groups have contributed impressive syntheses of their own. The *Z*-alkene-containing, 15-membered ring of nakadomarin A has been constructed by ring-closing alkene metathesis,[28–32] ring-closing alkyne (RCAM) metathesis and semi-reduction,[33–34] and by macrolactamization.[35] In their pioneering work, Nishida and co-workers achieved a *Z:E* ratio of 1:1.8 by using catalyst **1** to close the 15-membered ring from **32a** (**Scheme 8**). Subsequent syntheses by the groups of Kerr,[29] Dixon,[30] and Zhai,[31] using either substrate **32a**, **32b**, or **31** resulted in only slightly improved *Z:E* ratios (up to 2:1). Nilson and Funk[33] were the first to employ a two-step RCAM–semi-reduction to afford the *Z* alkene as the sole product. Dixon's group embraced this approach as well,[34] but later reported a collaborative effort with the Schrock and Hoveyda labs, making use of the recently developed *Z*-selective, tungsten-based metathesis catalyst



Scheme 8. Final Step in the Synthesis of (–)-Nakadomarin A by Catalyst-Controlled *Z*-Selective RCM. *(Ref. 36)*

15.[36] Use of this catalyst with **31** produced (–)-nakadomarin A in 63% yield and 94% *Z*-selectivity, the highest *Z*-selectivity observed in a synthesis of nakadomarin A by RCM.

Huang and co-workers reported the first asymmetric total synthesis of the alkaloid (–)-haliclonin A using catalyst **1** for RCM, followed by hydrogenation, to form the saturated macrocycle of the molecule.[37] At a later point in the synthesis, an RCAM with molybdenum benzylidyne catalyst **12**[38] closed the second, unsaturated, 15-membered ring of compound **33**, affording intermediate **34**. Partial hydrogenation installed the desired *Z*-alkene geometry (**Scheme 9**).[37] It is worth noting that the alkyne metathesis and partial hydrogenation steps were both tolerant of the unconjugated alkene, and no isomerization was noted.

4.1.2. The Ansatrienins

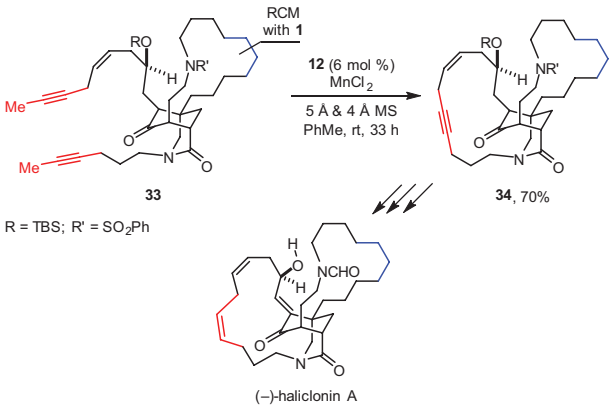
The ansatrienins,[39a-c] a subclass of the ansamycins,[39] bear an all-trans conjugated triene subunit in their macrocyclic core. Cross-coupling[40] and alkenylation[41] approaches to this triene fragment have been successfully employed in syntheses of some of the members of this class of natural products. The application of an RCM between two diene units to furnish an all-trans triene—an approach that certainly would appear to harbor risk—was central to two successful syntheses.[42–43] Hayashi and co-workers reported an asymmetric total synthesis of the anticancer drug (+)-cytotrienin A, where RCM successfully provided the macrocyclic ring containing the all-trans triene (**eq 1**).[42] Krische's group rapidly assembled a related tetraene-containing RCM substrate using their C–H functionalization methodology, and completed the synthesis of trienomycins A and F (not shown).[43]

4.1.3. Other Natural Products

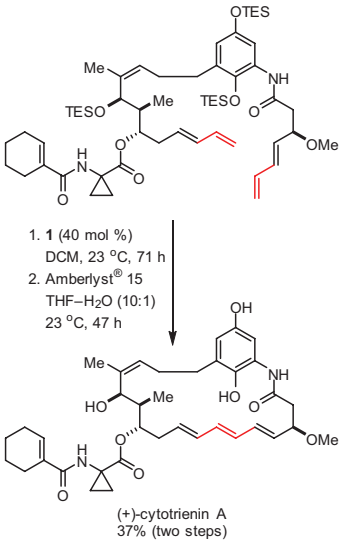
Krische's group utilized a ring-closing enyne metathesis (RCEYM) to form the macrocyclic ring in their total synthesis of 6-deoxyerythronolide B (**Scheme 10**).[44] Some of the challenges that were overcome in this synthesis include: (i) Terminal alkene isomerization from **35** was the only observed product in the absence of ethylene. (ii) Enyne metathesis proceeded at 80 °C, converting the alkyne into a terminal diene but not into the macrocycle. To overcome this second challenge, the ethylene atmosphere was replaced with nitrogen after the enyne metathesis was complete, and the reaction mixture was then heated to 110 °C, accomplishing the desired ring closure. The macrocyclic diene **36** was then converted in a few steps into 6-deoxyerythronolide B. Together with Krische's efficient methods for assembling the precursor, this RCEYM process was strategically advantageous.

