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Metathesis of heteroatom-substituted olefins and alkynes: Current scope and limitations

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Abstract

The use of vinyl- or alkynyl derivatives of the type C=C–X or C≡C–X (where X is an heteroatom) as substrates for metathesis increases further this reaction's versatility. Selected examples illustrating recent progress in this area of research are presented. Current scope and future potential developments are discussed.

Keywords: Metathesis; Vinyl derivatives; Alkynyl derivatives

1. Introduction

Over the last 10 years or so, thanks to the development of well-defined catalysts (Fig. 1), diene and enyne metathesis in their various versions: ring-closing metathesis (RCM), ring-opening metathesis (ROM) and cross-metathesis (CM) have emerged as major tools for the synthesis of complex molecules [1]. The product of the widely used diene metathesis is an olefin that can be further modified but only to a limited extent and generally with low regioselectivity (unless the olefinic carbons are clearly different for steric or electronic reasons) [2]. Therefore, in most literature examples, the newly formed double bond is either present in the final product or undergoes only simple chemical transformations in which regioselectivity is not a problem (e.g. hydrogenation, dihydroxylation or epoxidation). The product of enyne metathesis is a conjugated diene that offers more possibilities for further conversions. For example, the enyne metathesis/Diels–Alder reaction sequence has been used in several instances in total synthesis [3]. Enyne RCM/cyclopropanation has also been described [4].

On the other hand, olefinic double bonds bearing heteroatom substituents (e.g. vinyl silanes, vinyl halides, enol ethers, etc.) offer vast functionalization possibilities and, of course, regioselectivity is not a problem anymore (Scheme 1). However, whether these versatile synthetic intermediates can be generally prepared by metathesis of dienes or enynes remains unclear. In particular, a key question that has not yet been fully answered, is whether Fisher carbene species (formed during the first cycle of electron-rich olefin metatheses) are reactive enough for the catalytic cycle to proceed [5].

The present review aims at summarizing our knowledge of metathesis when applied to heteroatom-substituted olefins or acetylenes, with emphasis on the perspectives of the metathesis products as synthetic intermediates. Accordingly, we will restrict ourselves to substrates leading to "productive" metathesis (i.e. when the heteroatom is incorporated in the product). For example the RCM of 1-substituted olefins in which the substituent is lost in the process is of limited synthetic interest and will not be discussed. The review is not intended to be exhaustive and only limited examples (usually the most recent ones) will be provided for illustrating our purpose.

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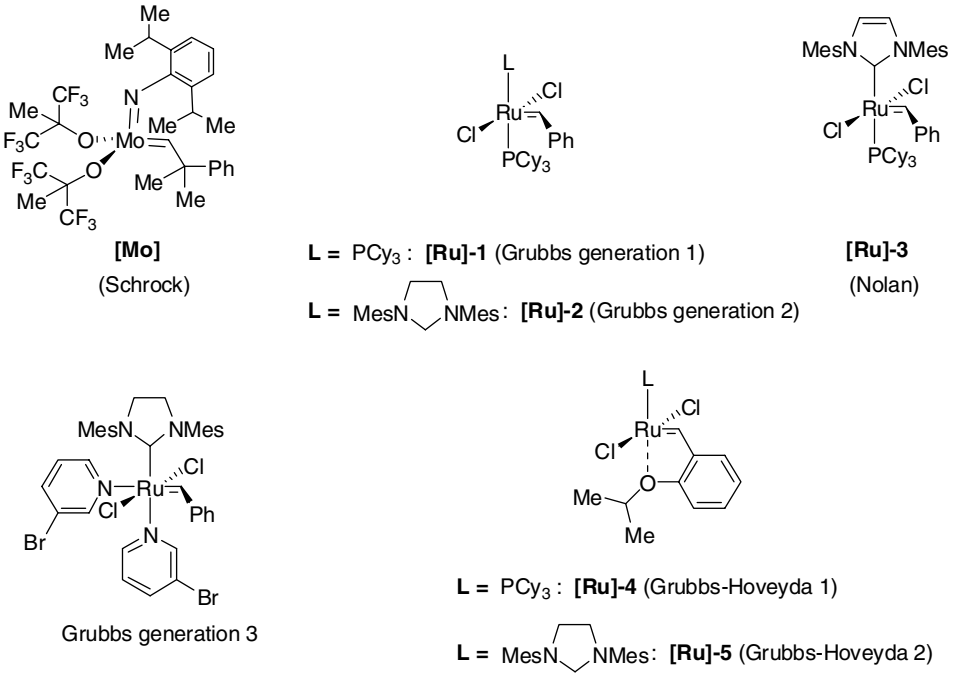
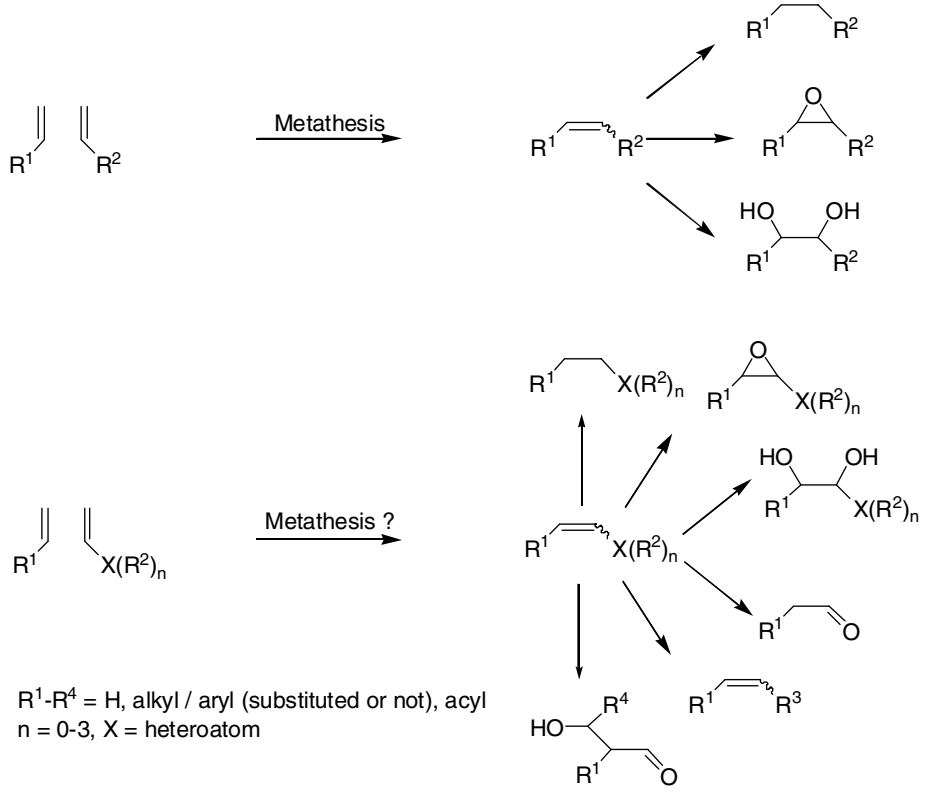


Fig. 1. Most frequently used olefin metathesis catalysts.



Scheme 1.

2. Vinyl and alkynyl silanes

2.1. Cross-metathesis (CM)

2.1.1. Ene-ene

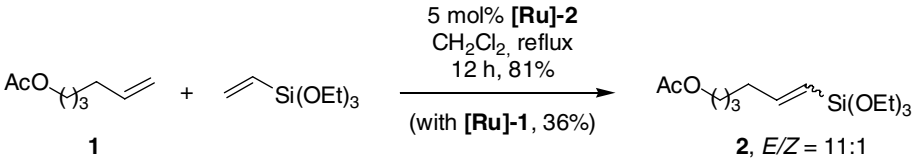
Pioneering methodological and mechanistic studies by Pietraszuk, Marciniec and Fischer have shown that cross-metathesis between vinylsilanes substituted by alkoxy-, siloxy- or electron-withdrawing groups and cyclic or acyclic alkenes can be efficiently catalyzed by Grubbs generation 1 and 2 complexes (hereafter called **[Ru]-1** and **[Ru]-2**, respectively) [6]. Cross-metathesis of vinyl(trialkoxy)silanes with terminal olefins (including vinyl sulfides (see Scheme 73)) allows the construction of internal (trialkoxy)silylalkenes with high *E*-selectivity (Scheme 2). The more active **[Ru]-2** catalyst was required for this CM reaction since **[Ru]-1** led to a diminished yield (81% vs. 36%) [7].

The newly formed (trialkoxy)silylalkene can participate in cross-coupling or cycloaddition reactions. For example, Marquez et al. used a cross-metathesis/cyclopropanation reaction sequence to synthesize bicyclo[3.1.0] hexane derivatives substituted at the tip of the cyclopropane ring (Scheme 3) [8]. The diastereoselectivity of the intramolecular carbene-mediated [2+1] cycloaddition is moderate (4:1).

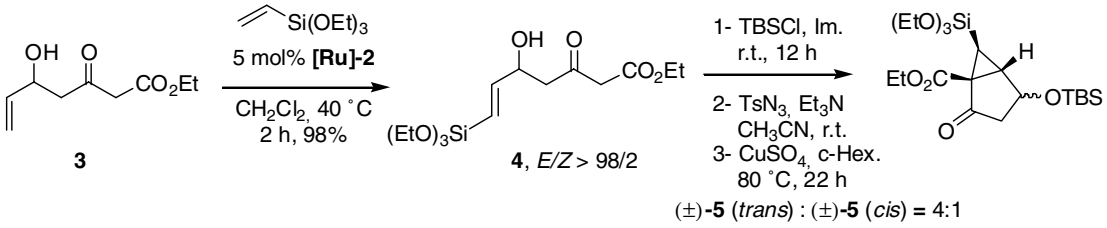
2.1.2. Ene-yne

The ene-yne cross-metathesis reaction [9] between unsymmetrical alkenes and silylated alkynes has been studied by Lee et al. [10]. Depending on the position of the alkyne (internal or terminal), the regiochemistry changes: a 1,3-relationship between the silyl substituent and the alkene is observed with terminal alkyne **6** whereas a 1,2-relationship is observed with internal alkyne **9** (Scheme 4). The regioselectivity is proposed to originate from the balance of steric interactions during the [2+2] cycloaddition of the propagating alkylidene ruthenium species. Minimisation of steric interactions may be operative in the cycloreversion of the ruthenacyclobutene, accounting for the observed stereoselectivity. This proposed mechanism was supported by a control experiment [10].

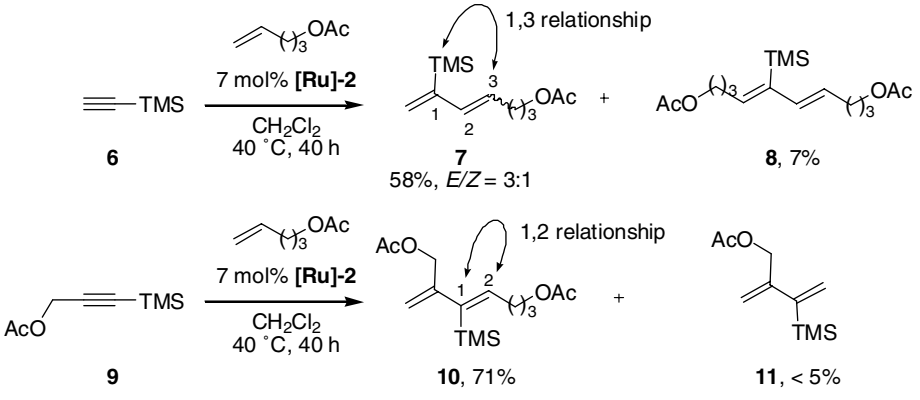
An efficient cross-metathesis reaction is observed when the propargylic position is substituted by an oxygenated moiety. When the acetoxy group of alkyne **9** is replaced by a pentyl group, low conversion is observed (not shown).



Scheme 2.



Scheme 3.



Scheme 4.

