Synthesis of Semiochemicals via Olefin Metathesis

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KEYWORDS. Semiochemicals, biopesticides, olefin metathesis, catalysis, green chemistry

ABSTRACT. Semiochemicals are substances or mixtures that carry messages and are used for communication between individuals of the same or different species. Semiochemicals that are used in pest control are called biopesticides. Conventional pesticides, which are generally synthetically derived and unnatural, inactivate or kill the pests, whereas biopesticides are naturally occurring compounds that attract insects to a trap or interfere with their reproduction. There are several advantages to biopesticides. Compared to conventional pesticides, biochemical-based pesticides are often less toxic and therefore pose a significantly lower impact

on human health and the environment. Moreover, the biopesticides are pest selective and as such, do not negatively impact other organisms such as insects, mammals or birds. Other advantages of biopesticides include high potency, meaning that smaller amounts of biopesticide are required, less resistance by target organisms, and the ability to biodegrade more quickly than conventional pesticides.[1-3] Although the biochemical-based pesticides are very promising materials, their production is often cumbersome and their application is often limited. So far, most of the biopesticides are synthesized by multistep, classical organic reactions which are not economical and pose high environmental impact. However, in recent decades, many efforts have been done to implement cost-effective and safer chemical procedures for the widespread application of biochemical-based pesticides. The purpose of this perspective is to draw the attention of the green chemistry community to the applicability of olefin metathesis reactions in environmental benign and cost-effective biopesticide synthesis. In this article, we review seminal work on the total synthesis of biopesticides using olefin metathesis as a key reaction step, and in doing so, we hope to inspire new ideas for forthcoming olefin metathesis based biopesticide development.

Introduction

One of the most widely used biochemical pesticides are insect pheromones. The pheromones are biochemicals which are excreted by insects and able to trigger a social response. In general, the pheromones can be categorized as sex, territorial, signal, epideictic, aggregation, alarm, releaser, primer, and trail pheromones.[4] From the point of pest control, the naturally occurring insect sex and aggregating pheromones are important classes of biochemical pesticides. These compounds can be used to regulate insect pests by non-toxic mechanisms and

pose no risk to human health. They can be used as attractants (trapping mode) where the bait (a pheromone containing mixture) has to mirror the female scent exactly to capture males. The presence of isomeric impurities, at levels as low as 0.1%, could have an adverse effect on the effectiveness of the bait. On the other hand, pheromones can be applied to disrupt mating and thus disrupt insect reproduction. In this method, a larger amount of biopesticide is applied to the agricultural fields in order to confuse mating pests by overloading their sensory receptors.[5,6] This technique does not require ultra-pure components and can be successful with a mixture of stereoisomers.

Although the biochemical-based pesticides are very promising as sustainable materials, their production is not cost effective and consequently their market price is not competitive with other commercially available, synthetic pesticides. The synthesis of pheromones with classical organic preparation techniques is often cumbersome, it is neither economically profitable nor environmentally benign. However, in recent decades, there has been considerable effort to develop cost-effective and safer, synthetic routes to naturally occurring pesticides.

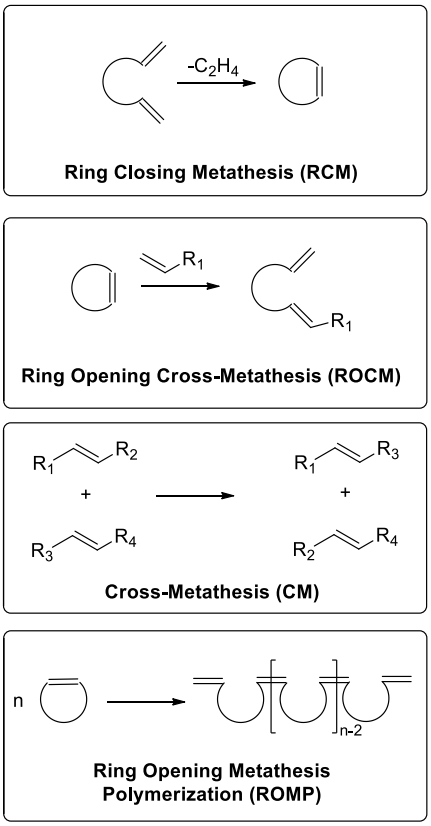
The olefin metathesis reaction has become an important method within industry and its use has produced innovative materials, petrochemicals and pharmaceuticals.[7,8] In 2005, the Nobel Prize in Chemistry was awarded to the three chemists who were involved with the discovery of novel catalysts for the metathesis reaction and the elucidation the reaction mechanism. The application of metathesis reactions within the field of green chemistry is emerging,[9] and notably, the application of olefin metathesis reactions to biopesticide synthesis is receiving much attention.

The word “metathesis” is from the Greek meaning “change of position” or “transposition.” During olefin metathesis reactions, two C=C double bonds are reorganized to

form two new C=C double bonds with an exchange of the olefin substituents (Scheme 1). The reaction is catalyzed by an organometallic species, which, in earlier protocols, was formed *in situ* from multiple components. The industrial application of metathesis reactions beyond the petroleum industry became viable when stable, highly efficient and well-defined systems were available.

A wide range of catalysts has been shown to initiate metathesis reactions. Catalysts are mostly derived from high oxidation state transition metal halides ($MoCl_5$, WCl_6) and main group metal alkyl co-catalyst ($AlEt_3$, $SnBu_4$).[10] The most active and widely used catalysts are molybdenum and ruthenium based systems. The molybdenum-based systems[11,12] are sometimes more active than the ruthenium systems; however, they usually suffer from high oxygen and moisture sensitivity. Therefore, their industrial and large-scale applications are often limited. Recent efforts have led to the formulation of molybdenum catalysts with paraffin-wax,[13] which increased their stability and ease of handling outside of a glovebox. This formulation could potentially expand their industrial relevance.[14] On the other hand being more stable to water and oxygen, the ruthenium catalyst systems have a high functional group tolerance.[15,16]

Scheme 1. The four classes of olefin metathesis reactions



The development of highly active catalyst systems is relevant not only from an economical but green chemistry point of view. Highly active catalytic systems require less energy and lower catalyst loading making chemical conversions even more environmentally benign, in addition to cost-effective. Indeed, the application of catalysis to chemical synthesis is in accordance with the Principles of Green Chemistry.[17] This is especially true for metathesis where the atom economy of the reactions may reach 100% in reactions such as **ROCM** and **ROMP**. Therefore, the application of metathesis chemistry in the valorization of sustainable feedstock materials is an excellent strategy for the development of green and sustainable chemical technologies. Consequently, the synthesis of insect pheromones using olefin metathesis is an emerging area. In this review, we summarize the pioneering work and achievements in the total synthesis of semiochemicals using olefin metathesis as a key reaction step.

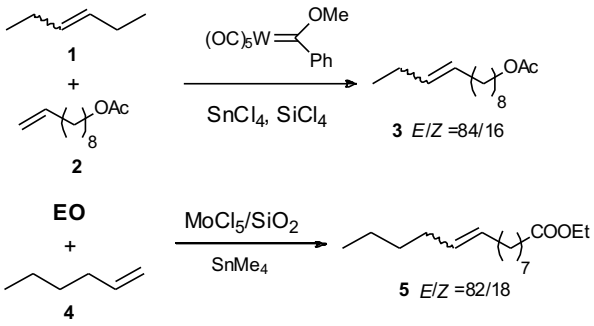
Pheromone synthesis via cross-metathesis (CM)

Many of the insect pheromones are long chained, unsaturated hydrocarbon derivatives, which can be originated from fatty alcohols.[18] Although many of them are relatively simple molecules, their synthesis is often cumbersome due to the well-defined number, position and the stereochemistry of the unsaturated bonds. The classical routes to produce these compounds involved Wittig reactions that generate a large amount of phosphine-oxide waste from the stoichiometric ylide reagent.[19] An alternative and an environmentally benign synthetic procedure is the usage of the cross-metathesis (**CM**) reactions using renewable starting materials, including plant oils (palm, rapeseed, and soybean).[20–26] Since the discovery of stereoselective (*Z* and *E* selective) metathesis catalyst systems, the application of **CM** reactions in pheromone synthesis has become more attractive and more commonplace.