In their synthesis of (+)-neopeltolide, Fuwa and co-workers utilized a chemoselective cross-metathesis (CM) to form an α,β-unsaturated ester from a terminal alkene and methyl acrylate, ultimately facilitating pyran formation by an oxa–Michael cyclization (**Scheme 11**).[45] Since the pendant styrenyl group in substrate **37** was also poised to competitively undergo an undesired RCM, the ability of the proximal hydroxyl group to form an intramolecular H….Cl interaction between the OH and the Cl in the substrate-bound catalyst was key to accomplishing the selective CM leading to **38**. When the proximal OH was protected with a BOM group, a significant amount (46–71%) of the ring-closed product was formed. Finally, RCM of intermediate **39** with catalyst **2** afforded the macrocyclic, trisubstituted alkene **40**, which was then hydrogenated to the saturated macrolactone, constituting a formal synthesis of (+)-neopeltolide. Hoveyda, Schrock, and Yu also reported the synthesis of (+)-neopeltolide, making extensive use of alkene metathesis to construct the natural product (not shown).[46]

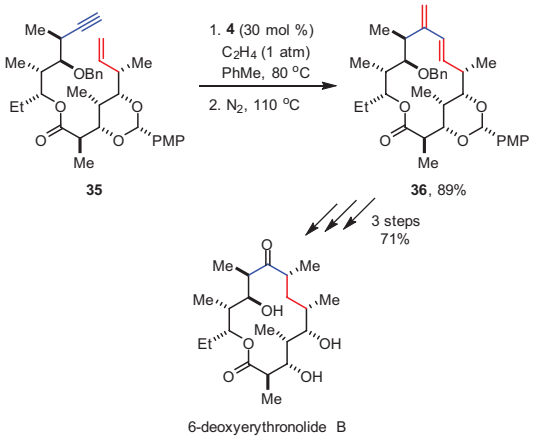
Kita and Kigoshi reported an asymmetric total synthesis of the marine macrolides mycalolides A and B, and evaluated both an RCM



Scheme 9. Ring-Closing Alkyne Metathesis (RCAM) Step in Huang's Asymmetric Total Synthesis of (–)-Haliclonin A. *(Ref. 37)*



eq 1 *(Ref. 42)*



Scheme 10. Ring-Closing Enyne Metathesis (RCEYM) in Krische's Total Synthesis of the Polyketide 6-Deoxyerythronolide B. *(Ref. 44)*

and a CM approach (**Scheme 12**).[47] In their work, the RCM strategy suffered from low selectivity for the desired alkene geometry; even after extensive optimization, it proceeded in only a 63% yield and an *E:Z* ratio of 2.7:1. The CM approach was more successful; the reaction of **41** with **42** proceeded to give **43** in 77% yield and an *E:Z* ratio of 5:1. Although adhering to the rules[48] for best-case CM substrates (Type 1 and Type 2 alkenes), this CM is remarkable for the extreme complexity of both reaction partners used in close to equimolar amounts.

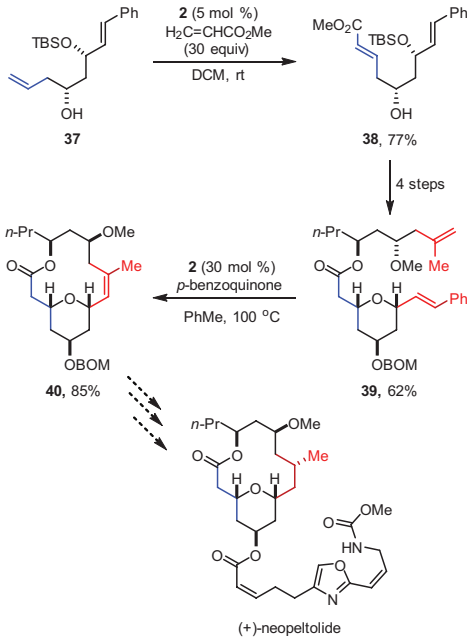
Krische and co-workers synthesized swinholide A using their asymmetric, hydrogen-mediated C–C bond-forming methodology and alkene metathesis each at multiple stages (**Scheme 13**).[49] An enantioselective, iridium-catalyzed allylation provided product **46**, which underwent CM with acrolein catalyzed by **2** to afford dihydropyran hemiacetal **47**; this product was elaborated into a key fragment for convergent coupling. Construction of a second fragment began with a diastereo- and site-selective iridium-catalyzed allylation to supply **48**, which was subjected to CM with *cis*-1,4-diacetoxy-2-butene. The resulting allylic acetate **49** underwent palladium-catalyzed Tsuji–Trost cyclization to give a *cis*-2,4-disubstituted vinyl tetrahydropyran **50**. The two fragments were elaborated and coupled, yielding the final metathesis substrate, **51**. In the presence of **4**, intermediate **51** was converted, via sequential CM–RCM, into the dimeric macrodiolide swinholide A in 25% yield, as well as via an RCM of the monomer, into the macrolide hemiswinholide in 43% yield. This final step that directly affords two natural products is striking for its efficiency in the presence of two other alkenes, a host of unprotected hydroxyl groups, and numerous other Lewis basic sites.