This reactivity dependence upon the nature of the propargylic substituent is a general trend for metathesis reaction involving silylated alkynes (vide infra). Olefins substituted at the remote position by a bromine atom, an ester, imide, ether or ketone function can be submitted to the CM reaction with silylated internal alkynes (Scheme 5) [10]. Alkenes containing alcohols or aldehydes result, respectively, in low conversion or partial decomposition.

2.1.3. Ene-diyne

Unsymmetrical silyl substituted 1,3-diynes react in cross-metathesis reaction with 1-octene [11]. Good yields of the corresponding products are obtained (Scheme 6). Although the reason for the observed regioselectivity is not perfectly clear, the role of the bulky triethylsilyl group in directing the metal carbene attack on the less hindered alkyne moiety is important. It is to be noted that, under the same conditions, 1,4-bis-trimethylsilanyl-buta-1,3-diyne does not afford cross-metathesis products. The *E*/*Z* ratio greatly depends on the nature of the alkyne substituent.

2.1.4. Yne-yne

Cross-metathesis between C-silylated alkynes and alkynes is rare [12]. In synthetic studies towards (−)-terpestacin, a naturally occurring angiogenesis inhibitor, Jamison used Cumins' Mo-based catalyst **16** [13] to promote the metathesis reaction between internal alkyne **17** and 1-trimethylsilylpropyne (Scheme 7) [14]. The desired product was obtained in 36% yield. Tolerance of polar functional groups is worth noting since ethers, ketones, acetals and olefins are not affected during this transformation.

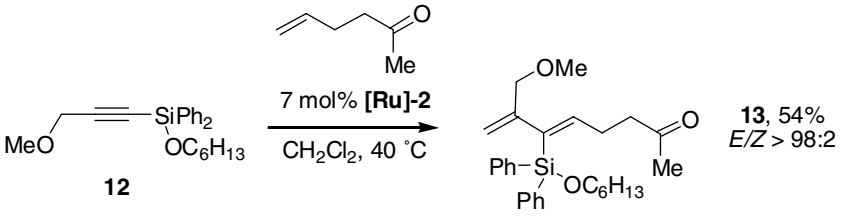
2.2. RCM

2.2.1. Ene-ene

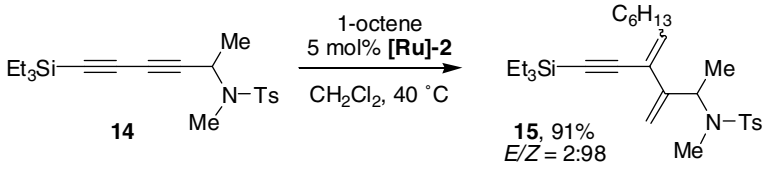
The first examples of ring-closing metathesis reactions between vinylsilanes and alkenes were disclosed by Chang and Grubbs [15]. The alkoxyvinylsilanes **20** can be transformed into the corresponding cyclic siloxanes in good yields using 3–5 mol% of the highly active **[Mo]** catalyst which is less sensitive to steric hindrance than **[Ru]-2** (Scheme 8). Mild oxidative conditions were used to transform the six-membered cyclic siloxane **21** into aldehyde **23** in good yield. This three-step sequence allows an easy anti-Markovnikov hydration/oxidation of a remote olefin.

These cycloalkenylsiloxanes can also act as nucleophiles in inter- or intramolecular palladium-catalyzed cross-coupling reactions with aryliodides or alkenylbromides or iodides (Scheme 9). Extensive studies by Denmark and Yang [16] have shown that the intermolecular coupling reaction was not sensitive to the steric or electronic nature of the aryliodides. Moreover, the reaction was proved to be stereospecific and tolerant of functional groups.

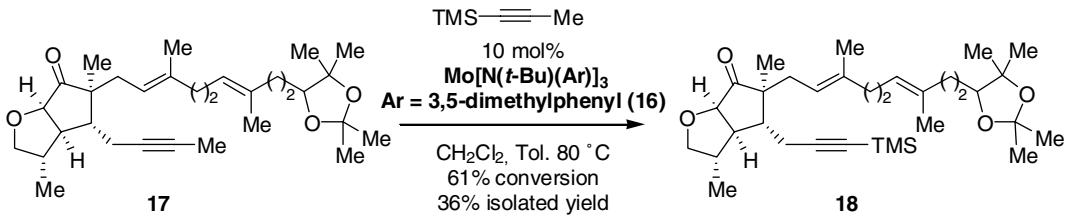
In the intramolecular version, 9- to 12-membered cycloalkadienes bearing the 1,3-*cis–cis* diene moiety can be easily synthesized, as can be seen from Scheme 10. The method



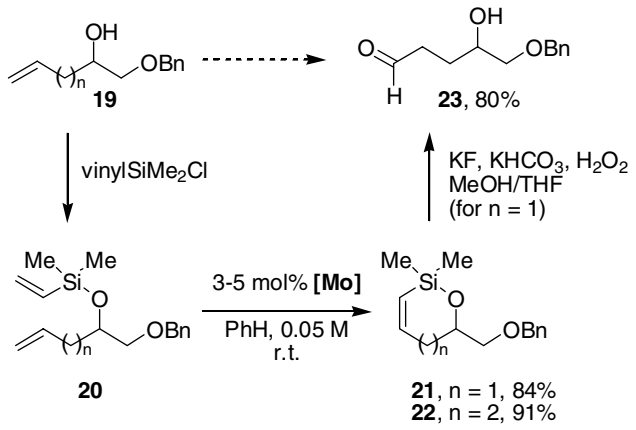
Scheme 5.



Scheme 6.



Scheme 7.



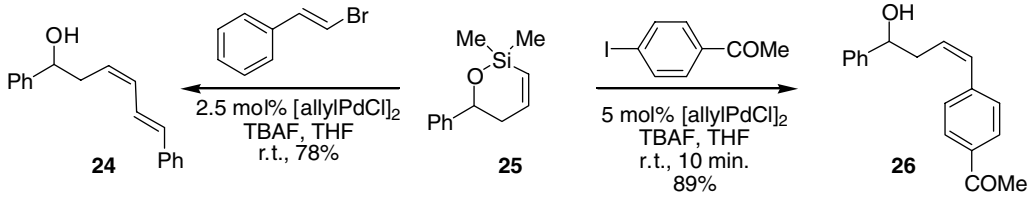
Scheme 8.

constitutes a nice way to access stereochemically pure *Z*-olefins. The vinyliodide appended at a remote position of the unsaturated siloxane **28** undergoes an intramolecular palladium-mediated cross-coupling, leading to the tetrahydrooxonine core structure of (+)-brasilenyne in 61% [17].

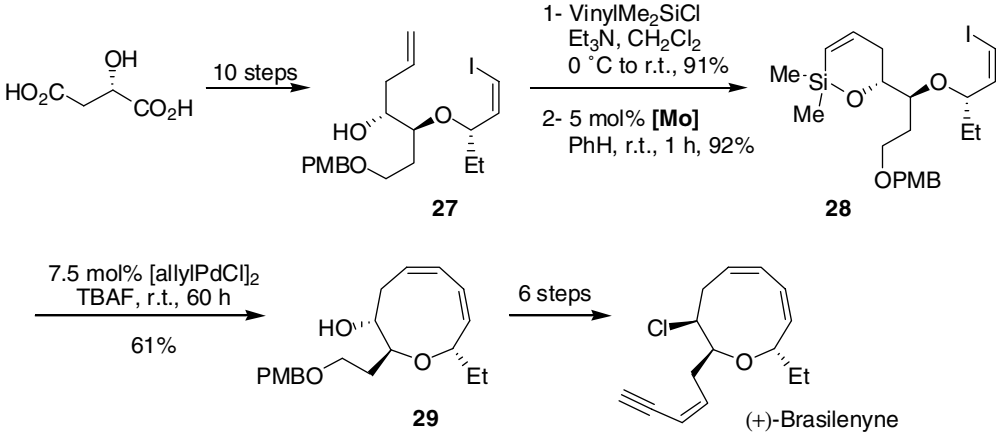
Precursors of trimethylsilyl-substituted dihydropyrans can be effectively synthesized by a [3,3]-sigmatropic rearrangement of linear ester **30**, under Ireland-Claisen conditions. This newly created vinylsilane **31** can then undergo a ring-closing metathesis to give the desired heterocycle in good yields [18]. 50 mol% of the **[Mo]** catalyst are necessary for this RCM reaction. When the silyl substituent in **31** is moved from the γ- to the β-position, only 2.5 mol% of the less active **[Ru]-1** are required for the cyclisation (83% yield, not shown) (see Scheme 11).

2.2.2. Ene-yne

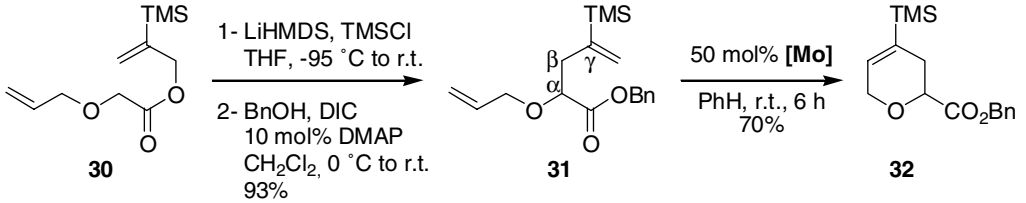
Lee developed a ruthenium-catalyzed dehydrogenative coupling of unsaturated alcohols **33a–d** with silanes to generate the corresponding silylethers [19]. The alkynylsilyloxy-tethered enynes **35a–d** underwent efficient RCM to give small- to medium-sized siloxacycles (Scheme 12). A 13-membered macrocycle **38** could also be prepared in



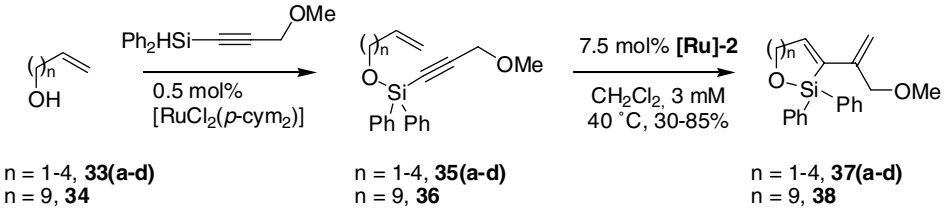
Scheme 9.



Scheme 10.



Scheme 11.



Scheme 12.

30% yield using this sequence. The high reactivity of the sensitive enynes **35a–d** could originate from a Thorpe-Ingold effect from the two phenyl substituents on the silicon atom.

As expected, in dienyne systems where several RCM are possible steric/electronic effects will govern the regioselectivity (Scheme 13).

However, when the steric and stereoelectronic environment of the olefin moieties are comparable, the size of the formed ring will be determinant (''group selectivity'') [20]. Initiation occurs indifferently at both alkenes but a rapid equilibration of the corresponding alkylidene ruthenium coupled with a faster ring-closure for the smaller cycle delivers siloxacycles **44** and **45** from **43** (Scheme 14). The larger the difference in tether-length, the better the group selectivity. For substrates of similar tether-length, Lee observed that an increase in reaction concentration led to a higher ratio of siloxacycles **44** to **45**.

2.2.3. Ene-diyne

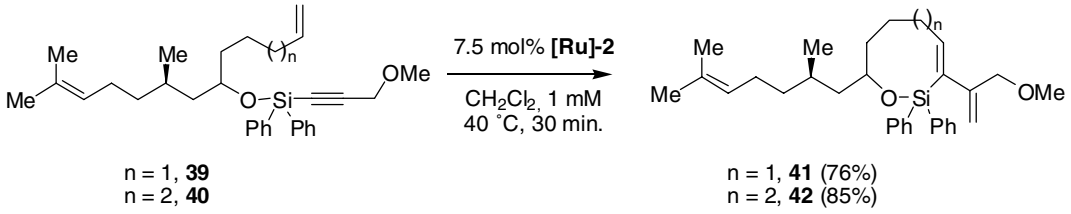
A special case of metallotropic [1,3]-shift has been reported during RCM studies of 1,3-diynes [11]. The outcome of the ring-closing metathesis reaction depends on whether the diyne is silyl-substituted or not (Scheme 15). Silyl enediyne **46** inhibits the [1,3]-shift of the intermediate ruthenium carbene. On the other hand, this shift has been observed when R is a hydrogen atom, an alkyl group, a linear or branched ether or acetate.