Early Mo and W examples

Early **CM** examples[27,28] (Scheme 2) predominately used ill-defined, homogeneous Fischer-type carbene tungsten[29–31] or heterogeneous molybdenum[32–36] catalytic systems. Most require toxic tin compounds as co-catalysts or promoters, which makes them potentially hazardous for human health and the environment. Typically, the *E*-olefin isomers were isolated as the major products. For example, the olefin metathesis of 1-hexene (**4**) with ethyl oleate (**EO**) using molybdenum as catalyst provided an 82:18 mixture of *E*:*Z* isomers, with the *E*-olefinic ester (**5**) as the major product (Scheme 2).[35]

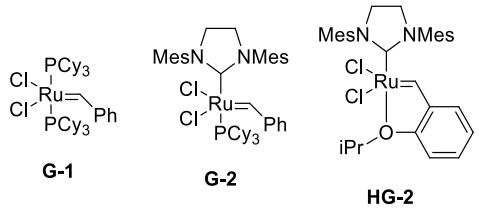
Scheme 2. Early pheromone metathesis examples (**EO** = ethyl oleate)



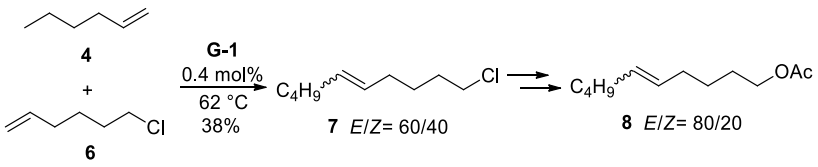
Ru-alkylidenes

The discovery of ruthenium-based metathesis catalyst systems (Scheme 3) opened a new era for the synthesis of pheromones having a wide range of functionalities. Due to the higher stability, functional group tolerance, and lower air and water sensitivity as compared to the molybdenum-based systems, ruthenium-based metathesis catalysts employing Grubbs catalysts have become dominant in the industrial applications of the olefin metathesis. The so-called second generation Grubbs- and Hoveyda-Grubbs catalysts (e.g., **G-2**, **HG-2**) are in general more active than the first generation one (e.g., **G-1**).[37] Using these catalysts, a high conversion of renewable feedstock including vegetable oils into value-added chemicals such as biopesticides can be achieved.

Scheme 3. Grubbs catalysts for ruthenium-based olefin metathesis reaction (**Mes** = 2,4,6-trimethylbenzene)

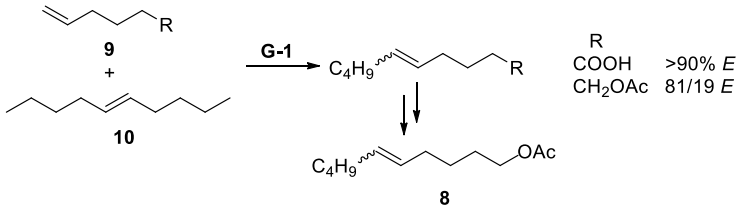


Scheme 4. Synthesis of the pheromone of *Anarsia lineatella* (**8**) from terminal alkenes



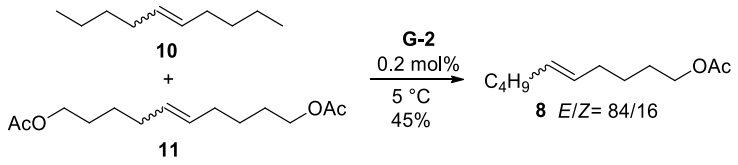
The synthesis of 5-decenyl acetate (**8**), the sex pheromone of peach twig borer (*Anarsia lineatella*), is one of the most extensively studied **CM** reactions (Scheme 4).[38,39] An example is the reaction of 1-chloro-5-hexene (**6**) and 1-hexene (**4**) in the presence of Grubbs catalyst, **G-1**, which provided the desired olefin **8** as an 80/20 mixture of *E*/*Z* isomers, respectively. The use of α-alkene **4** led to the formation of the sensitive Ru-methylidene species. However, the application of an internal alkene, 5-decene (**10**) instead, avoided the formation of the undesired Ru-methylidene intermediate and significantly increased the overall yield of **8** to 87% (Scheme 5).[39]

Scheme 5. Synthesis of the pheromone of *Anarsia lineatella* (**8**) from internal alkene **9** and **10**



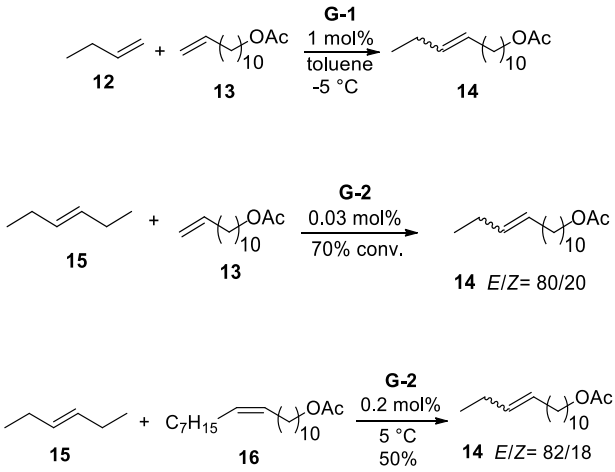
The use of symmetric, unsaturated diacetate, **11** and low temperature (5°C) gave **8** as a mixture of *E*/*Z* isomers (Scheme 6). A typical side reaction of ruthenium initiated olefin metathesis is double bond migration within the product, but under these conditions, the formation of side-product was negligible (less than 0.1%). This is highly important and should be considered, as the undesired isomers can have a negative impact on the effectiveness of the pheromone as a biopesticide.[40,41]

Scheme 6. Synthesis of pheromone of *Anarsia lineatella* **8** by cross-metathesis of internal alkenes



Another highly relevant example of this discussion is the synthesis of omnivorous leafroller's (*Platynota stultana*) pheromone (**14**).[38,39,42] Three synthetic routes to **14** that involve olefin metathesis as a key reaction step are shown in Scheme 7. In the first example, the metathesis reaction of 1-butene (**12**) and acetate **13** using Grubb's catalyst **G-1** provided the pheromone **14** as a mixture of *E*/*Z* isomers. Notably, the metathesis of compounds **15** and **16** with **G-2** provided an isomeric mixture of the pheromone in a ratio similar to that of the naturally-occurring mixture (*E*/*Z*= 82/18).[43]

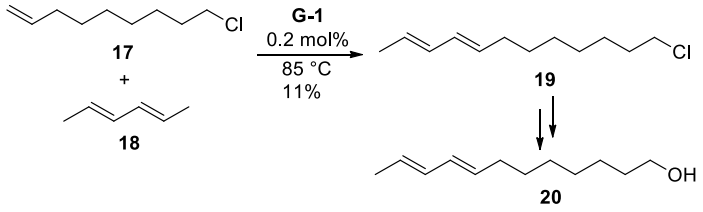
Scheme 7. Three different routes to *E*-9-decenyl-acetate (**14**), the pheromone of *Platynota stultana*



The synthesis of the codling moth (*Cydia pomonella*) pheromone (**20**) is noteworthy since the conjugated *E*,*E* double bond system of the pheromone was constructed using **G-1** catalyzed olefin metathesis reaction (Scheme 8).[38] Reaction of 2,4-hexadiene (**18**) with the chloro olefin **17** provided the desired *E*,*E* dienyl intermediate **19** which was then converted to the pheromone **20**. Although the yield of the metathesis reaction is low (11%), this reaction is highly relevant as it

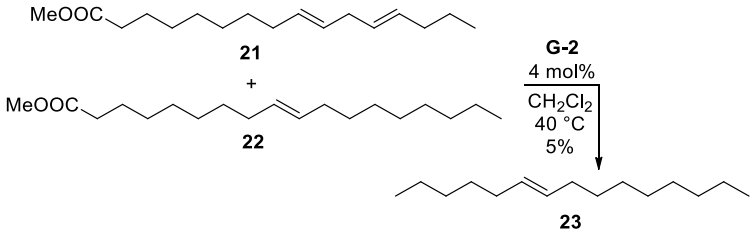
demonstrates the applicability of metathesis reactions in the synthesis of conjugated double bond systems.[44–47]

Scheme 8. Synthesis of pheromone of *Cydia pomonella* (**20**)



The use of non-edible vegetable oil derivatives, as renewable feedstock from tobacco (*Nicotiana tabacum*), were also investigated as starting materials for the synthesis of semiochemicals using the Grubbs catalyst, **G-2**.[48] The cross-metathesis of methyl esters, **21** and **22**, resulted in the formation of 6-pentadecene (**23**), an alarm pheromone component of the acarid mite (Scheme 9). Unfortunately, the 5% yield of desired product, **23**, is quite low.

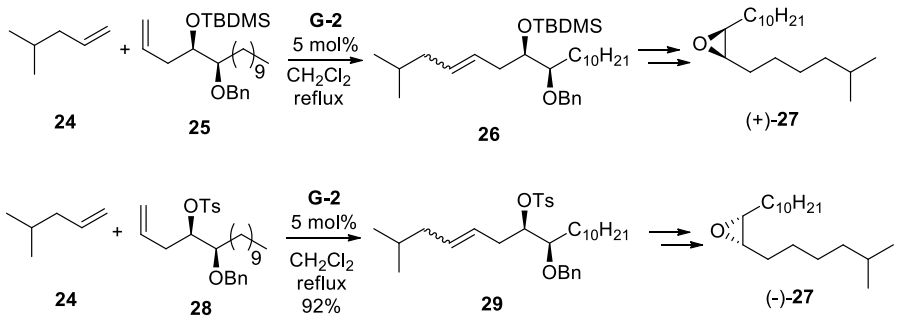
Scheme 9. Cross-metathesis of **21** and **22** provided the pheromone of acarid mite (**23**)



Cross-metathesis of chiral compounds is a very effective tool for introducing chirality into organic molecules and has great relevance to the synthesis of enantiomerically pure, chiral pheromones. For example, an enantiodivergent synthesis of both enantiomers of disparlure, the gypsy moth (*Porthetria dispar L.*) pheromone, has been reported. (+)-Disparlure [(+)-**27**] was prepared from the chiral intermediate, **26**, which was prepared via a **CM** reaction using Grubbs

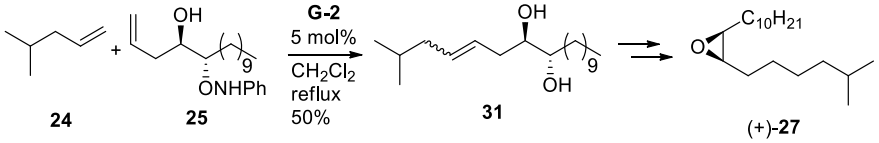
catalyst, **G-2** (Scheme 10).[49] Similarly, the corresponding enantiomer of the pheromone, (-)-**27**, was prepared from intermediate **29**.