4.1.4. Tiacumicin B Aglycon

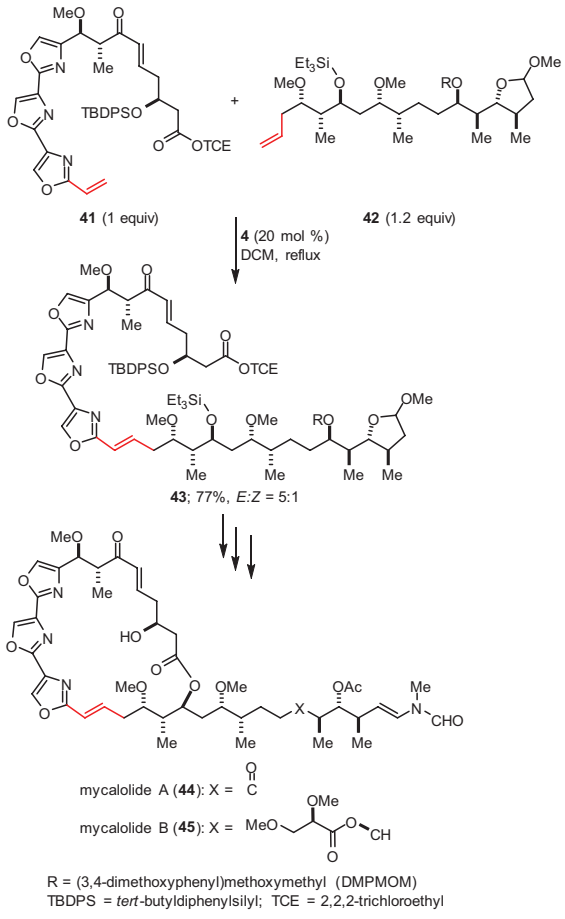
In 2015, three research groups concurrently reported syntheses of tiacumicin B, with each group utilizing alkene metathesis in their synthesis (**Scheme 14**).[50–52] Zhu and co-workers targeted a protected form of the tiacumicin B aglycon,[50] whereby ester-linked ring-closing metathesis precursor **52a** underwent the desired RCM macrocyclization in the presence of **2**, with only deprotection required to complete the synthesis. Gademann's group targeted the protected tiacumicin B aglycon and utilized a macrocyclic RCM similar to that used in Zhu's synthesis, closing the diene fragment of **52b**.[51] Gademann's substrate underwent a more efficient ring closure, reminding us of the significant effect that different protecting group strategies can have on macrocyclization by RCM (and indeed by any method). The authors also reported a procedure to isomerize the undesired *Z* alkene to the *E* alkene allowing material to be recycled. Altmann's group reported a synthesis of the tiacumicin B aglycon, in which they employed a CM to assemble the linear precursor to the natural product.[52] Complex **4** catalyzed the synthesis of tetraene fragment **53**, attaining the highest *E/Z* ratio of the three syntheses (6.7:1). Yamaguchi esterification with a vinyl boronate containing fragment and Suzuki macrocyclization completed the synthesis.