2.3. Tandem reactions

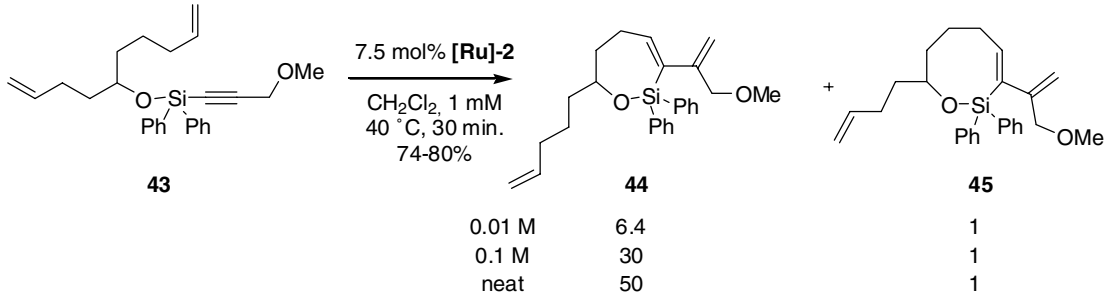
2.3.1. CM–RCM

A new connectivity pattern of siloxane-based 1,3-dienes **52** was developed by Lee et al. using a regio- and stereoselective tandem CM–RCM reaction of alkynyl silyloxy-tethered enynes [21]. A first metathesis event occurs intermolecularly between the silyloxyenyne and an alkene. The intermediate alkylidene ruthenium species then undergoes a ring-closing metathesis in the *endo*-mode to give the corresponding siloxacycle possessing a 1,3-dienic system (Scheme 16).

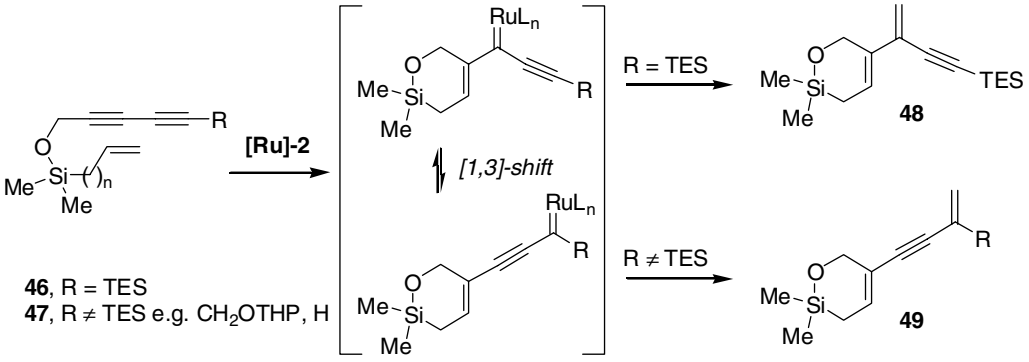
The silicon atom deactivates the acetylenic system of silyloxyalkynes towards CM and RCM, mainly for steric reasons. However, it is possible to restore the reactivity when the propargylic position is substituted by an oxygen atom, allowing a coordination between the ruthenium catalyst and the alkoxy (or acyloxy) moiety that maintains a higher concentration of productive alkylidene intermediates (Scheme 17 [21], see also Scheme 5).



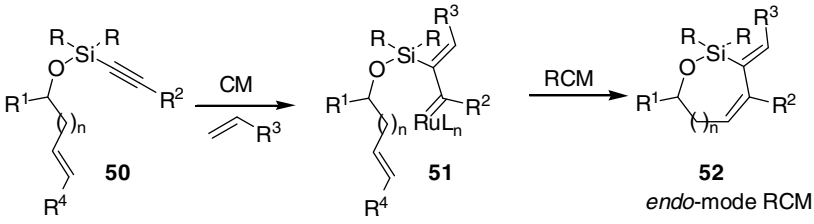
Scheme 13.



Scheme 14.

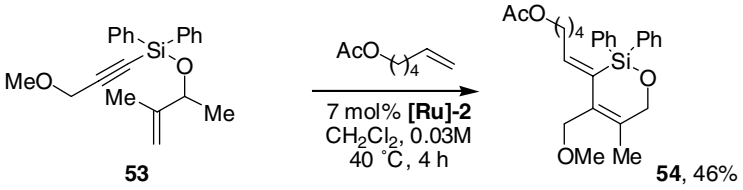


Scheme 15.

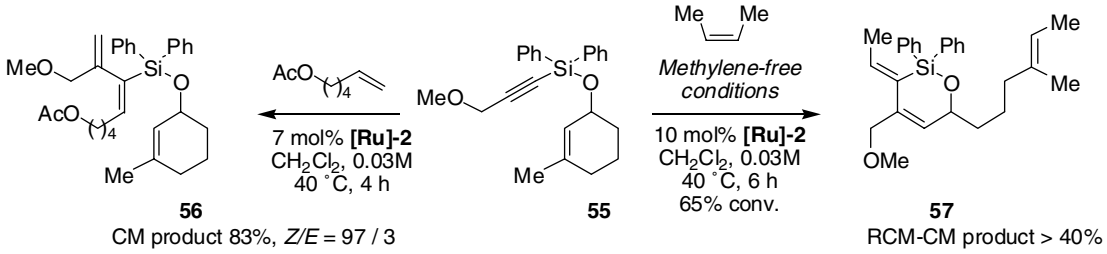


Typical substituents include: R, R_4 = Me, Ph; R_1= alkyl; R_2 = H, CH_2OCH_3; R_3 = $(CH_2)_n$-OAc,

Scheme 16.



Scheme 17.



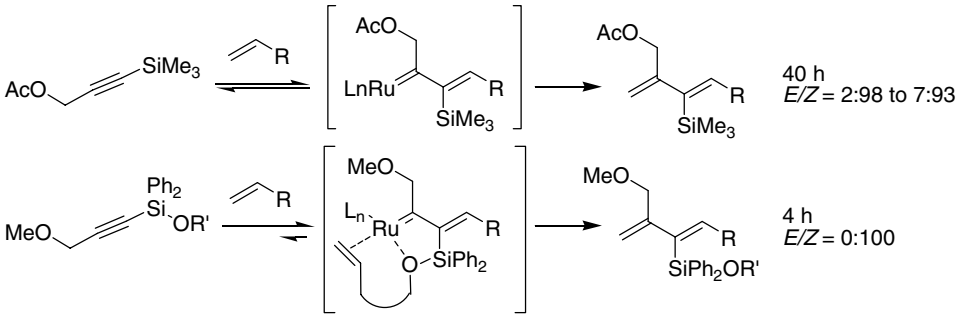
Scheme 18.

Trisubstituted olefins are generally less reactive than 1,1- or 1,2-disubstituted alkenes in this sequence. Using standard conditions, substrate **55** is converted to the cross-metathesis product **56**, the trisubstituted alkene being reluctant to ring-close. However, **55** can be converted to the CM–RCM siloxacycle **57** using the methylene-free metathesis conditions [22] recently introduced by Diver (Scheme 18).

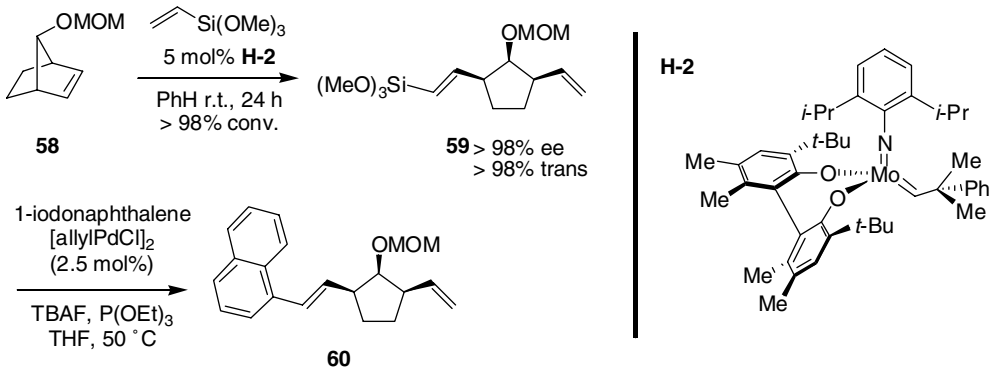
In addition to a higher substrate reactivity, the oxygen atom substituting the silicon center also imparts a higher *E*/*Z* stereoselectivity. These effects are proposed to originate from a complexation of the ruthenium metal center to the oxygen atom, thereby modifying the relative rates of the stereodetermining steps (Scheme 19) [21].

2.3.2. ROM–CM

Strained [2.2.1] bicycles readily undergo a ring-opening reaction which could be coupled with a cross-metathesis event (ROM/CM). Asymmetric versions (AROCM) of this tandem reaction have been developed by Schrock and Hoveyda, using molybdenum-based chiral carbenic complexes [23]. Among the latter, the biphen-based complex **H-2**



Scheme 19.



Scheme 20.

proved to be superior for the AROCM with electron-rich alkenes. In Scheme 20, the 1,2,3-trisubstituted cyclopentane **59** was obtained with complete stereo- and enantioselectivity from the norbornene derivative **58** using 5 mol% of catalyst **H-2**. The vinylsilane moiety was then exploited in a palladium cross-coupling reaction with 1-iodonaphthalene. The coupled product **60** was obtained in 51% yield overall.

Vinyltrimethylsilane and vinyltrimethoxysilane are good olefinic partners for this tandem Mo-catalyzed asymmetric AROCM, although the steric bulk of the silyl substituents slows down significantly the reaction rate compared to styrenes. Another factor which could explain the reduced rate is chelation and hyperconjugative effects of the silylated *anti* Mo-alkylidenes **A** and **B**, respectively, leading to a decrease in Lewis acidity of the catalytic species and reduced availability of the productive *syn* carbenic intermediate (Fig. 2).

2.3.3. RCM–RCM

Tandem dienyne metathesis of alkynyl silaketals such as **61** combines an enyne RCM and a diene RCM [24]. When symmetrical alkynyl silaketals are submitted to this tandem dienyne metathesis, the [5.4.0] bicyclic system **62** is obtained. Removal of the temporary tether yields the corresponding diol **63** in good yields as a single isomer (Scheme 21).

When unsymmetrical alkynylsilaketals are used, product distribution is dependent upon the length of the tether and its substitution as previously noted in Section 2.2 (vide supra). In alkynylsilaketal **64**, the different steric environment of the two olefinic moieties allows initiation at the less hindered unsaturation and tandem metathesis yields a single bicyclic siloxane **65** in 78% yield. In silaketal **67**, the steric discrimination between the two initiation sites is not efficient and a 1.5:1 mixture of the two possible siloxanes **68** and **69** is obtained (the structure of the major and minor compounds were not attributed) (Scheme 22) [24].

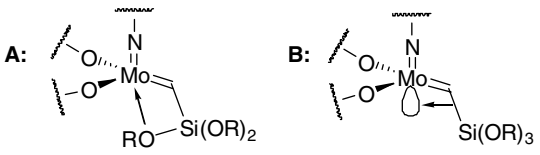


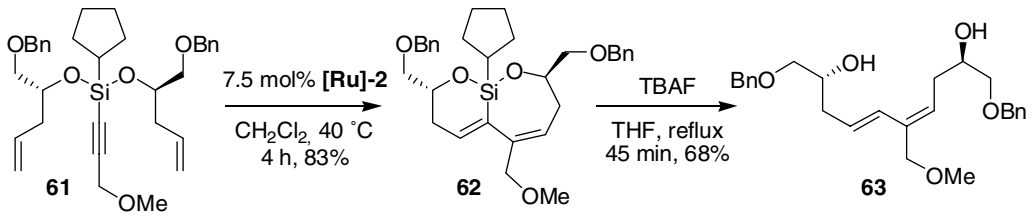
Fig. 2. Chelation and hyperconjugative effects in trialkoxysilylated Mo-alkylidene catalysts.