Scheme 10. Enantiodivergent synthesis of both enantiomers of disparlure (**27**)



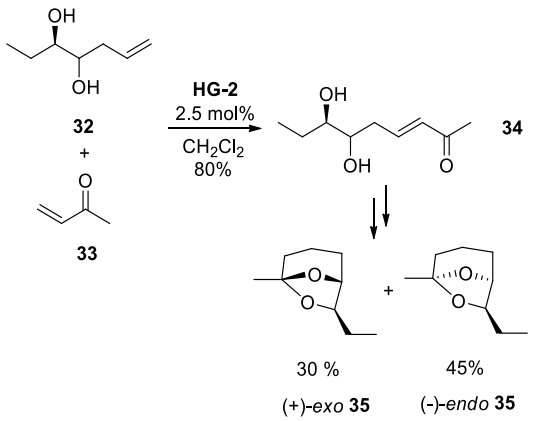
A second, total synthesis of (+)-disparlure and its *E*-isomer using asymmetric catalysis was reported by Kim who employed commercially available D-proline as a chiral catalyst for the synthesis of **25** (Scheme 11).[50]

Scheme 11. Synthesis of pheromone **(+)-27** from optically active amino alcohol (**25**)



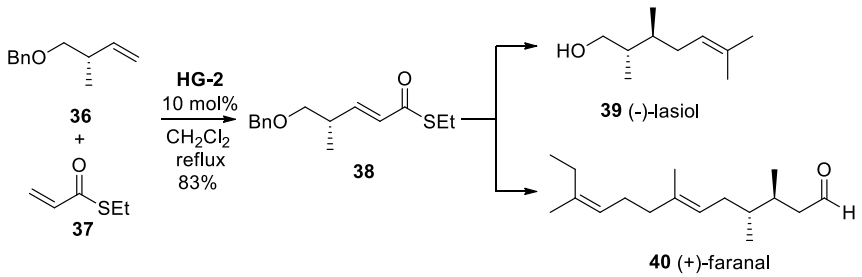
In another example, the (+)-*exo* and the (-)-*endo* stereoisomers of brevicomin (**35**), a pheromone of numerous species of the *Dendroctonus* family, were synthesized from commercially available starting materials via **CM** (Scheme 12).[51]

Scheme 12. Synthesis of the *exo* and *endo* isomers of brevicomin (**35**)



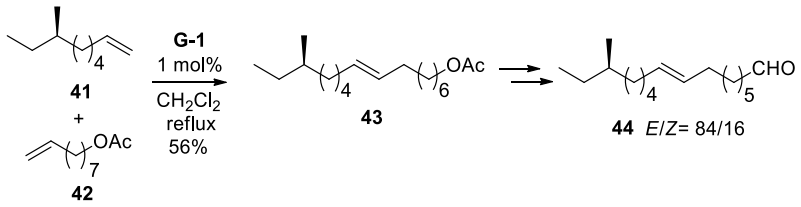
The pharaoh ant (*Monomorium pharaonis*) trail pheromone (+)-faranal (**40**) and Lasius meridionalis ant pheromone (-)-lasiol (**39**) have been synthesized using **CM** reactions. The synthetic route to **39** involved six steps. The key metathesis reaction provided the desired enone, **38**, in a high yield of 83%. (+)-Faranal was also prepared from intermediate **38**, in a total of nine steps (Scheme 13).[52]

Scheme 13. Synthesis of pharaoh ant (*Monomorium pharaonis*) pheromones (**39** and **40**)



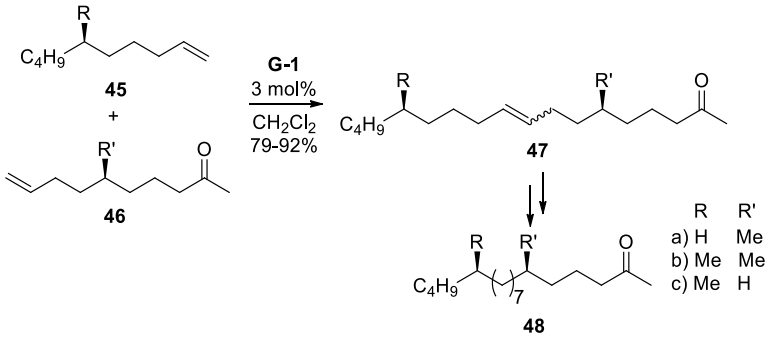
The olefin-containing aldehyde **44** is the sex pheromone of some species from the *Trogoderma* genus. The key step in the total synthesis was a cross-metathesis reaction of alkenes **41** and **42** that provided intermediate **43** in moderate yield of 56% (Scheme 14). Higher stereoselectivity was obtained using the less reactive catalyst **G-1**. Moreover, application of **G-2** led to a high degree of undesired double bond migration resulting in a mixture of olefins as the reaction products (Scheme 14).[53]

Scheme 14. Synthesis of pheromone **44**, the sex pheromone of species from the *Trogoderma* genus



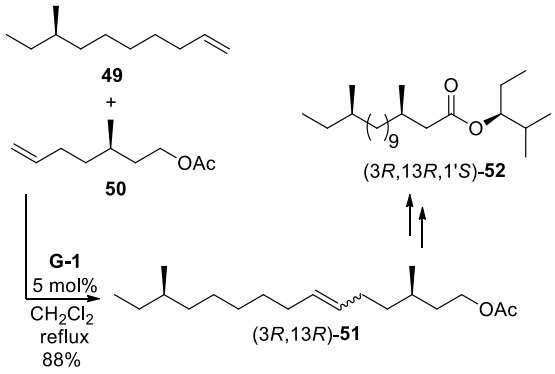
Cross-metathesis was used to prepare the stereoisomers of female-produced, sex pheromone of *Lyclene dharma dharma* moth, along with the stereoisomers of selected derivatives (Scheme 15).[54]

Scheme 15. Synthesis of moth (*Lyclene dharma dharma*) pheromone stereoisomers



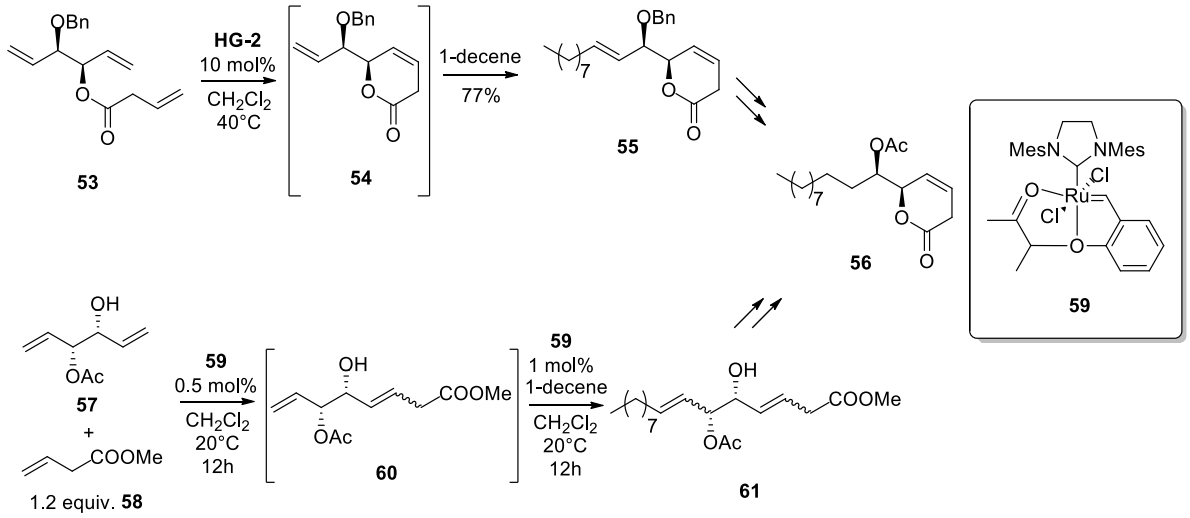
Cross-coupling reactions using Grubbs catalyst systems were used to produce four isomers of (3*R*,13*R*,1'*S*)-1'-ethyl-2'-methylpropyl-3,13-dimethylpentadecanoate (**52**) which are pheromone components from the Paulownia bagworm (*Clania variegata*) (Scheme 16).[24] Biological testing of each stereoisomer indicated that the (3*R*,13*R*,1'*S*)-isomer, **52**, is bioactive one (Scheme 16).[25]