4.2. Macrocyclic Ring Closure by Other Means

Hoye and co-workers synthesized (+)-peloruside A—a cytotoxic marine macrolide that is being evaluated for use against paclitaxel-resistant cancers—by utilizing a relay RCM between the tethered alkenes to



Scheme 11. CM and RCM Key Steps in Fuwa's Concise Total Synthesis of (+)-Neopeltolide. *(Ref. 45)*

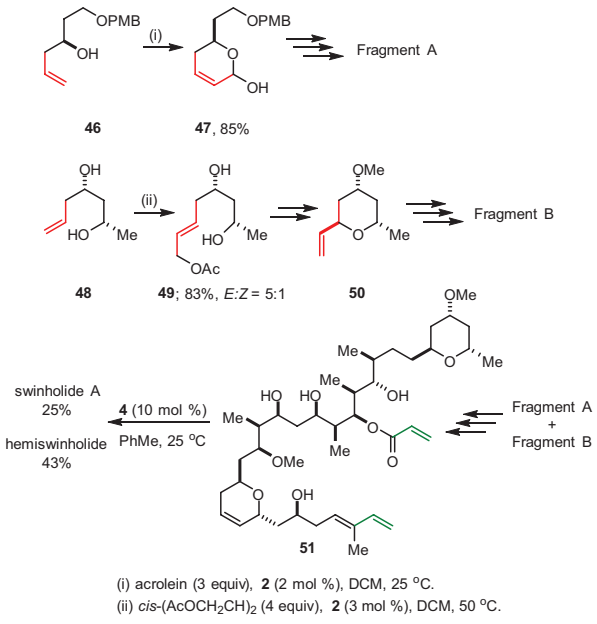


Scheme 12. CM between Two Advanced Intermediates in Kita and Kigoshi's Total Synthesis of Mycalolides A and B. *(Ref. 47)*

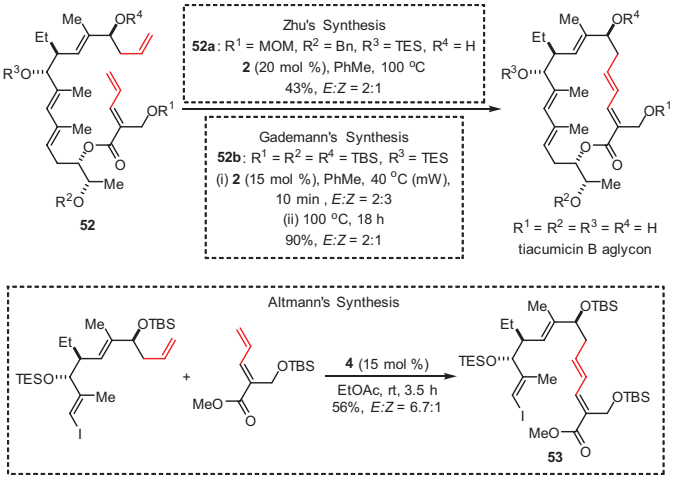
construct the trisubstituted alkene group present in the natural product (**Scheme 15**).[53] Two tethering approaches, one via a silaketal (**54**) and the other via an ester linkage (**55**), were investigated. Each tether contained an (*R*)-citronellene derived tail, initially incorporated to enable efficient enzymatic resolution of the diastereomeric mixtures of alcohols. This tail was cleaved during the metathesis step and the two routes converged to a substrate with differentially protected alcohol groups. This fragment was coupled to a polyol fragment via an aldol addition, after which a macrolactonization–deprotection sequence completed the synthesis of peloruside A.

Volchkov and Lee completed the asymmetric total synthesis of (–)-amphidinolide V by employing metatheses at multiple stages in the synthesis (**Scheme 16**).[54] RCEYM of silyl-tethered enyne **56** formed the desired silacycle **57**, which was ring-opened and coupled to provide polyene **58**. RCM of the latter compound led to an 8-membered silacycle (**59**). Subsequent elaboration, including allylic transposition, gave a fragment corresponding to roughly half of the target. Acetylenic intermediate **60** was subjected to enyne metathesis with ethylene, catalyzed by **2** to afford the salient 1,3-diene, **61**. Ultimately, fragments **59** and **61** were combined to complete the synthesis of (–)-amphidinolide V. Another member of the amphidinolide family, (–)-amphidinolide K, was synthesized by Lee and co-workers, whose work featured strategic use of enyne metathesis (not shown).[55]

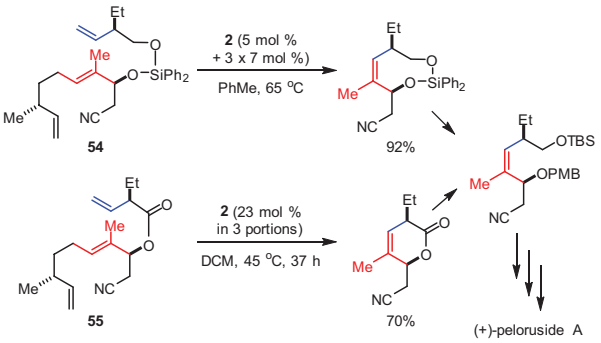
In their total synthesis of disorazole C_1, an antifungal and anticancer macrocyclic natural product, Hoveyda and co-workers employed a number of metathesis steps to tackle the construction of the C_2-symmetric dimeric macrocycle (**Scheme 17**).[56] The disorazole C_1 ring contains two conjugated triene units, within which are found four *Z*-configured carbon–carbon double bonds. The convergent, stereoselective route employed required the RCM of a *Z*-vinyl iodide tethered to a *Z*-vinylborane in the precursor **68**, which was assembled with the help of a number of *Z*-selective cross-metathesis steps. A