3. Ene- and ynamides

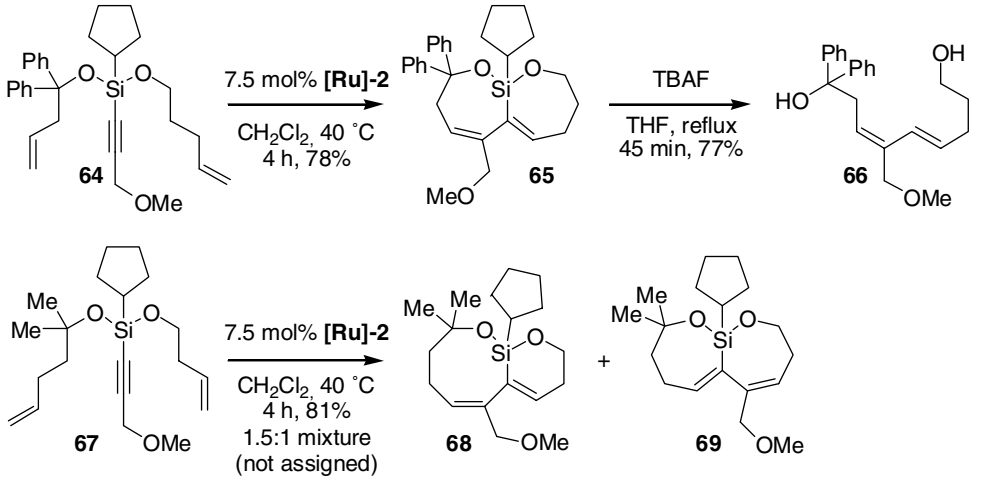
3.1. RCM

3.1.1. Ene-ene RCM

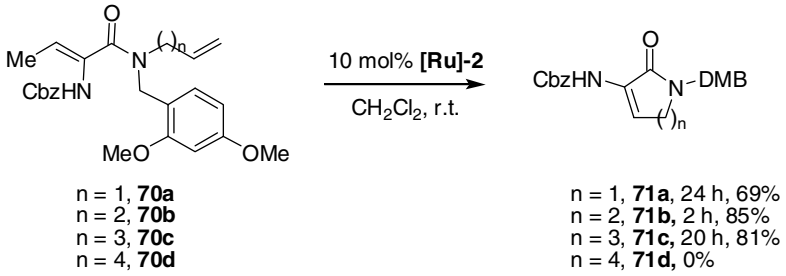
α-Amino acrylamides **70a–c** can be efficiently transformed into α-amino α,β-unsaturated lactams **71a–c** using ring-closing metathesis reactions (Scheme 23) [25]. A limitation to this method was observed for the RCM of substrate **70d** leading to the eight-membered heterocycle **71d**. The amide needs to be *N*-protected (various benzyl-like protecting groups) since no reaction occurred with the unprotected nitrogen atom under a variety of conditions. This approach was used to construct sublibraries of



Scheme 21.



Scheme 22.

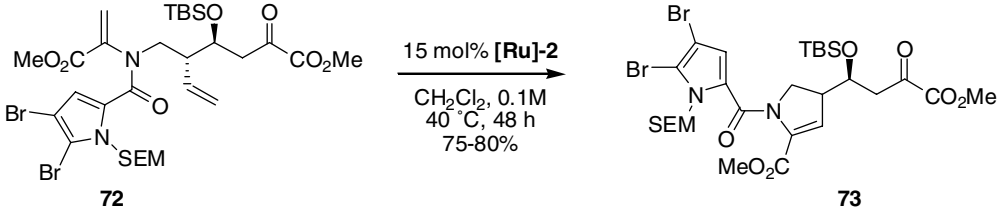


Scheme 23.

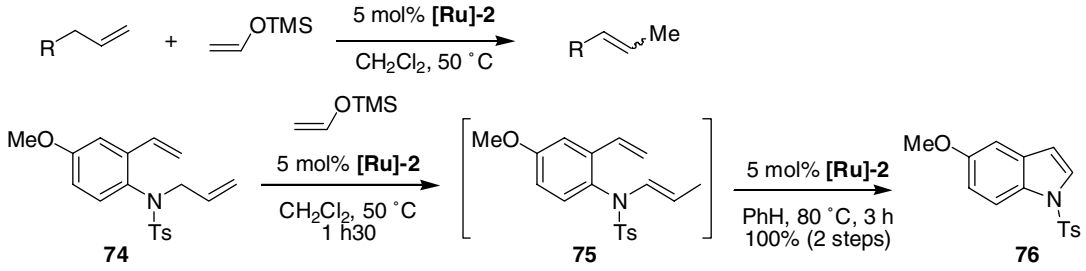
small-molecules that could be of interest for further development in medicinal chemistry.

Ring-closing metathesis of alkene-enamide derivative **72** was used as a key step in Overman's studies towards the total synthesis of palau'amine [26]. Functional groups like α-ketoesters, SEM- or silyloxy-protecting groups or bromine atoms are tolerated under the mild conditions of this metathesis (Scheme 24).

Note: When terminal olefins and vinyloxytrimethylsilane were allowed to react in the presence of a sub-stoechiometric quantity of **[Ru]-2**, a non-metathetic behaviour of the ruthenium catalyst was observed, resulting in migration of the



Scheme 24.



Scheme 25.

double bond from the terminal to an internal position (Scheme 25). A similar (but slower) reaction was noted using ethylvinyl ether but not vinyl acetate [27]. This general strategy has been used for the synthesis of indole **76** via RCM of isomerized compound **75**.

3.1.2. Enyne RCM and tandem enyne RCM/[4+2] cycloaddition

Ene-ynamine ring-closing metathesis was reported independently by Mori [28] and Hsung [29] in 2002. This transformation gives access to (chiral) 1,3-dienes possessing a nitrogen substituent at C2. RCM of **77** led to the piperidine **78** that could be further reacted with a highly reactive dienophile to furnish hexahydroquinoline **79** in 58% overall (Scheme 26(a)) [28]. Ynamides can also participate in this tandem RCM/[4+2] sequence, leading to bicyclic lactam **84** (Scheme 26(b)) [29].

A tandem yne-enamine RCM/[4+2] cycloaddition of **85** was developed by Pérez-Castells and co-workers (Scheme 27) [30]. The rapid [4+2] cycloaddition of 3-propenylindole **86** with DMAD limits the dimerization and leads to **87**, featuring the prototypic structure of carbazole alkaloids.

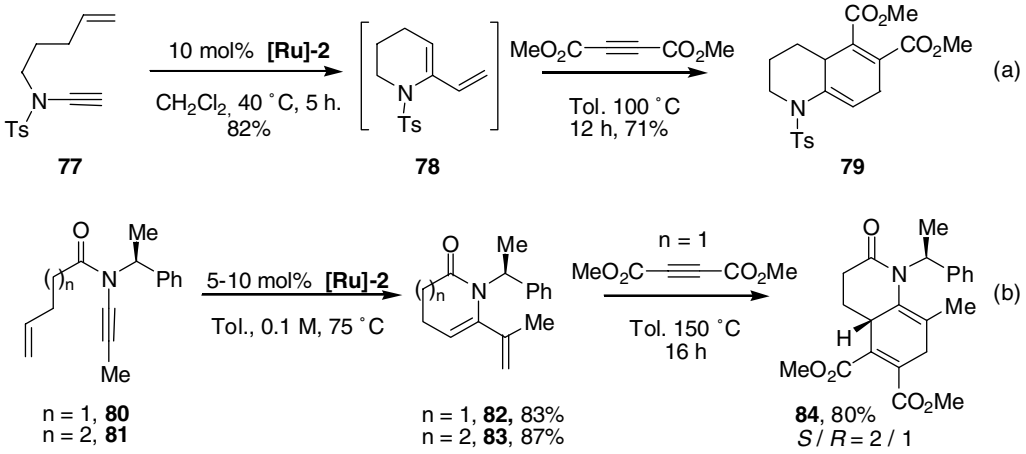
Tandem RCM/RCM of diene-ynamides were reported by Hsung and co-workers (Scheme 28) [29]. Product distribution was dependent upon the tether-length and olefin-migration side-reactions. The group-selectivity [20a] for the tandem reaction of **89** was increased compared to the reaction of substrate **88** (6:1 vs. 1:1), due to a better initiation-site discrimination.

4. Vinyl and alkynyl ethers, silyl enol ethers and siloxyalkynes

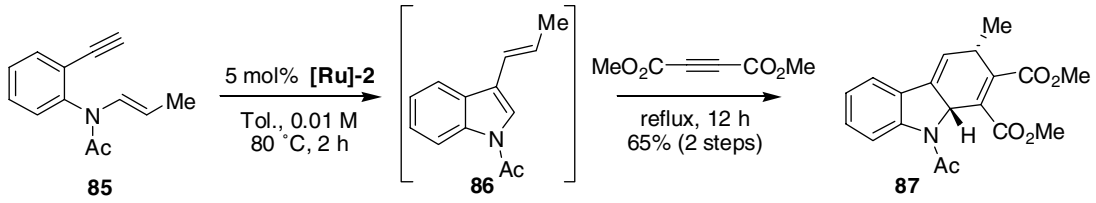
4.1. Vinyl and alkynyl ethers

In 1994 Grubbs reported the first metathesis involving enol ethers, catalyzed by well-defined metal alkylidene catalysts. Treatment of acyclic olefinic enol ethers (generated from the corresponding olefinic esters by stoechiometric use of the Tebbe reagent or related reagents), with 5–12 mol% **[Mo]** afforded the corresponding cyclic enol ethers in good yields. In contrast ruthenium alkylidene **[Ru]-1** catalyzed the slow dimerization of the starting material without formation of the cyclic enol ethers [31]. The lack of reactivity of the first generation Grubbs' catalyst was confirmed by Clark in his seminal work on the synthesis of brevetoxin sub-units [32]. However, one year later **[Ru]-1** was shown to catalyze the ring-closure of certain vinyl ethers in benzene at reflux at low concentration (0.017 M). No metathesis reaction occurs with **96**, **97** and **98**. This catalyst appears to be sensitive to the presence and position of substituents in the acyclic substrate (Scheme 29) [33].

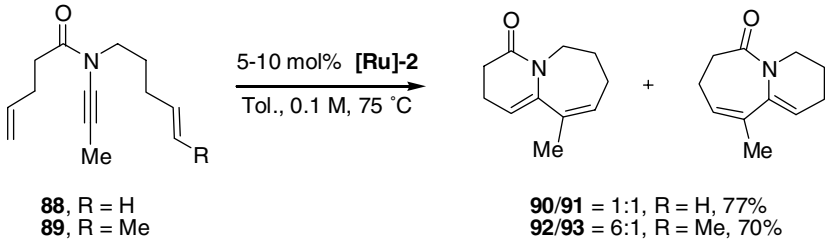
Based on Grubbs'preliminary results [31], Nicolaou's group investigated a new strategy for the direct formation of cyclic enol ethers from olefinic esters using Tebbe or



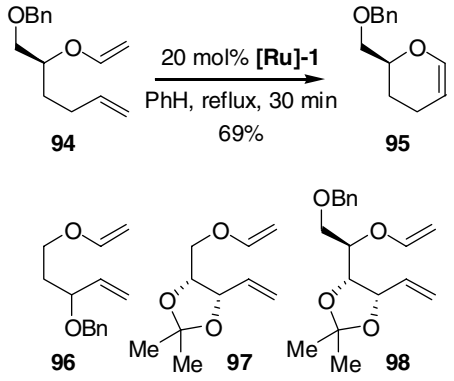
Scheme 26.