Scheme 16. Synthesis of pheromone of *Clania variegata* (**52**)



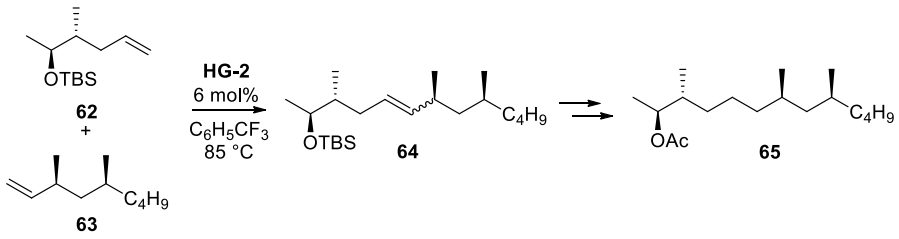
The total synthesis of (-)-6-acetoxy-5-hexadecanolide [(5*R*,6*S*)-**56**], the pheromone of the mosquito *Culex pipiens fatigans* and *Culex quinquefasciatus*, was carried out by one-pot ring-closing and cross-metathesis (**RCM/CM**) reactions (Scheme 17),[57,58] based on the general method of Piva *et al*.[59,60]

Scheme 17. Synthesis of **56**, the pheromone of *Culex pipiens fatigans* and *Culex quinquefasciatus*



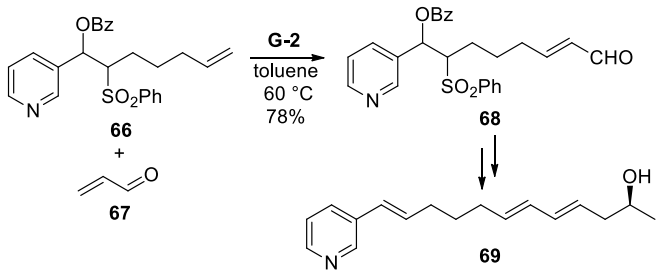
The total synthesis of the female sex pheromone of *Macrodiprion nemoralis* (**65**) via **CM** using a Hoveyda-Grubbs second generation catalyst was reported by Loh *et al.* (Scheme 18).[61]

Scheme 18. Synthesis of the sex pheromone of *Macrodiprion nemoralis* (**65**)



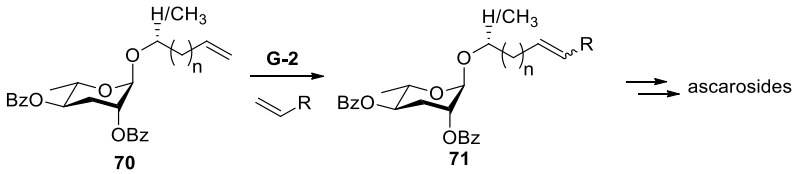
The triene haminol-A (**69**), an active substance towards nematode *Caenorhabditis elegans*, was synthesized using **G-2** catalyzed olefin metathesis. The key **CM** step involved the alpha-alkene **66**, with its masked alkene, and crotonaldehyde (**67**). The reaction provided key intermediate **68** that was eventually converted to the final product **69** after unmasking of the alkene via elimination of an acyloxysulfone (Scheme 19).[62]

Scheme 19. Synthesis of haminol-A (**69**)



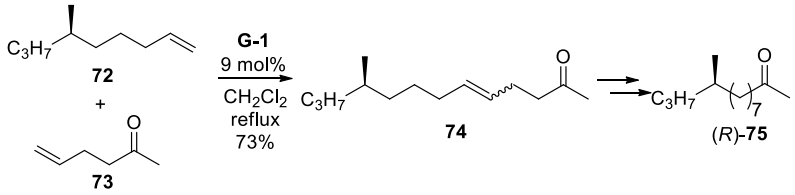
The *Caenorhabditis elegans* secretes ascarosides that can act as semiochemicals. More than 20 ascarosides were synthesized as potential dauer pheromones that are important to nematode development (Scheme 20).[63]

Scheme 20. Synthesis of dauer pheromones of *Caenorhabditis elegans* via **CM**



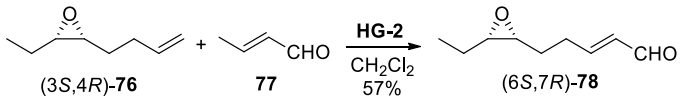
The enantiospecific total synthesis of (*R*)-10-methyl-2-tridecanone female sex pheromone of Southern corn rootworm (*Diabrotica undecimpunctata howardi*) (**75**) has been reported. The nine-step synthesis features a cross-metathesis as the key transformation. Reaction of (*R*)-6-methyl-1-nonene (**72**) and 5-hexen-2-one (**73**) in the presence of Grubbs catalyst **G-1** provided the key intermediate **74** in moderate yield of 73% (Scheme 21).[64]

Scheme 21. Synthesis of pheromone of *Diabrotica undecimpunctata howardi* (**75**)



The male pheromone of the red-necked longhorn beetle (*Aromia bungi*), **78**, was prepared via a ruthenium catalyzed **CM** reaction of optically pure (3*S*,4*R*)-**76**, and but-2-enal (**77**) (Scheme 22). The requisite alkenyl epoxide (3*S*,4*R*)-**76** was synthesized from *Z*-penten-2-ol in three steps that employed a Sharpless oxidation reaction and a catalytic amount of D-(-)-diethyl tartarate. Both optically active enantiomers of the pheromone were synthesized in high *ee*. The enantiomer of the target pheromone, (6*R*,7*S*)-**78**, was prepared by using L-(-)-diethyl tartarate, in Sharpless oxidation.[65]

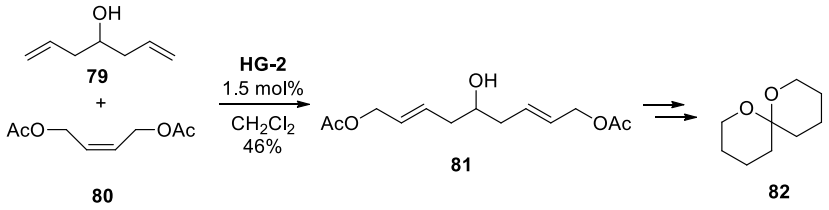
Scheme 22. Synthesis of **78**, pheromone of *Aromia bungi*



A cross-metathesis reaction was a key transformation in the total synthesis of a racemate mixture of pheromone **82**, a ketal isolated from fruit flies *Dacus oleae* and *Bactrocera oleae* (Scheme 23).

Intermediate **81** was obtained in 46% in the **CM** involving commercially available starting materials **79** and **80** and catalyst **HG-2**.[65]

Scheme 23. Synthesis of the pheromone of *Dacus oleae* and *Bactrocera oleae* (**82**)

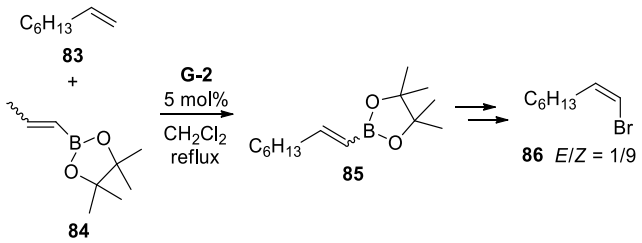


Z-selective Ru-alkylidene catalyzed cross-metathesis reactions

The Grubbs first generation (**G-1**) and second generation (**G-2**) catalysts showed predominantly *E* selectivity (80%);[66] however, a high percentage of insect pheromones have *Z*-alkene moieties. Consequently, cross-metathesis reactions were not the transformation of choice. Such compounds were mostly synthesized by Wittig reaction with stabilizer ylides or by the reduction of alkynes with hydroboranes or Lindlar catalyst.[19] Unfortunately, borane reduction suffer a similar liability as Wittig reactions, namely the stoichiometric amount of side products from the reagents, while the Lindlar catalysts contain toxic lead-salts. A greener, synthetic approach would be preferable.

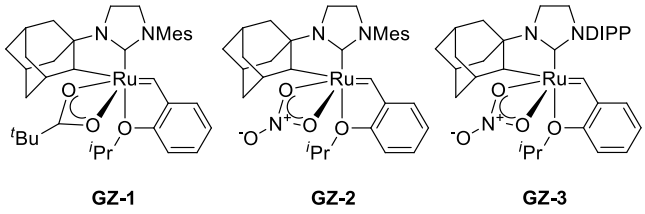
Early examples of synthetic routes to target compounds containing *Z*-alkenes using ruthenium catalyzed **CM** required additional modification of intermediate *E*-alkenes. For example, metathesis of **83** and **84** produced the *E*-vinyl borane (**85**) as the major product, which was subsequently transformed to the desired *Z*-vinyl bromide intermediate as a mixture of stereoisomers (Scheme 24).[67]

Scheme 24. Synthesis of *Z*-alkenes via *E*-vinyl-boron intermediate



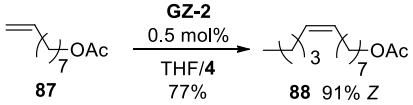
The selectivity limitation of the early ruthenium catalysts has been addressed and *Z*-selective Ru catalysts have been reported (**GZ-1**) which enables the convenient synthesis of *Z*-alkenes with reasonable yields and stereoselectivity.[68] Some of these catalysts are already commercially available (Scheme 25).