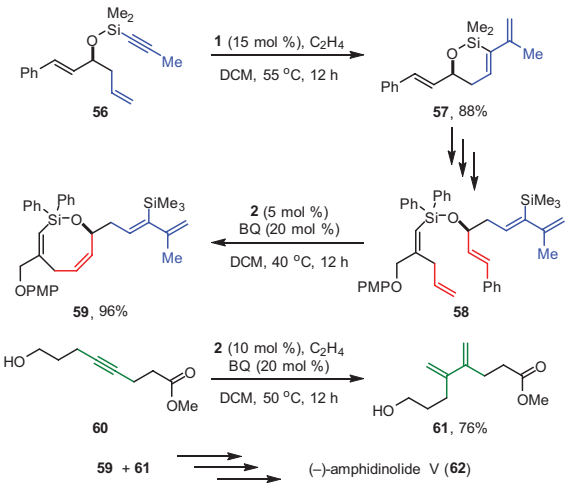
Scheme 13. CMs and CM–RCM Sequences Employed in Krische's Total Synthesis of the Actin-Binding Marine Polyketide Swinholide A. *(Ref. 49)*



Scheme 14. RCM and CM in the Synthesis of Tiacumicin B Aglycon. *(Ref. 50–52)*



Scheme 15. Relayed, Tethered RCMs in Hoye's Total Synthesis of Peloruside A. *(Ref. 53)*



Scheme 16. Enyne Metatheses and RCM in Lee's Asymmetric Total Synthesis of (–)-Amphidinolide V. *(Ref. 54)*

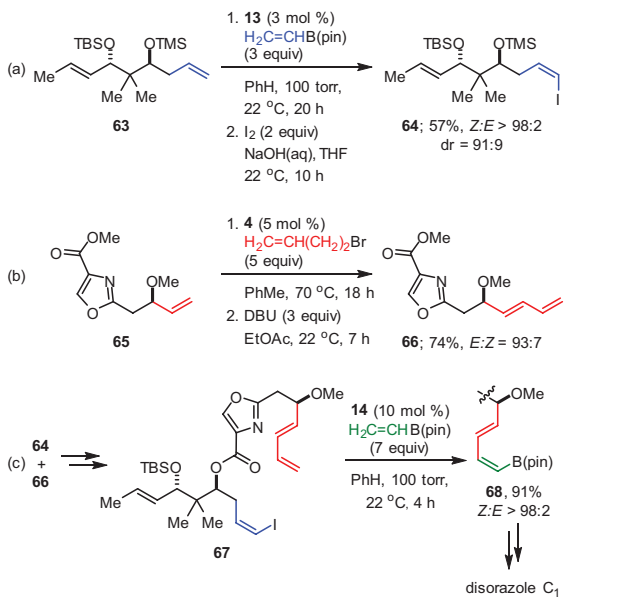
double Suzuki cross-coupling strategy served to dimerize compound **68**, affording less than 2% of the unimolecular cross-coupling product. A careful deprotection led to completion of the synthesis of disorazole C_1.

5. Tandem Metatheses

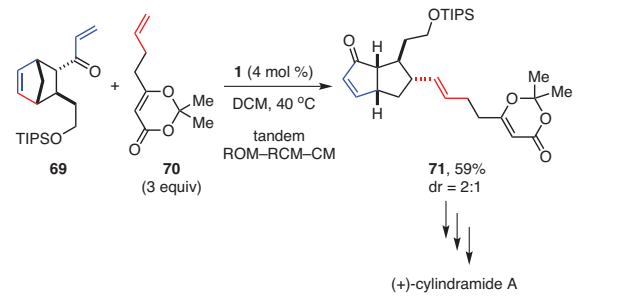
In their synthesis of (+)-cylindramide A, Hart and Phillips developed a tandem ROM–RCM–CM sequence to rearrange a bicyclo[2.2.1]-heptene into the bicyclo[3.3.0]octene core of (+)-cylindramide A (**eq 2**).[57] In the presence of GI (**1**) and the butenyl-substituted dioxinone **70**, the metathesis cascade substrate **69** was transformed into the desired bicyclo[3.3.0]octene **71** with incorporation of the butenyl-substituted dioxinone. This work showcases how the reliably predictable stereochemical relationships generated in the course of Diels–Alder reactions can be transferred to very different ring topologies via tandem metathesis chemistry.