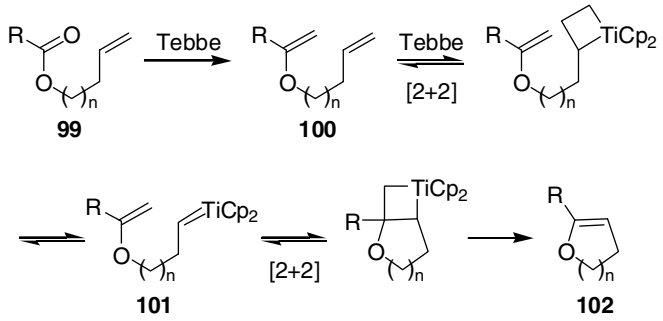
Scheme 27.



Scheme 28.



Scheme 29.



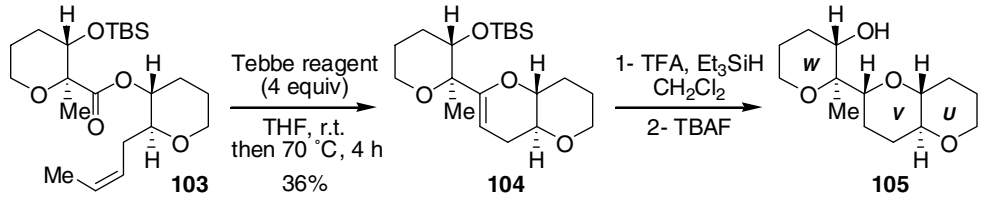
Scheme 30.

Petasis reagents [34a]. Scheme 30 shows the general concept of this approach. One equivalent of Tebbe reagent mediates the conversion of ester **99** to enol ether **100** and a second equivalent induced ring-closing metathesis to provide **102** via formation of the intermediate titanium alkylidene **101**.

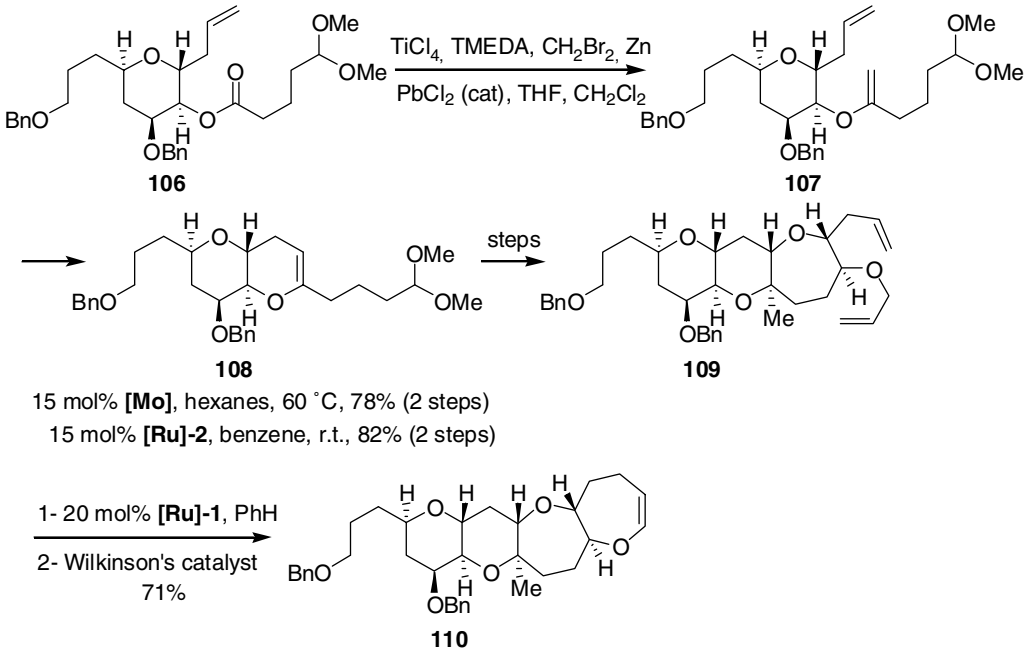
Using this approach, a large series of olefinic esters, precursors of polycyclic fused ethers, was prepared and submitted to excess Tebbe reagent. The direct cyclization occurs in moderate to fair yield. To illustrate this methodology, preparations of the JKL, OPQ and UVW ring systems of maitotoxin, a potent marine neurotoxin, were accomplished. Conversion of the olefinic ester **103** furnished the cyclic enol ether **104** in moderate yield. Treatment of **104** with Et_3SiH in the presence of TFA followed by desilylation furnished the UVW framework **105** (Scheme 31) [34b]. In this otherwise elegant an efficient method, the use of excess Tebbe reagent and the modest yield during the cyclization step constitute obvious weak points.

Rainier's synthesis of (±)-hemibrevetoxin B, which possesses a *trans–syn–trans*-fused polycyclic ether system, was based on the sequential conversion of olefinic esters to olefinic enol ethers by the Utimoto–Takai procedure [35] followed by **[Mo]**- or **[Ru]-2**-catalyzed RCM. The ester **106** was first converted to vinyl ether **107** which was then submitted to the ring-closure conditions. The use of either **[Mo]** or **[Ru]-2** gave the cyclized enol ether **108** in similar yields. A short sequence including RCM reaction and olefin isomerization provided the hemibrevetoxin A–D ring system **110** via **109** (Scheme 32) [36].

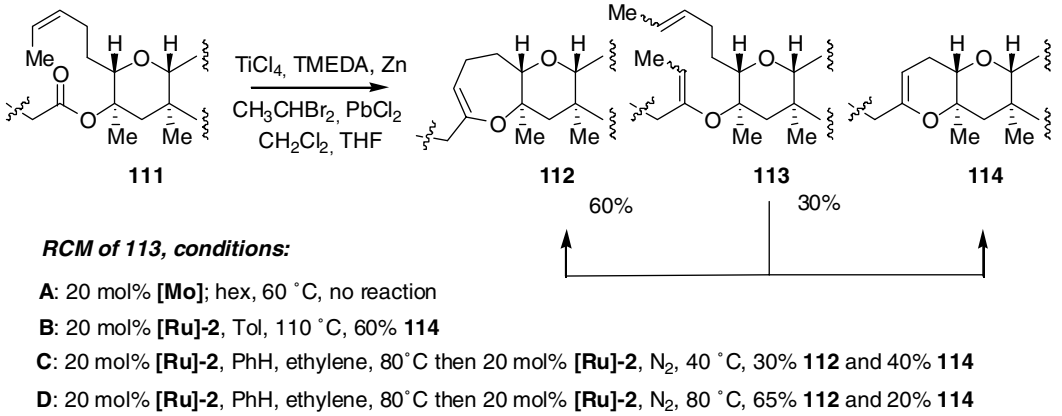
Continuing its research efforts in this field, the Rainier's group was able to directly convert acyclic olefinic esters to cyclic enol ethers. The success of this cyclization appears to be strongly dependent on the titanium alkylidene formed by the Utimoto–Takai procedure. Using 1,1-dibromoethane instead of 1,1-dibromomethane considerably increased the cyclization effectiveness. This approach was nicely illustrated by the recently described total synthesis of gambierol, a marine polyether toxin [37]. The intermediate **111** afforded the cyclized enol ether **112** along with the side product **113** which could be converted into **112** using **[Ru]-2**. The formation of **114** resulting from isomerization of **113** could be minimized by working under an ethylene atmosphere (Scheme 33).



Scheme 31.



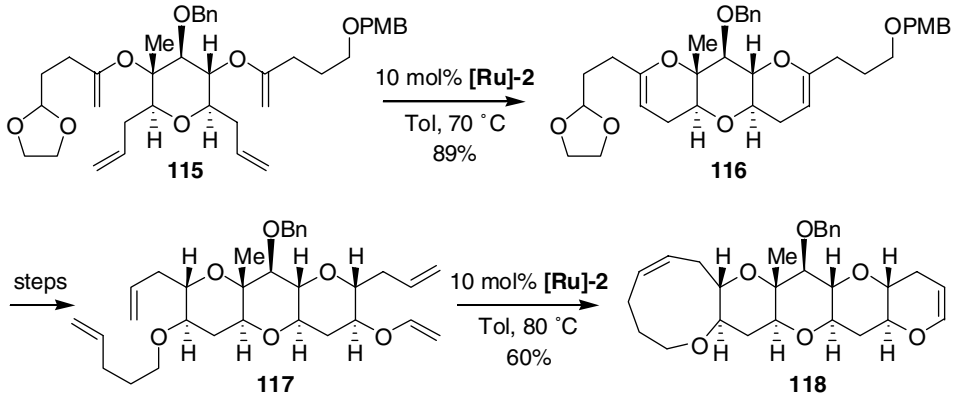
Scheme 32.



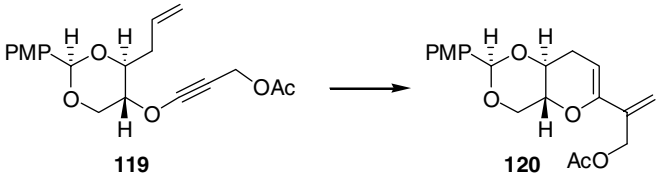
Scheme 33.

Enol ether RCM was used in Clark's total synthesis of gambieric acid. A two-directional approach to build polycyclic ethers was designed [38] in which a **[Ru]-2**-induced cyclization of the bis(enol ether) **115**, afforded the key tricyclic ether **116** in excellent yield. After multi-step conversion of **116** to the alkene **117**, a second double-RCM reaction was performed. Although in preliminary work [39] Clark reported that the best yields were obtained using **[Ru]-1**, **[Ru]-2** (10 mol%) was used for the formation of the nine- and six-membered cyclic ethers from **117**, to afford the pentacyclic ether **118**, corresponding to the F–J ring system of gambieric acid, in good yield (Scheme 34).

The ring-closing enyne metathesis reaction of olefinic alkynyl ethers was also employed to synthesize cyclic ethers for the preparation of polyethers. The RCM reaction of olefinic alkynyl ethers was investigated using various con-



Scheme 34.



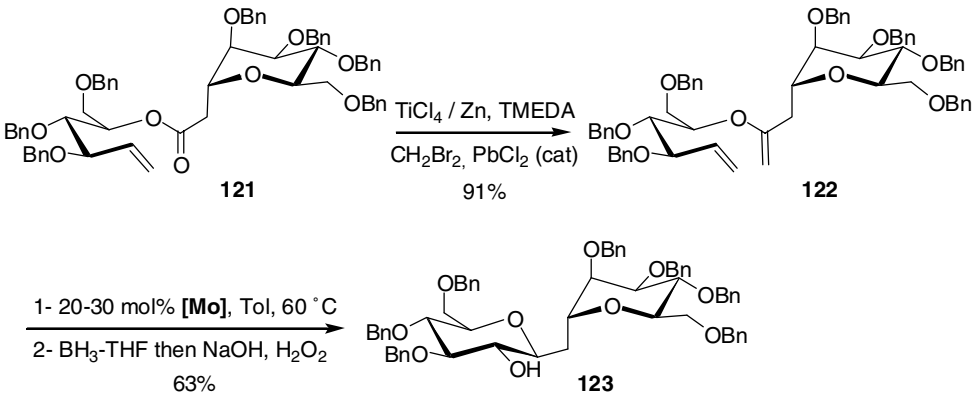
Scheme 35.

ditions and the best results were obtained by using Grubbs' second generation catalyst under an ethylene atmosphere. Without ethylene the reaction progresses slowly and lower yields are obtained (Scheme 35) [40a,40b]. Recently Clark's group reported a **[Ru]-1** catalyzed sequence involving an enyne RCM of olefinic alkynyl ethers followed by an olefin CM. This approach is a good method for preparing six- and seven-membered cyclic ethers bearing functionalized side chains. A one-pot procedure was also investigated with success [40].