Scheme 25. *Z*-selective catalysts (Mes = 2,4,6-trimethylbenzene, DIPP = 2,6-di-isopropylbenzene)



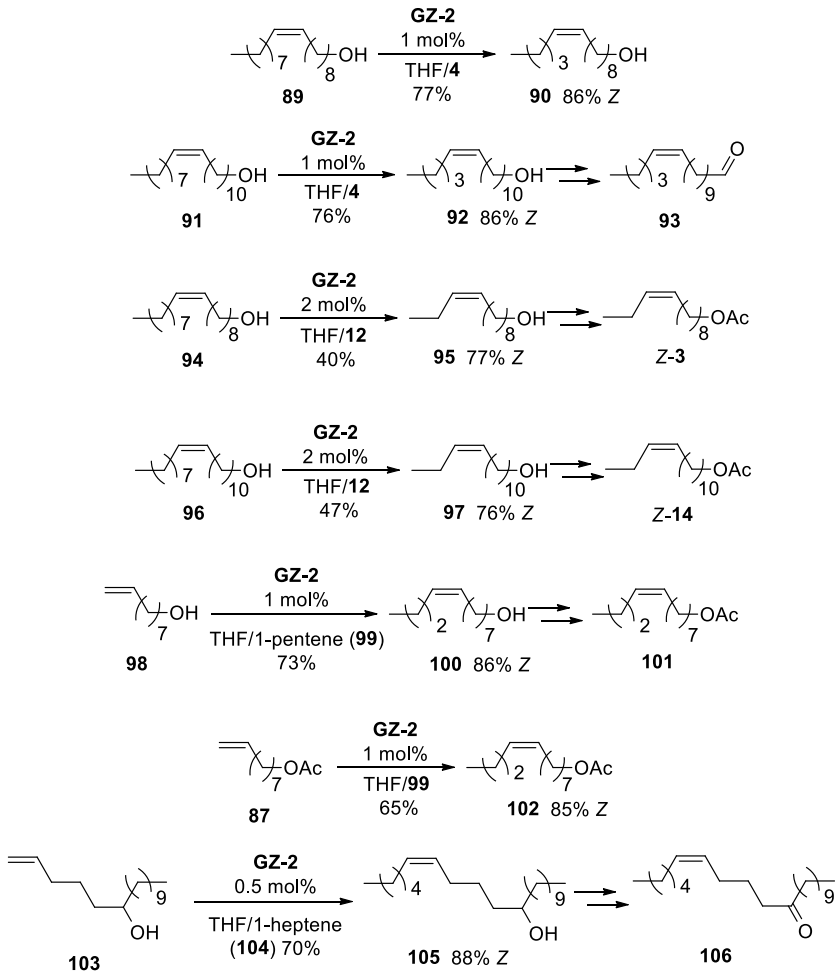
The utility of these improved catalysts was demonstrated in the total synthesis of pheromone **88** (Scheme 26). The synthesis is one of the first industrially relevant examples of the use of a C-H activated Grubbs catalyst **GZ-2**,[69] is a highly efficient ruthenium catalyst (TON = ca. 1000) that can be employed for the synthesis of *Z*-olefin containing pheromones and biomaterials using low catalyst loading (e.g., 0.5 mol%).

Scheme 26. Synthesis of pheromone **88**



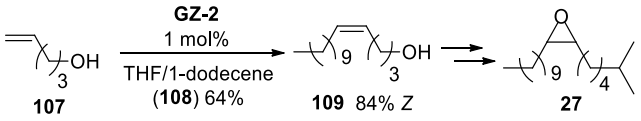
The use of catalyst, **GZ-2**, produced the *Z*-alkenyl pheromone **88** in good yield (77%) and high *Z* to *E* selectivity (91% *Z*) in only one step, instead of six steps as previously reported in the literature.[70] One year after the publication, the synthesis of seven additional pheromones were reported using the same catalyst.[71,72] The **CM** reactions proceeded with good yields (76%-88%) and stereoselectivity (76-86% *Z*) (Scheme 27).

Scheme 27. Synthesis of seven *Z*-monoene pheromones



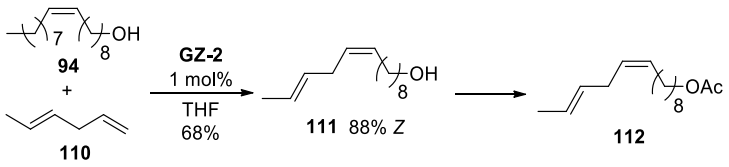
The **GZ-2** catalyst was also employed to prepare racemic disparlure (**27**) in which the key metathesis reaction gave predominately the *Z*-alkenyl intermediate **109** in moderate yield (64%) and good selectivity (84% Z). (Scheme 28).

Scheme 28. Synthesis of disparlure (**27**)



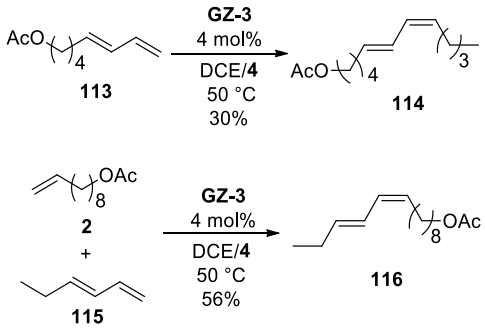
An advantage of the **GZ-2** catalyst is that it does not tend to react with *E*-alkenes. The selectivity provides a new route for the preparation of unconjugated *E*,*Z* dienes. The reaction between *E*-1,4-hexadiene (**110**) and **94** resulted in the exclusive formation of unconjugated **111**, which then subsequently could be acylated to **112**, the pheromone of olive pyralid moth (*Euzophera pinguis*). The use of **GZ-2** simplified the route to **112** to just 2 steps instead of the formerly reported six steps (Scheme 29).[73,74]

Scheme 29. Synthesis of isolated diene (**112**), the pheromone of *Euzophera pinguis*



Further catalyst development led to the identification of **GZ-3** (see Scheme 25 for structure),[75] a catalyst that enables the synthesis of *conjugated E*,*Z*-dienes. **GZ-3** does not react and isomerize *E*-double bonds, making possible the synthesis of *E*,*Z* conjugated dienes. For example, dienes **114** and **116** were prepared with high *Z*-selectivity (>90%) while retaining the *E*-configurations of the starting materials **113** and **115**, albeit in low to moderate yields (Scheme 30).

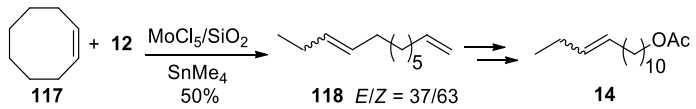
Scheme 30. Synthesis of conjugated dienes with **GZ-3**



Application of ring-opening cross-metathesis (ROCM)

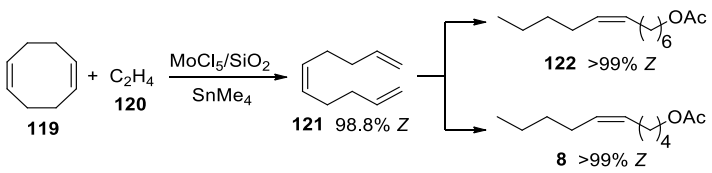
Ring-opening cross-metathesis (**ROCM**) provides a convenient and unique method to produce *Z*-alkenes. The use of molybdenum catalysts has been extensively studied in this area of olefin metathesis. The previously mentioned omnivorous leafroller pheromone (**14**) was successfully prepared using **ROCM** (Scheme 31).[76]

Scheme 31. Synthesis of omnivorous leafroller pheromone **14** via **ROCM**



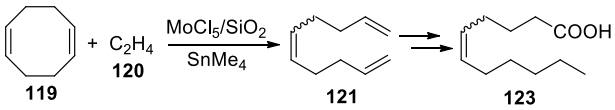
In another example, *Lepidoptera* sex pheromones **122** and **8** were generated using the **ROCM** reaction. The key step produced the expected *Z*-triene, **121**, with excellent *Z*-selectivity (98.8%). The *Z*-triene was subsequently converted to the pheromones **122** and **8** (Scheme 32).[77]

Scheme 32. Synthesis of *Lepidoptera* pheromones (**122** and **8**)



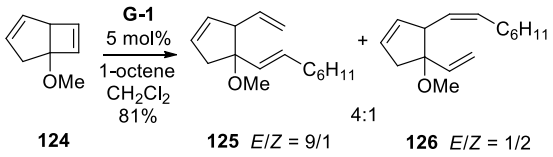
The natural occurring pheromone, **123**, of the Varied carpet beetle (*Anthrenus verbasci*) is a mixture of stereoisomers (*E*/*Z* = 15/85). The earlier reported preparations of the pheromone employed Witting reactions that provided mixtures of *E*/*Z* isomers with contrasting selectivities (*E*/*Z* = 25/75[78] and *E*/*Z* = 82/18).[79] **ROCM** (Scheme 33) made it possible to synthesize the exact *E*/*Z* ratio of isomers found in the naturally occurring pheromone by changing the metathesis conditions and preparing *E*/*Z* = 1/99 and *E*/*Z* = 79/21 mixtures then mixing them to get the desired ratio.[80]