5.1. Enyne Metatheses

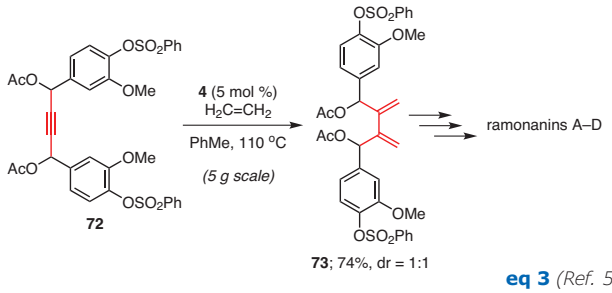
Ramonanins A–D are spirocyclic phenylpropanoid tetramers that show cytotoxic activity against lines of human breast cancer cells. In the first total synthesis of these lignan natural products, Sherburn's group. targeted a dimethylene tetrahydrofuran intermediate that could be dimerized to a mixture of the different ramonanins (**eq 3**).[58] Starting from vanillin, the authors arrived at **72**, the alkyne-bridged diacetate substrate for enyne metathesis, after four steps. Enyne metathesis with ethylene, catalyzed by **4**, furnished the diene diacetate **73**. Hydrolysis of the diacetate, tetrahydrofuran ring formation from the resultant diol, and cleavage of the benzenesulfonate protecting groups afforded the desired dimerization precursor, which was taken to generate the natural product targets by intermolecular Diels–Alder cycloadditions.



Scheme 17. *Z*-Selective CM and RCM in Hoveyda's Convergent, Diastereoselective, and Enantioselective Total Synthesis of Disorazole C_1. *(Ref. 56)*



eq 2 *(Ref. 57)*

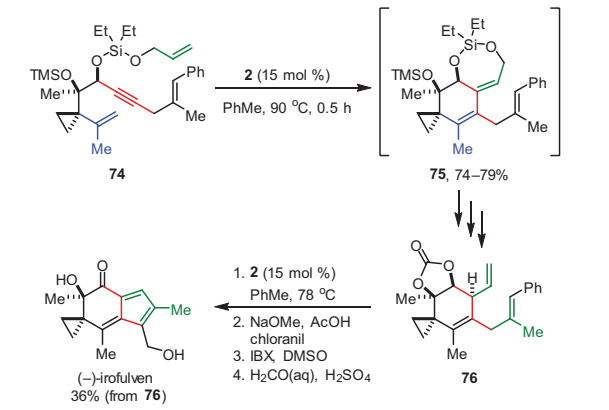


eq 3 *(Ref. 58)*

5.2. Ene-yne-ene Metatheses

Tandem, ring-closing ene-yne-ene metathesis (RCEYEM) sequences are powerful for the construction of bicyclic ring systems and have been applied in a number of different natural product syntheses in the past decade.

Movassaghi's group reported particularly non-obvious metathesis-based approaches to the semisynthetic illudin derivatives (–)-acylfulvene and (–)-irofulven, the latter being an especially active antitumor agent against a variety of solid tumors (**Scheme 18**).[59] Silyl-tethered RCEYEM substrate **74** underwent the desired metathesis cascade catalyzed by GII (**2**) providing **75**, which was then converted into **76** via a reductive allylic transposition. The resulting intermediate **76** underwent RCM in the presence of **2** to form the cyclopentane ring of the illudins. Oxidation with DDQ or chloranil and IBX (*ortho*-iodoxybenzoic acid) furnished (–)-acylfulvene (not shown), and reaction of (–)-acylfulvene with aqueous formaldehyde provided (–)-irofulven.



Scheme 18. RCEYEM and RCM in Movassaghi's Enantioselective Total Synthesis of (–)-Irofulven. *(Ref. 59)*

Spectacular use of RCEYEM was demonstrated in the enantioselective total synthesis of three tetracyclic kempene diterpenes (**Scheme 19**).[60] Tandem RCEYEM substrate **77**, when heated in the presence of GII (**2**), gave rise to intermediate **78**, possessing the tetracyclic core of the kempenes. The key to the success of this complexity-building transformation was the substitution pattern of each of the unsaturated reaction partners, which was carefully considered so that the order of reaction was the proper one to yield the desired product outcome. Following the synthesis of **78**, protecting group exchange, ketone reduction, and acylation afforded the kempene natural products.