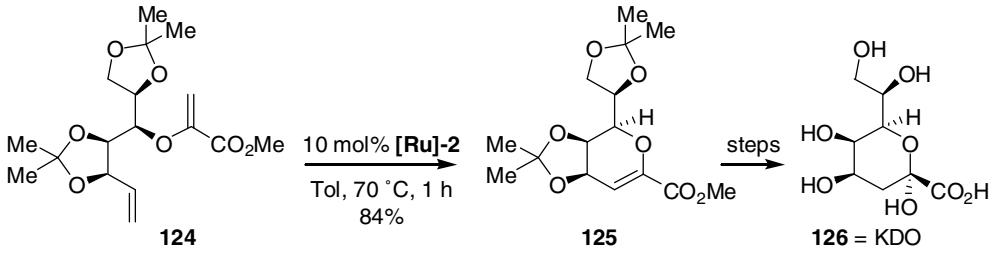
Based on the sequential procedure in which an ester is converted into an enol ether by methylenation and then cyclized by RCM, Postema developed a new methodology to prepare *C*-glycosides [41]. The Scheme 36 illustrates this approach for the synthesis of β-*C*-disaccharides. The olefinic ester **121** was first converted to the corresponding olefinic enol ether **122** in excellent yield using the Utimoto–Takai system. The acyclic enol ether **122** was then treated with Schrock's catalyst leading to an intermediate glycal which was converted to the β-*C*-disaccharide **123** with complete stereoselectivity. The metathesis reaction could be also accomplished in the presence of **[Ru]-2**, however, it was necessary to add the catalyst portionwise during the course of reaction [41a,41c]. This work was applied to the synthesis of branched β-*C*-tetrasaccharides with a triple cyclization [41b].

Rutjes et al. recently reported the RCM reaction of α-substituted enol ethers using **[Ru]-1**, **[Ru]-2**, **[Ru]-5** or **[Mo]** as catalysts. Preliminary studies showed that six- and seven-membered oxygen heterocycles could be efficiently prepared. It is to be noted that unhindered terminal olefins are isomerized and not cyclized while increasing the steric environment in the vicinity of the terminal olefin completely prevents isomerization and leads to the desired cyclized products. This methodology was applied to the formal synthesis of 3-deoxy-D-*manno*-2-octulosonic acid (KDO) (Scheme 37) [42].

The same strategy was also envisaged in an approach to the total synthesis of zoapatanol. The intermediate oxepene



Scheme 36.



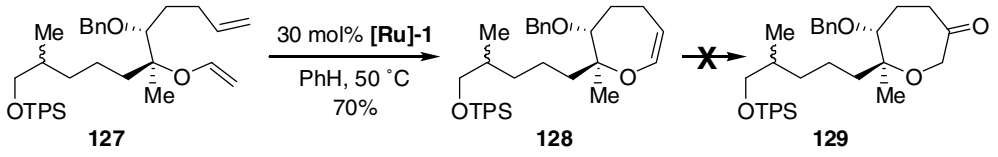
Scheme 37.

128 could be prepared in good yield from the acyclic olefinic enol ether **127** using 30 mol% **[Ru]-1** in benzene at 50 °C. Unfortunately, due to the impossibility to convert the oxepene to oxepanone **129**, this route was abandoned (Scheme 38) [43].

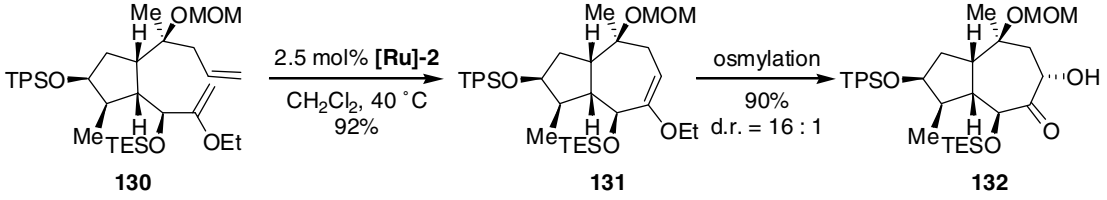
With the aim of building the bicyclic framework found in the natural sesquiterpene lactones thapsigargins, Ley et al. employed the key RCM reaction of the olefinic vinyl ether **130**. The reaction works very well when **[Ru]-2** is slowly added to the reaction mixture, affording the cyclized enol ether **131** in excellent yield. Osmylation of **131** led to the desired α-hydroxy ketone **132** (Scheme 39) [44].

Recently, Hoveyda and Schrock reported the first asymmetric RCM reaction of olefinic enol ethers [45]. Desymmetrization of the acyclic triene **133** to afford the cyclized enol ether **134** was effected in excellent yield and high enantiomeric excess using the chiral Schrock-Hoveyda catalyst **135** (Scheme 40). The use of other (Ru- or Mo-based) chiral catalysts also led to the formation of the dihydropyrane derivative but with low enantioselectivity (e.e. <10%). This method was also used for the highly enantioselective formation of five-membered cyclic ethers. Preliminary mechanistic models indicate that the catalyst reacts first with the less hindered terminal olefin. If all terminal olefins are equivalent in terms of steric hindrance, the metathesis proceeds with low enantioselectivity.

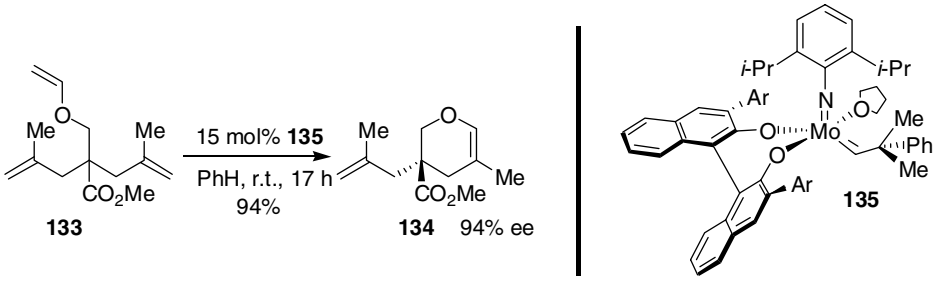
The cross-metathesis of enol ethers with alkynes was also investigated. In their seminal paper, Diver et al. described a **[Ru]-2**-catalyzed enyne cross-metathesis reaction involving vinyl ethers. (*Z*)/(*E*) Mixtures of electron-rich dienes were obtained which underwent [4+2] cycloadditions (Scheme 41, Eq. (1)) [46a]. Fischer carbenes,



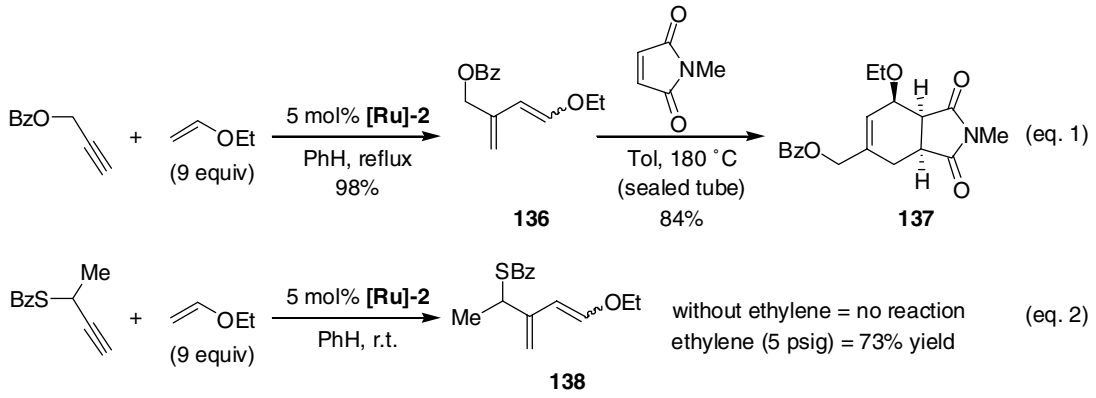
Scheme 38.



Scheme 39.



Scheme 40.



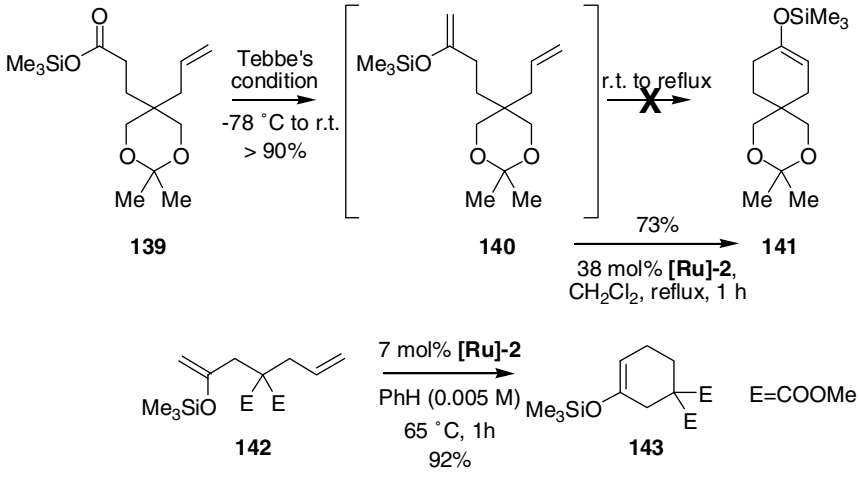
Scheme 41.

resulting from the reaction of enol ethers with **[Ru]-2** were suggested as intermediates. The process tolerates a wide range of functional groups on the alkyne moiety; however, thiobenzoates were reported to be poor reaction partners. Nonetheless, under an ethylene atmosphere, the enyne cross-metathesis reaction proceeds in benzene at room temperature to provide the desired dienes. The ethylene probably accelerates the reaction and at the same time prevents the decomposition of the ruthenium–methylidene intermediate (Scheme 41, Eq. (2)) [46b].

4.2. Silyl enol ethers and siloxyalkynes

The metathesis of vinyl ethers was successfully extended to silyl enol ethers. The groups of Shibasaki [47] and Nakagawa [48a] reported independently the first preparations of cyclic silyl enol ethers from acyclic alkenyl ketones using the RCM reaction. Initially Shibasaki wished to apply Nicolaou's sequence (see Scheme 30) [34]. Upon treatment of the silyl ester **139** with an excess of Tebbe reagent at low temperature the acyclic silyl enol ether **140** was formed. Unfortunately, the second (RCM) step failed and only decomposition products were formed. When **140** was isolated and then treated with **[Ru]-2** the corresponding cyclic silyl enol ether **141** was formed in 73% yield. Further optimization of the reaction conditions showed that under dilute conditions and using benzene as solvent the desired cyclic enol ether could be obtained in almost quantitative yield (Scheme 42). Similarly, Nakagawa prepared substituted 4-methoxy- and 4-siloxy-1,2-dihydroquinolines in excellent yield. **[Ru]-2** had to be used as no reaction occurred with the less active **[Ru]-1**. This methodology was also applied to the synthesis of key intermediates for anti-malarial agents [48b].

In comparison to Shibasaki's results, Aggarwal reported that trimethylsilyl enol ethers lacking *gem* dialkyl or diester groups did not undergo RCM. However, switching to a more hindered silyl group (TBS), conversion to the desired cyclic silyl enol ethers could be achieved [49]. The presence of the bulky TBS group probably increases the starting material stability. In addition it is conceivable that, for trimethylsilyl enol ethers, initiation takes place at the more electron-rich double bond, leading to an unstable/unreactive α-silyl-substituted metal carbene **145** whereas, for TBS enol ethers, the increased steric bulk forces the precatalyst to attack the terminal olefin giving



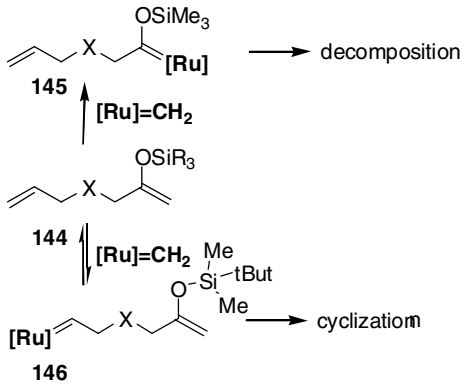
Scheme 42.

the ruthenium alkylidene **146** which can react with the silyl enol ether moiety to afford the cyclized product (Scheme 43).