Scheme 33. Synthesis of *Anthrenus verbasci* pheromone **123**



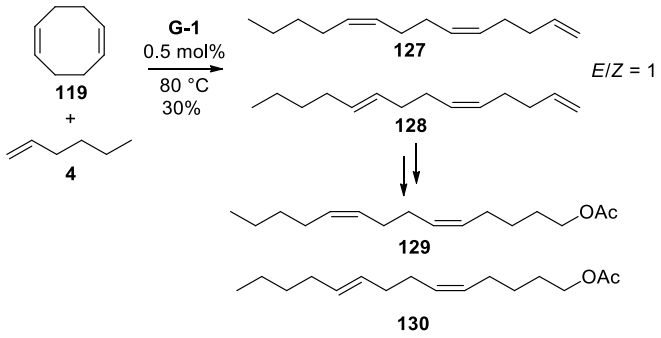
The brown algae pheromones, **125** and **126** were synthesized with moderate regioselectivity (4:1 ratio of **125**:**126**) and stereoselectivity (*E*/*Z* ratios of 9/1 and 1/2) (Scheme 34).[81]

Scheme 34. Synthesis of brown algae pheromones (**125** and **126**) with 1-octene



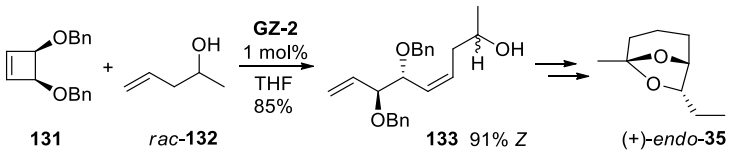
Similar to the above mentioned examples, **G-1** catalyzed routes to produce Glossyplur (**130**) the pink bollworm (*Pectinophora gossypiella*) pheromone as a mixture of *E*/*Z* isomers, as can be seen in Scheme 35.[38]

Scheme 35. Synthesis of pheromone of *Pectinophora gossypiella* (**130**)



The (+)-*endo* enantiomer of the already mentioned brevicomin (**35**) was formed with excellent enantioselectivity by applying an asymmetric ring-opening cross-metathesis (**AROCM**) with the *Z*-selective catalyst **GZ-2** (Scheme 36).[82]

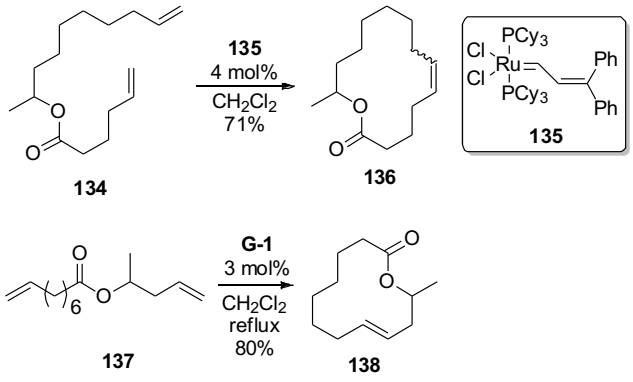
Scheme 36. Synthesis of brevicomin (**35**)



Ring-closing metathesis (RCM) examples

Ring-closing metathesis (**RCM**) reactions are also proven to be useful in pheromone synthesis. Due to unfavourable enthalpic and entropic effects, the formation of medium- and large-sized rings are a more complex synthetic task in general, compared to small ring closures. However, **RCM** is amongst the most straightforward entries into large ring systems and favorable compared to all current alternatives. **RCM** has also been used for the construction of bridged systems that are so ubiquitous in natural products. Two, early examples of the use of Ru catalyzed **RCM** reactions to produce macrocycles are shown in Scheme 37. In the first example, the aggregation pheromone of the flat grain beetle (*Cryptoletes pusillus*) **136** was generated in moderate yield (71%) from the diene **134** using the conjugated Ru catalyst, **135**.[83,84] In the second example, macrocycle **138** was produced from **137** using **G-1** in good yield (80%).

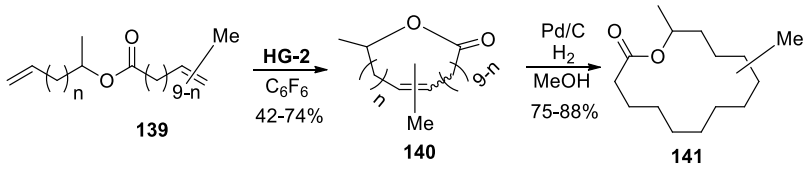
Scheme 37. Preparation of pheromone macrocycles **136** and **138**



The methyl substituted 11-dodecanolidines (2-, 4-, 6-, 8-, and 10-methyl-11-dodecanolide) (**141**) were prepared from the appropriate terminal dienes using ruthenium catalyst **HG-2**. **RCM** followed by reduction of the resulting olefin provided pheromone-like compounds **141** (Scheme 38). The synthesis and its **RCM** reaction were essential to the identification of the putative

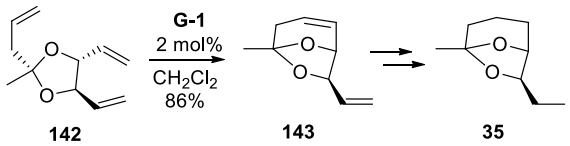
semiochemical, 2-methyl-11-dodecanolidine that is secreted by mantellid frogs (*Gephyromantis moseri*).[85]

Scheme 38. Preparation of pheromone-like macrocyclic esters (**141**) by olefin metathesis followed by hydrogenation



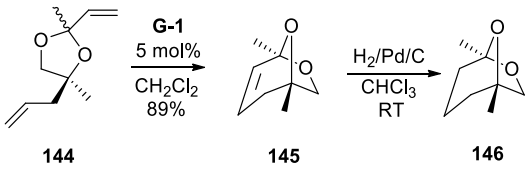
RCM has been used in the preparation of chiral compounds such as brevicomin (**35**). The synthesis of brevicomin via **CM** and **AROCM** reactions were highlighted earlier in this review. In this example, the stereoselective construction of the 6,8-dioxabicyclo[3.2.1]-octane skeleton of brevicomin was produced by the desymmetrization of triene substrate **142** via ring-closing metathesis (Scheme 39).[86]

Scheme 39. Synthesis of brevicomin (**35**) via **RCM**



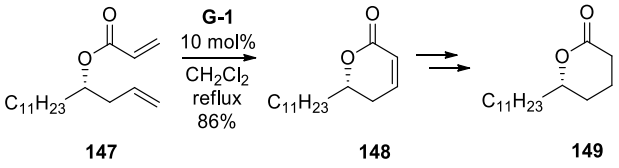
The synthesis of (-)-frontalin, the pheromone of the southern bark beetle (*Dendroctonus frontalis*), was also achieved in only four steps and high yield using **RCM** as a key step (Scheme 40). Cyclization of the diene precursor **144** using ruthenium-catalyzed **G-1** gave the tricyclic ketal **145** that was reduced to give (-)-frontalin. This was the first report of the formation of small ring bridged oxygen heterocycles using **RCM**.[87]

Scheme 40. Synthesis of (-)-frontalin, pheromone of *Dendroctonus frontalis* (**146**)



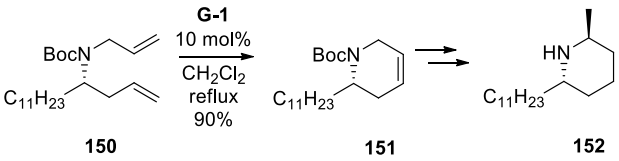
The enantioselective, total synthesis of the oriental hornet (*Vespa orientals*) pheromone, **149**, was completed by using **G-1** (Scheme 41).[88]

Scheme 41. Synthesis of pheromone of *Vespa orientals* (**149**)



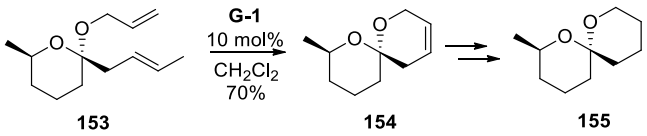
Intermediate (**147**) was synthesized later using L-proline as a chiral inductor and closed in the same **RCM** fashion to produce **148**.[89] The synthesis of fire ant (*Solenopsis invicta)* pheromone (**152**) employed a similar **RCM**-reduction protocol (Scheme 42).[89]

Scheme 42. Synthesis of pheromone of *Solenopsis invicta* (**152**)