Yang, Li, and co-workers reported the stereoselective total syntheses of the alkaloids (–)-flueggine A and (+)-virosaine B, derived in a biomimetic fashion from (–)-norsecurinine and (+)-allonorsecurinine, which were each constructed via relay RCEYEM.[61] An *N*-Boc-protected, commercially available, D-proline-derived Weinreb amide served as the starting material to construct the RCEYEM substrate possessing a heptadienoate chain. This tethering strategy successfully controlled the direction of ring closure in the cascade process. Both diastereomers of the RCEYEM substrate could be successfully carried through the reaction sequence to furnish both (–)-norsecurinine and (+)-allonorsecurinine, which were ultimately converted into their more complex relatives.

In 2016, Smith's group reported a total synthesis of (±)-morphine that makes use of an RCEYEM sequence (**Scheme 20**).[62] In the presence of catalyst HGII (**4**), the desired RCEYEM proceeded to give the intermediate tetracycle **81**, which, after amine deprotection, underwent an intramolecular 1,6-addition forming **82**, a final reduction away from morphine.

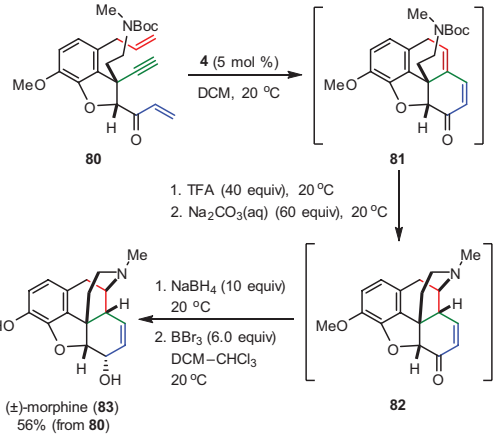
6. Ring-Opening Cross-Metathesis

A collaborative synthesis of the potent antifungal agent (±)-hippolachnin A has been disclosed by the groups of Wood and Brown. This complex natural product has an unusual structure that features six contiguous stereocenters, a quaternary center, and a congested compact core. The two groups had arrived at similar and "complementary" approaches and sought to design a collaborative synthesis playing to the strengths of each of their separate syntheses. In their combined strategy, the [2 + 2] photocycloaddition of quadricyclane and an α,β-unsaturated acid chloride ultimately forged the tricyclic ROCM precursor **84**, which underwent ethylenolysis catalyzed by **1** to give **85** (**Scheme 21**).[63] Strategically, the use of ring-opening metathesis to afford the bis-alkenyl bicycle served to introduce two two-carbon groups that would give rise to two of the four ethyl groups present in the natural product. This method of ethyl group introduction is distinct from other approaches to hippolachnin A.

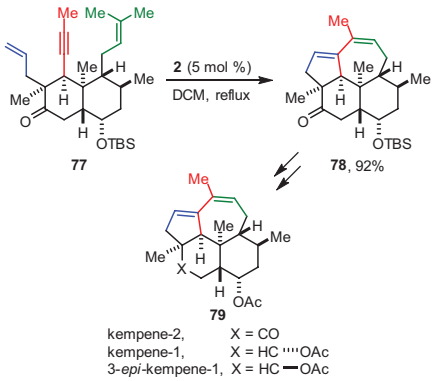
7. Cross-Metathesis

Kim and co-workers developed a procedure for the installation of a *Z*-enyne fragment, which they applied to the synthesis of (+)-3-(*Z*)-laureatin and *ent*-elatenyne (**Scheme 22**).[64] In the key CM step in the synthesis of *ent*-elatenyne, a protected enyne bearing a tethered allyl ether reacted with the terminal alkene of **87** to provide the enyne CM product **88** with high *Z*-selectivity.

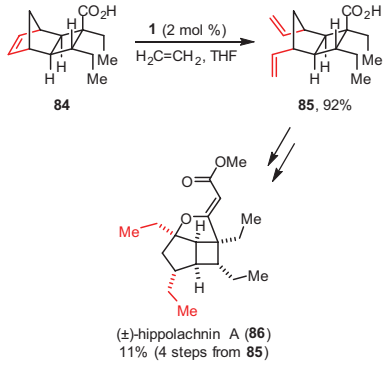
The first applications of Grubbs *Z*-selective ruthenium metathesis catalysts[65] to natural product synthesis were reported by the Grubbs group, when they prepared, in stereochemically pure form, nine lepidopteran female sex pheromones that had been approved by the EPA as insecticide alternatives (**Scheme 23**).[66] Starting from two different seed-oil derivatives, CM with a variety of terminal alkenes provided, either directly or after one step, seven different