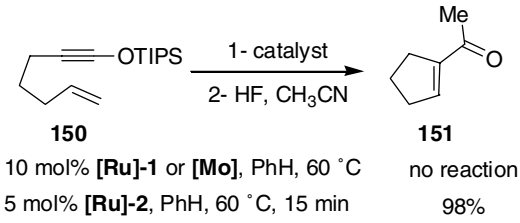
This methodology was recently employed in an elegant total synthesis of the neotropical poison-frog alkaloid (−)-205B [50]. The RCM reaction of the kinetic silyl enol ether **148**, prepared from the methyl ketone **147**, in the presence of Grubbs' second generation catalyst afforded the tricyclic ring system **149** (Scheme 44).

A strategy based on intramolecular ruthenium-catalyzed enyne metathesis for preparing functionalized enones **151** via the formation of enoxysilanes followed by protodesilylation was also described [51]. The reaction proceeds only with **[Ru]-2** in benzene at 50–60 °C. In particular, using **[Mo]**, no cyclization was observed (Scheme 45). A wide range of functionalized and substituted siloxyalkynes was tested to illustrate the usefulness of this method. A mechanism involving initiation at the terminal olefin as opposed to the alternative initial reaction of the catalyst with the alkyne moiety appears more favorable, and is supported by several NMR experiments. This strategy was successfully used in the preparation of eremophilones **154** and **155** characterized by a *cis*-fused decalin backbone. Cyclization of the siloxyalkyne-alkene in the presence of **[Ru]-2** followed by protodesilylation provided the methyl enone **153** in good yield (Scheme 46) [52].

In the course of their preparation of the potent *n*AChR agonist (+)-anatoxin **158**, Martin's group encountered synthetic problems that could be solved by using the strategy shown in Scheme 47 [53]. **[Ru]-2**-catalyzed enyne metathesis of siloxyalkyne **156** furnished the cyclized product **157**, featuring the masked methyl enone, in 55% yield. The reaction works best in toluene at 70 °C under an ethylene atmosphere. In the absence of ethylene, the reaction required a longer reaction time (21 h vs. 5 h) and led to lower yields (44–46%) of **157**. Unfortunately all attempts to deprotect the methyl ketone and amine failed.



Scheme 43.



Scheme 45.

5. Vinyl and alkynyl phosphonates and analogues

5.1. Vinylphosphonates and phosphonamides

5.1.1. RCM

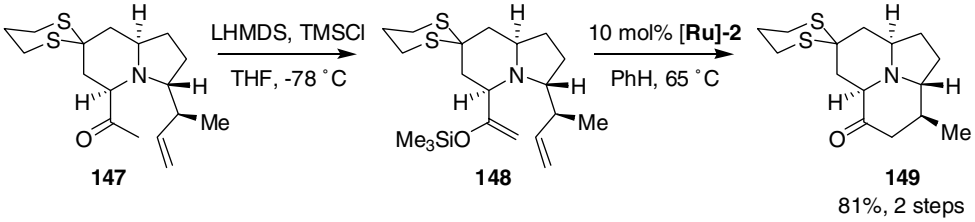
Hanson and Stoianova were the first to report a preparation of *P*-heterocycles by RCM of acyclic vinylphosphonates or phosphonamides (Scheme 48) [54].

In general the reaction worked well using **[Ru]-1** as the catalyst although in some cases (e.g. for R = Ph) the reaction was sluggish. Shortly afterwards, the same team developed an RCM-mediated desymmetrization of nonracemic pseudo-C_2-symmetric phosphonamides that led to *P*-heterocycles containing a stereogenic phosphorus atom (Scheme 49) [55].

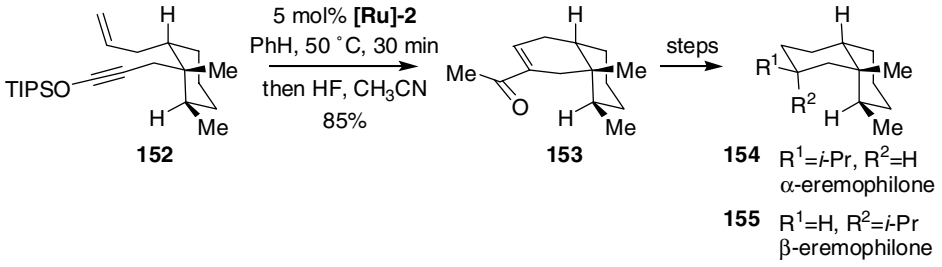
van Boom et al. reported a very efficient preparation of sugar-derived cyclic phosphonamides **165**. Using **[Ru]-2**, quantitative yields were obtained whereas **[Ru]-1** was less efficient (45% after several days, Scheme 50) [56].

The same team reported an enyne metathesis of alkynylphosphonates **166** and of the corresponding borane complexes **167**, providing an entry into bicyclic phosphorus-containing heterocycles **168** and **169**, respectively (Scheme 51) [57].

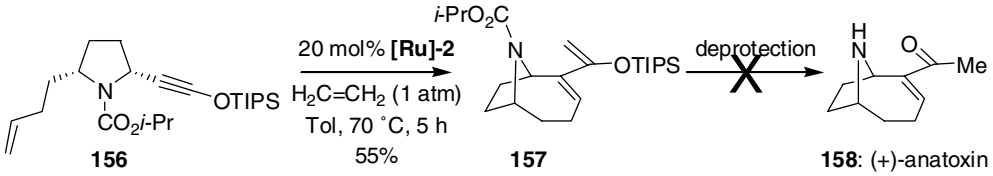
Diene RCM has recently found an application in nucleic acid chemistry [58]. In order to obtain conformationally restricted internucleotide connections, Nielsen et al. submitted a series of unsaturated dinucleotide precursors to RCM. Although, probably for steric reasons, dinucleotide **170** featuring a 2′-methylene nucleoside moiety failed to



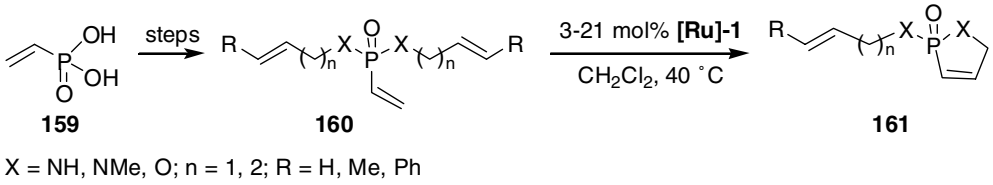
Scheme 44.



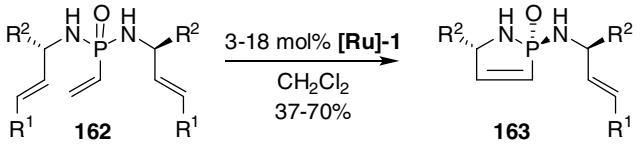
Scheme 46.



Scheme 47.



Scheme 48.



Scheme 49.

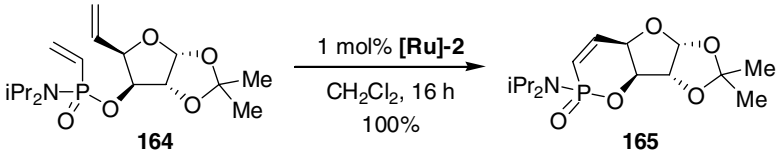
cyclize, the 2′-allyl analogue **172** was converted in modest yield into the desired constrained product **173** using **[Ru]-2** as catalyst in the presence of cuprous chloride as a phosphine scavenger [59] (Scheme 52).

5.1.2. CM

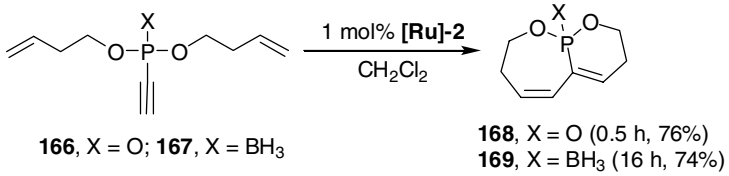
Using the highly active **[Ru]-2** catalyst, Grubbs et al. reported in 2001 the first preparation of vinylphosphonates by coupling of diethylvinylphosphonate with a series of terminal olefins and styrenes (Scheme 53) [60].

The substituted vinyl phosphonates **176** were obtained as (*E*)-isomers exclusively. A large variety of functionalities, including alkyl halides, acetates and unprotected aldehydes were tolerated. Importantly, no dimerization of the starting vinylphosphonate was detected.

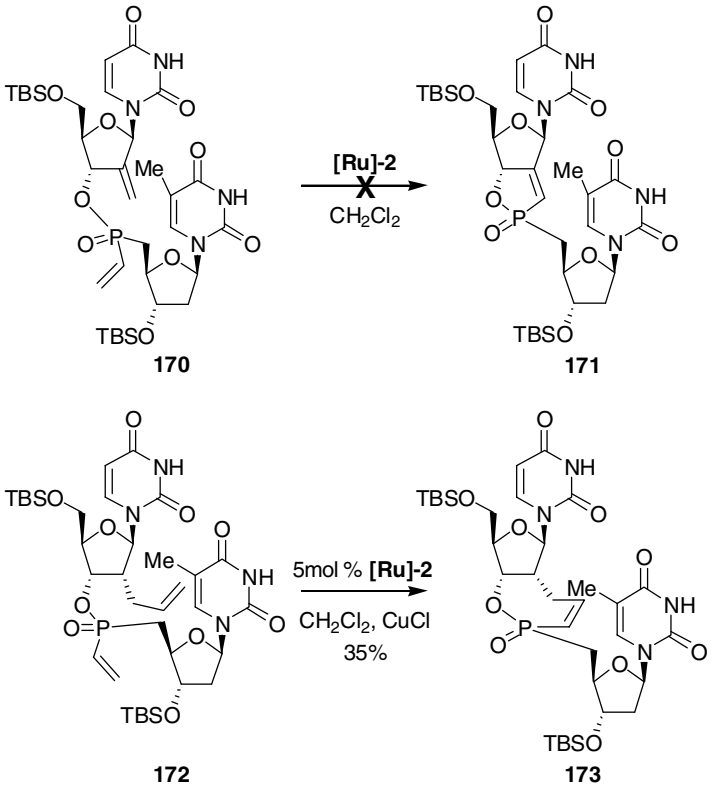
In the same year, an intermolecular application of the above method was developed by Lera and Hayes, high-



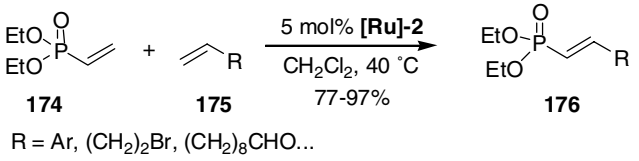
Scheme 50.



Scheme 51.



Scheme 52.



Scheme 53.

lighting the choice of **[Ru]-2** in terms of activity and functional group compatibility (Scheme 54) [61].

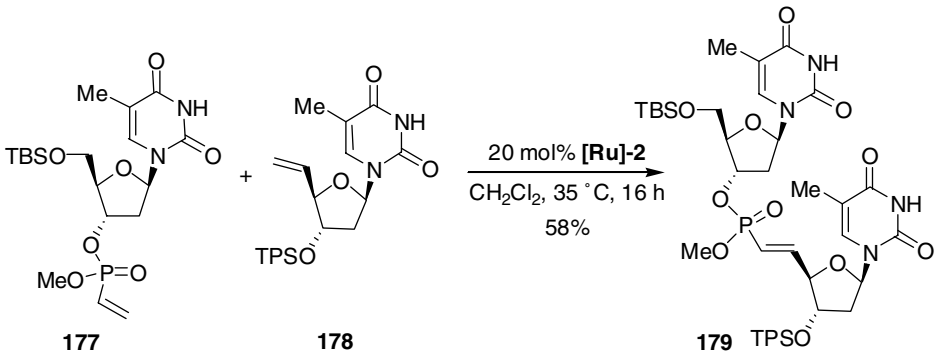
Under similar conditions, in the presence of two equivalents of diethyl vinylphosphonate, Martin's team published the preparation of an advanced precursor of a sugar nucleotide analogue **181** that was obtained along with the homodimer derived from **180** (25%) (Scheme 55) [62].