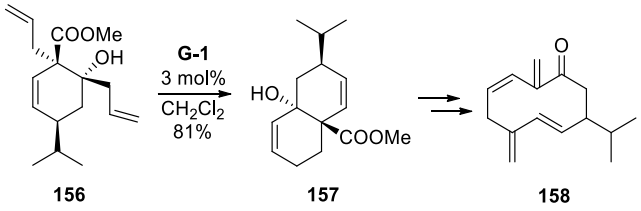
Olefin metathesis reaction can also be used for the total synthesis of biologically active spiro compounds including the semiochemical of the (*Andrena*) bee genus, **155**. The construction of the spiroketal **154** via ruthenium catalyzed ring-closing reaction of **153** was carried out with retention of the stereochemical integrity (Scheme 43). The **RCM** approach demonstrates an alternative method toward the efficient synthesis of spiroketals.[90,91]

Scheme 43. Synthesis of pheromone of *Andrena* bee genus (**155**)



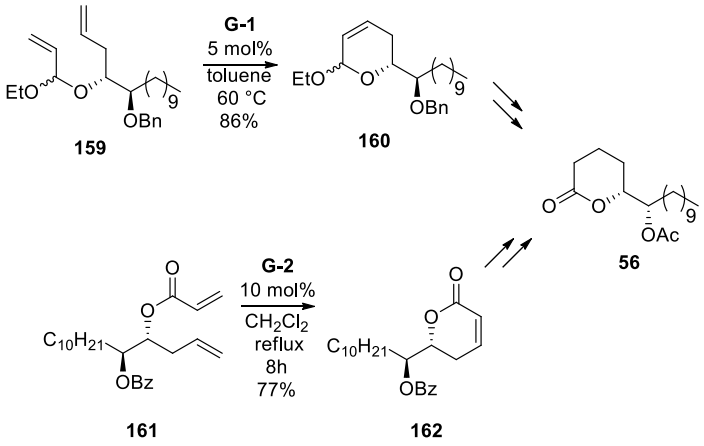
The sex pheromone, (±)-Periplanon C (**158**), of the American cockroach (*Periplaneta Americana)* was synthesized in eleven steps, including a **G-1** catalyzed **RCM** (Scheme 44). **RCM** provided **157** which was followed by ring enlargement by β-fragmentation in a new sequence for stereoselective synthesis of medium-sized (*Z*)-cycloalkenes.[92]

Scheme 44. Synthesis of American cockroach (*Periplaneta Americana)* sex pheromone (±)-Periplanon C (**158**)



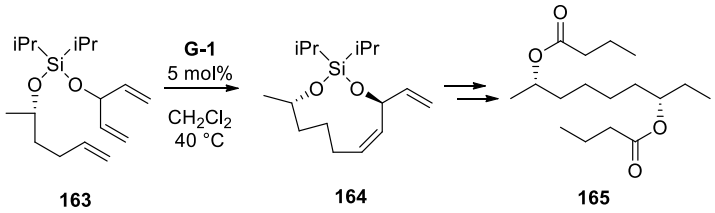
The attractant pheromone, **56**, of mosquito (*Culex pipiens fatigans*) was prepared from chiral building blocks[93] and from chiral additives[94] (Scheme 45). In both cases the key step of the pheromone synthesis is the ruthenium catalyzed formation of the six-membered ring from compound **159** and **161** respectively.

Scheme 45. Synthesis of pheromone of *Culex pipiens fatigans* (**56**) by ring-closing metathesis



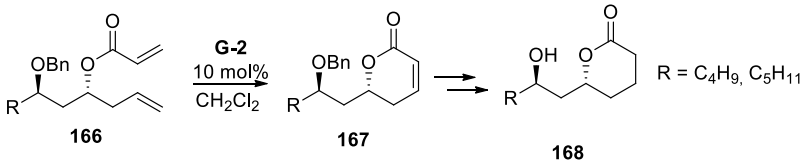
The enantioselective synthesis of **165**, the sex pheromone of the orange wheat blossom midge (*Sitodiplosis mosellana*) was reported by Pickett. The 2*S*,7*S* configuration was revealed to have the highest biological activity (Scheme 46).[95]

Scheme 46. Synthesis of pheromone of *Sitodiplosis mosellana* (**165**)



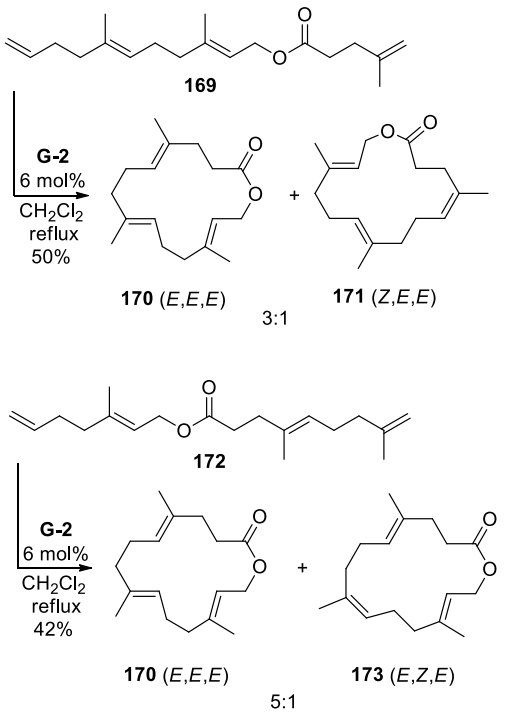
The two pheromones of the giant white butterfly (*Idea leuconoe*) pheromone (**168**) were synthesized by ruthenium (**G-2)** catalyzed **RCM** of **166** (Scheme 47).[96]

Scheme 47. Synthesis of pheromones of *Idea leuconoe* (**168**)



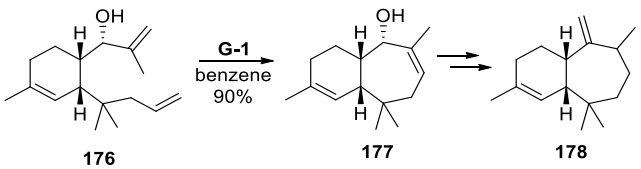
G-2 catalyzed **RCM** was used to construct the trieneyl pheromones of the small and large cabbage butterflies' (*Pieris rapae* and *P. brassicae*). The mixtures of three different stereoisomers [(*E*,*E*,*E*)-**170**, (*Z*,*E*,*E*)-**170**, (*E*,*Z*,*E*)-**170**] were prepared as shown in Scheme 48.[97]

Scheme 48. Synthesis of macrocyclic pheromones of *Pieris rapae* and *P. brassicae* (**170**, **173**)



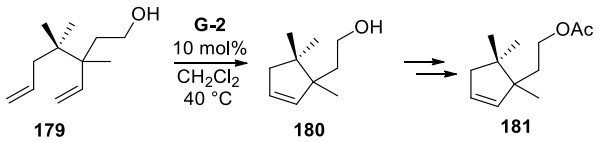
The semiochemical, **176**, of the sandfly (*Lutzomyia longipalpis*) was synthesised via a five-step sequence. The ability to conduct the ruthenium catalyzed **RCM** of **174** on preparative scale made it possible carrying out extensive bioassays of **176** (Scheme 49).[98]

Scheme 49. Synthesis of sandfly's (*Lutzomyia longipalpis*) pheromone **176**



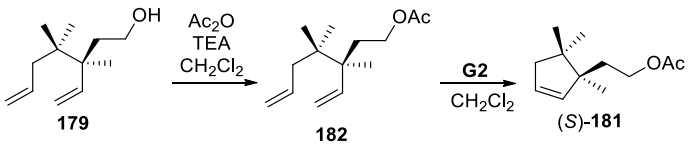
The enantioselective synthesis of the sex pheromone from the longtailed mealybug (*Pseudococcus longispinus*) was reported by Reddy. The synthesis employed racemic starting materials and involved a Meyer-Schuster-Claisen rearrangement and a **RCM** reaction using **G-2** as the catalyst (Scheme 50). The overall yield of the synthesis was 50%.[99]

Scheme 50. Synthesis of pheromone of *Pseudococcus longispinus*, **181**



Changing the order of the metathesis and acylation steps significantly improved the overall yield of **181** (from 50% to 71%) (Scheme 51). The starting material **179**, which features adjacent quaternary carbons, was generated by a Claisen rearrangement. The acylation of **179** followed by ruthenium catalyzed **RCM** led to the enantiomerically pure (*S*)-**181**.[100] Both enantiomers of the pheromone **181** were synthetized by this route. The (*S*)-(+)-enantiomer showed high activity towards male mealybugs while the (*R*)-(-)-enantiomer showed neither attractive nor inhibitory activity.