Scheme 20. Smith's Use of RCEYEM for a Key Strategic Cyclization That Forms the Tetracyclic Morphine Core. *(Ref. 62)*



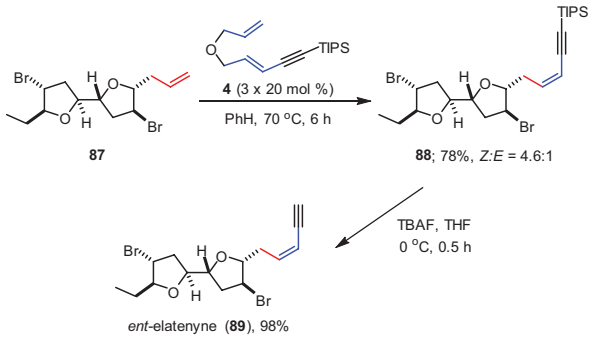
Scheme 19. Spectacular Use of RCEYEM by Schubert and Metz in the Enantioselective Total Synthesis of the Kempene Diterpenes. *(Ref. 60)*



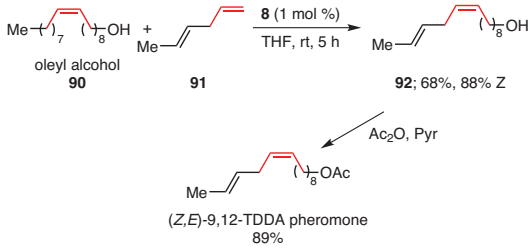
Scheme 21. ROCM in a Collaborative Total Synthesis by Wood and Brown of the Potent Antifungal Agent (±)-Hippolachnin A. *(Ref. 63)*

pheromones. The final two pheromones synthesized each required a total of four steps to complete. Though not structurally complex, these pheromones are otherwise challenging to synthesize because of the remoteness of the functional groups and necessity for control of alkene geometrical isomers. The metatheses employed each required catalyst loadings of 2 mol % or less, with Z-selectivities all greater than 75%. One CM partner, *trans*-1,4-hexadiene (**91**), underwent selective CM at the terminal position to afford **92**, not engaging the (*E*)-alkene moiety, owing to the catalyst's selectivity for *Z* alkenes.

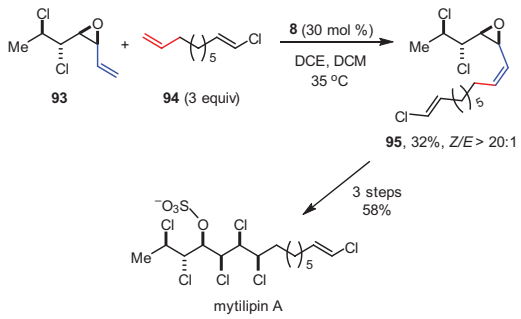
Our group's chlorosulfolipid syntheses took advantage of catalyst **8** for a highly *Z*-selective convergent cross-metathesis of two chlorinated partners (**Scheme 24**).[67] The stereoselective CM between the chlorine-containing vinyl epoxide **93** and the dienyl chloride partner **94** proceeded with very high *Z*-selectivity to give **95**, setting the stage for alkene chlorinolysis, a second dichlorination, and finally sulfation to complete a short synthesis of the chlorosulfolipid mytilipin A. The key aspect of selectivity in reaction partner **94** can be explained in part by the reduced reactivity of alkenyl chlorides and the low rates of cyclooctene formation; however, almost certainly, the key determinant of selectivity involves the recalcitrance of catalyst **8** to engage any kind of *E* alkene, thus sparing the chlorinated alkene moiety of **94** and product **95**.



Scheme 22. Relay RCM-CM in Burton and Kim's Total Synthesis of *ent*-Elatenyne. *(Ref. 64)*



Scheme 23. *Z*-Selective CM in Grubbs's Total Synthesis of Stereochemically Pure Insect Sex Pheromones. *(Ref. 66)*



Scheme 24. *Z*-Selective CM in Vanderwal's Direct Synthesis of Mytilipin A. *(Ref. 67)*

8. Conclusion

Over the past two decades, alkene metathesis has become an essential component of the synthetic chemist's toolbox. The syntheses presented in this review, and the many more which could not be discussed, are evidence of both the objective utility of alkene metathesis as well as the widespread adoption of metathesis as a go-to, reliable reaction in synthetic planning. The featured syntheses also serve to highlight some of the advances made in the field; catalyst and reaction design have overcome supposed limitations of reactivity or selectivity, and implementation in complex settings has illuminated new, non-obvious, and increasingly clever strategies to make use of alkene metathesis. We anticipate continued developments along both of these lines in the coming years.

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