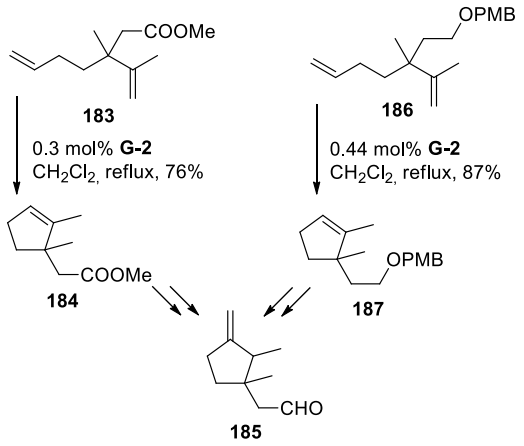
Scheme 51. Synthesis of pheromone of mealybugs [(*S*)-**181**]



Two alternative ways for the racemic synthesis of the female-produced sex pheromone, **185**, of the Pineapple mealybug (*Dysmicoccus brevipes*) was reported by Tabata. Key steps included an Ireland-Claisen rearrangement or conjugate addition for the preparation of the quaternary carbon

center and **RCM** for the construction of the cyclopentene ring.[101] The authors identified the absolute configuration of the biologically active component as (1*S*,2*S*)-**185** (Scheme 52).[102]

Scheme 52. Different synthetic routes for pheromone of *Dysmicoccus brevipes* (**185**) (PMB = 4-Methoxybenzyl)

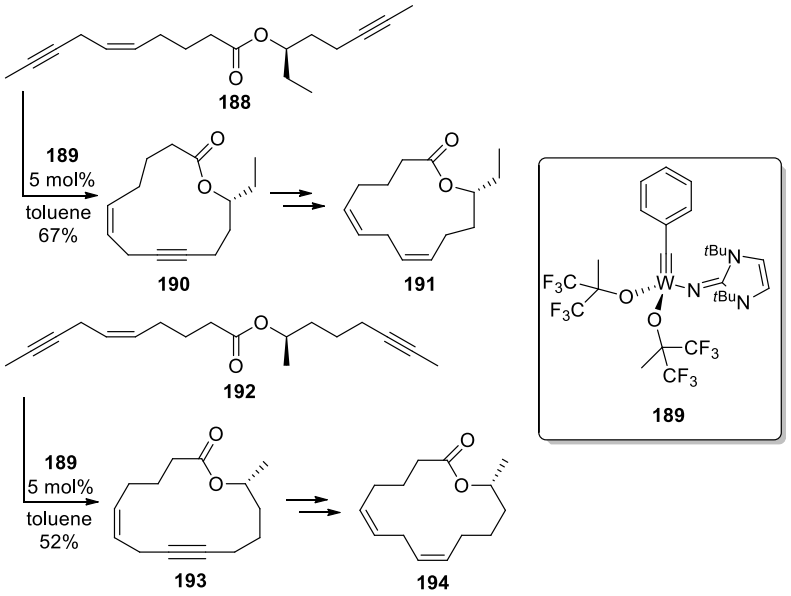


Other methods

RCAM (W and Mo)

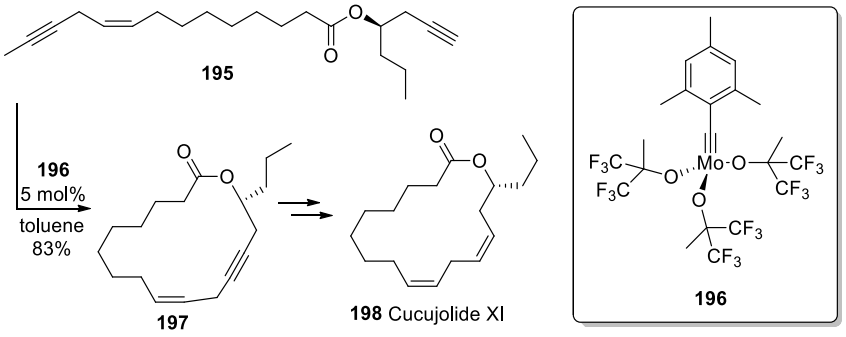
Ring-closing alkyne metathesis (**RCAM**) is an elegant method to form unsaturated macrocycles.[103,104] Cucujolides (macrolide lactones) are part of the pheromone mixtures of the cucujid grain beetle. Cucujolide V (**194**) and cucujolide X (**191**) compounds were synthesized via tungsten based homogeneous catalysis with high yield at moderate reaction condition (Scheme 53).[105]

Scheme 53. Synthesis of cucujolides, using tungsten metathesis catalyst (**189**)



From the same family of compounds, cucujolide XI was synthesized by **RCAM** using molybdenum catalyst **196**. The highly active organometallic complex, **196**, allowed the use of a terminal alkyne with excellent yield. Cucujolide XI was the first macrolide pheromone oxidized at the ω-4 position (Scheme 54). [106]

Scheme 54. Synthesis of cucujolide XI via **RCAM** using molybdenum metathesis catalyst **196**



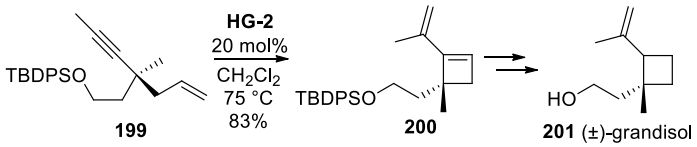
Ru-ENYNE

The enyne metathesis is a ruthenium-catalyzed bond reorganization of an alkene and an alkyne, resulting in a conjugated 1,3-diene.[68,69] There are two types. The first type is the cross-enyne

metathesis (**CEM**) in which the coupling partners are intermolecular. The second type is an intramolecular process in which the alkene and alkyne are within the same molecule. The reaction is referred to as a ring-closing enyne metathesis (**RCEYM**).[109]

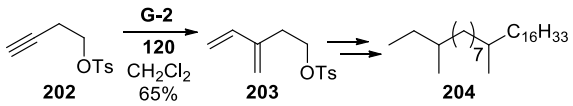
Grandisol, the primary constituent of the grandlure, is a mixture of four pheromones that comprise the sex attractant of the cotton boll weevil (*Anthonomus grandis*). Racemic grandisol was synthesized in eight steps and featured a microwave-assisted **RCEYM** as a key reaction sequence. Among the ten different catalysts tested, **HG-2** showed the best result in the cyclisation of **199** (Scheme 55).[110]

Scheme 55. Synthesis of pheromone of *Anthonomus grandis* (**201**) (TBDPS = *tert*-butyldiphenylsilyl)



A **CEM** using ethylene (**120**) and **202** provided **203** which elaborated to **204**, a component of the reproductive regulating queen ant pheromone (Scheme 56).[111]

Scheme 56. Synthesis of pheromone of queen ant (**204**)



Conclusion

This article summarizes the most relevant work in the area of semiochemical synthesis that features olefin metathesis as the key reaction step.

Semiochemicals are chemicals that insects use for communication and they have long been known to be important to the behaviour of insects. Thus, they can be used as biopesticides and tend to pose fewer risks than conventional pesticides. These compounds can attract insect pests to the traps and interfere with mating. The disruption of the mating pattern is achieved by application of a biopesticide to the fields in order to confuse mating pests by overloading their sensory receptors. Many of the pheromone preparations over the past decades were accomplished by classical organic preparation techniques; however, there has been considerable effort recently to implement cost-effective chemical processes to achieve economically profitable and environmentally benign procedures.

Olefin metathesis has evolved into an important transformation in recent decades and has been effectively applied to the synthesis of semiochemicals and the creation of innovative materials in the field of green chemistry, especially in oleochemistry.

The importance of olefin metathesis to the total synthesis of semiochemicals is obvious from the large number of successful examples presented in this review. Based on in this work, some interesting observation can be highlighted. (1) By using metathesis reactions for pheromone synthesis, new and/or shorter reaction pathways can be achieved. (2) Stereoselective synthesis is also now possible with the development of novel and improved catalysts that offer *Z* and *E* olefin selectivity. (3) Green chemical technologies may be developed by metathesis reactions that utilize renewable, alkenyl feedstock. (4) Olefin metathesis such as **ROCM** and **ROMP** reactions

can have high atom economy that may reach 100%. (5) Olefin metathesis opens up new possibilities in total synthesis.

This review also highlights industrial applications of olefin metathesis as judged from the large number of patents, in addition to academic applications, emphasizing the importance and the development of the topic to practitioners. Continued research on these synthesizes and catalysts should assist the development of new and exciting value-added chemical products.

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The manuscript was written through the contributions of all authors. All authors have given approval to the final version of the manuscript. ‡These authors contributed equally. (match statement to author names with a symbol)

ACKNOWLEDGMENT

We thank the Hungarian Academy of Sciences and National Research, Development and Innovation Office (NKFIH) for financial support under Grant Nos. OTKA NN 117986. The financial support of ENOPACK Ltd. is highly appreciated.

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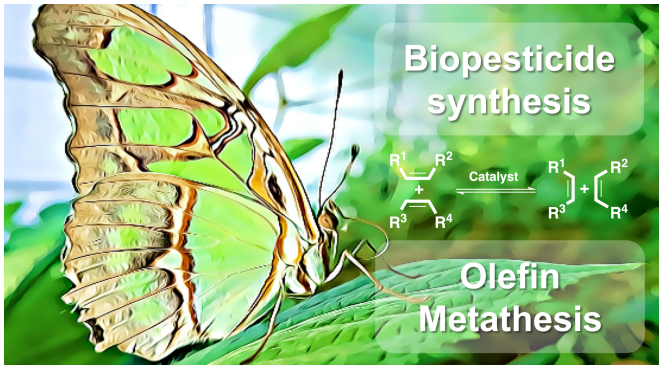
Graphical Abstract:



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