Very recently, the strategy was exploited by the same team, for the preparation of new potential inhibitors **184** of the mycobacterial galactan biosynthetic pathway (Scheme 56) [63].

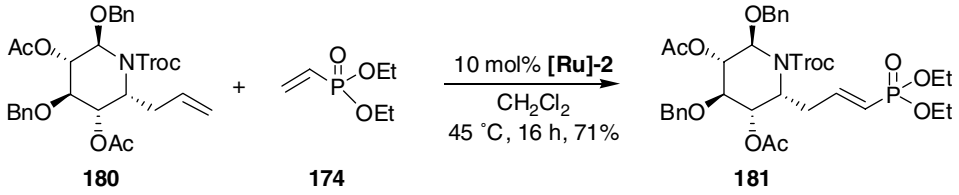
Interestingly in this case, only Nolan's catalyst **[Ru]-3** proved to be efficient unlike the closely related saturated analogue **[Ru]-2**.

5.2. Vinylphosphine oxides

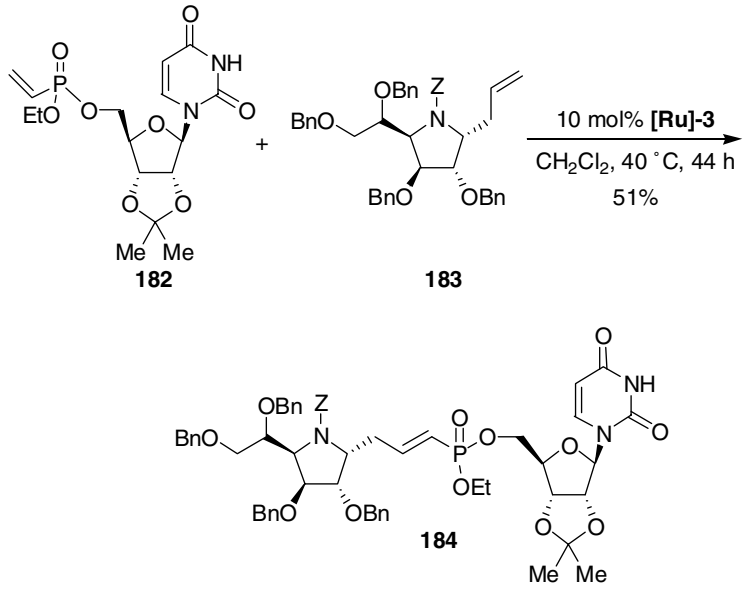
Using the protocol developed for the preparation of vinylphosphonates (Scheme 53), the preparation of vinyl-



Scheme 54.

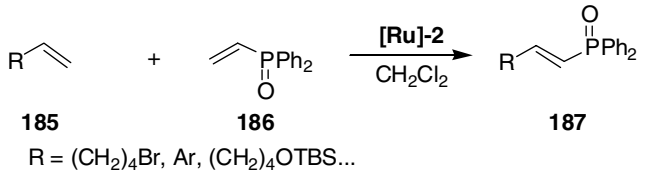


Scheme 55.

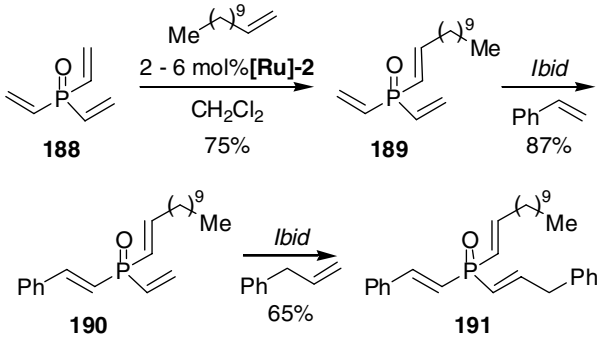


Scheme 56.

phosphine oxides was simultaneously reported by Grela et al. and Gouverneur's team (Scheme 57) [64,65].



Scheme 57.



Scheme 58.

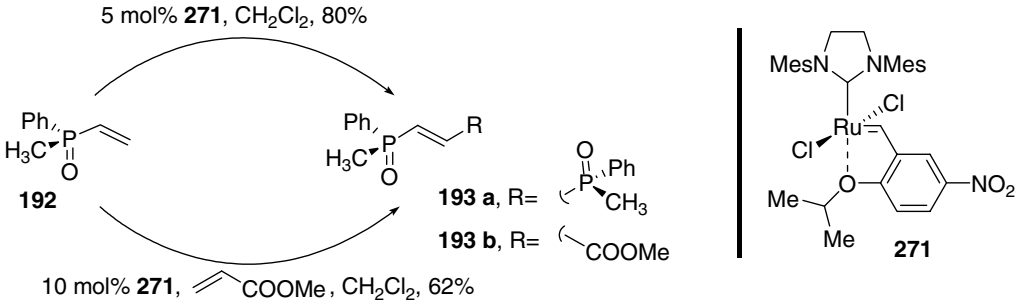
As exemplified in Scheme 58, starting from trivinyl phosphine oxide, Bisaro and Gouverneur recently published a strategy enabling a fully controlled stepwise access to novel racemic *P*-stereogenic products featuring two or even three different alkyl groups [66].

Although quite spectacular, this procedure did not involve any CM coupling with electron-deficient olefins. By making use of a very active nitro-substituted catalyst **271** derived from Hoveyda's catalyst **[Ru]-5**, Vinokurov et al. published very recently the CM of vinylphosphine oxides and electron-poor alkenes, including the homo-coupling of vinylphosphine oxides (Scheme 59) [67]. Compound **193** was isolated as a single *E*-isomer. The method provides an easy access to bidentate diphosphine oxide and diphosphine ligands.

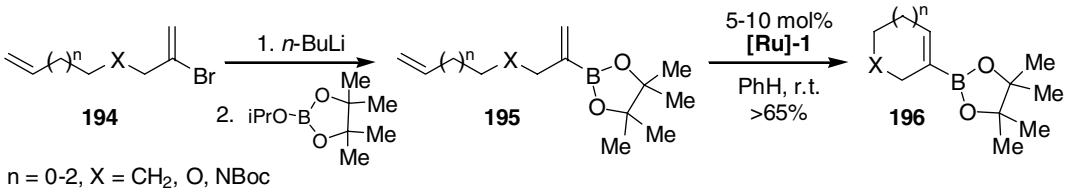
6. Vinyl and alkynyl boronates

6.1. RCM

In their pioneering work, Renaud and Ouellet demonstrated that RCM is a practical and reliable procedure for the synthesis of trisubstituted cyclic vinylboronates (Scheme 60) [68].



Scheme 59.



Scheme 60.

The reaction appeared to work well at room temperature, although it sometimes required a long time (up to 10 days for $X = O$, $n = 1$), affording very good yields of cyclic vinylboronates **196** using Grubbs catalyst **[Ru]-1** (**[Mo]** was not efficient). Although further conversion of the resulting boronates was not examined, this work clearly established a novel strategy for the assembly of hitherto unexplored frameworks through metathesis, broadening the scope of this powerful reaction.

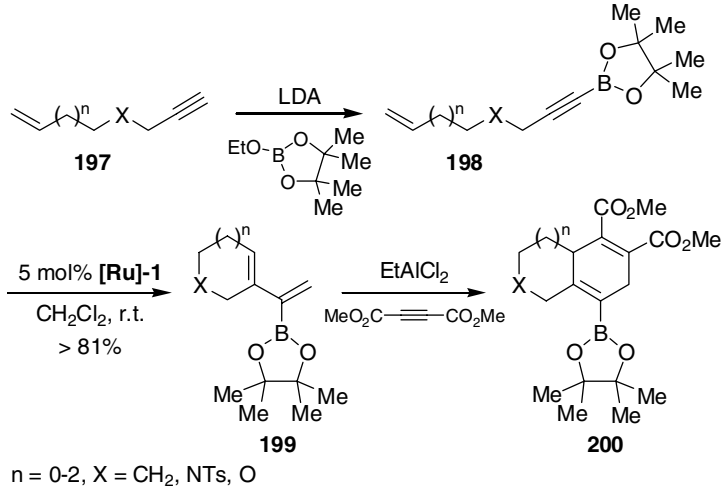
Shortly afterwards, Renaud et al. extended the method to the enyne ring-closing metathesis of acetylenic boronates **198**, offering a concise route to dialkenylboronates **199**, generally isolated in excellent yields [69]. In some cases, the boronic esters were directly converted under Lewis-acid-catalyzed conditions into Diels–Alder adducts **200** (Scheme 61).

The synthesis of the bicyclic dienylboronate **202** was also directly effected by tandem RCM of the dienyne precursor **201** (Scheme 62). Compound **202** was further converted either into a bicyclic unsaturated ketone or into an arylated product through Suzuki coupling with 3-bromobenzonitrile.

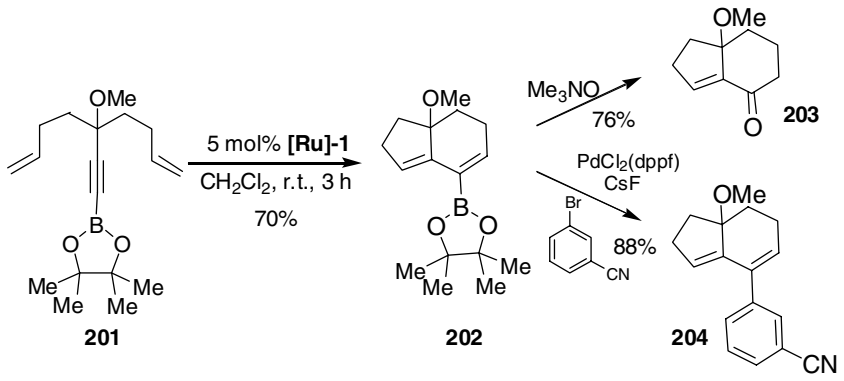
Micalizio and Schreiber introduced a very elegant strategy based on the use of borane linkers to enforce the regio- and stereochemistry of ring-closing metathesis reactions [70].

As shown in Scheme 63, mixed boronate esters were produced in situ by refluxing an allylic or a propargylic alcohol with an excess of diisopropylallylboronate. When performed in the presence of **[Ru]-1**, spontaneous RCM occurred to provide cyclic boronic esters **208** and **209**, respectively.

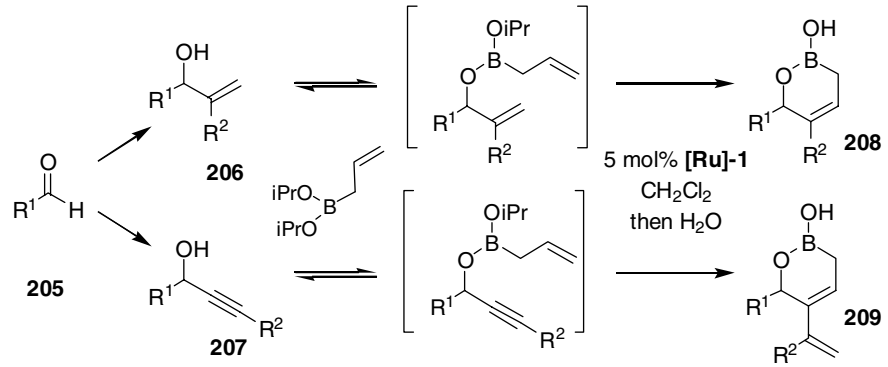
The cyclic boronates were exploited further (Scheme 64). The cyclic allylboronic esters were either converted into stereodefined trisubstituted olefins under oxidizing conditions



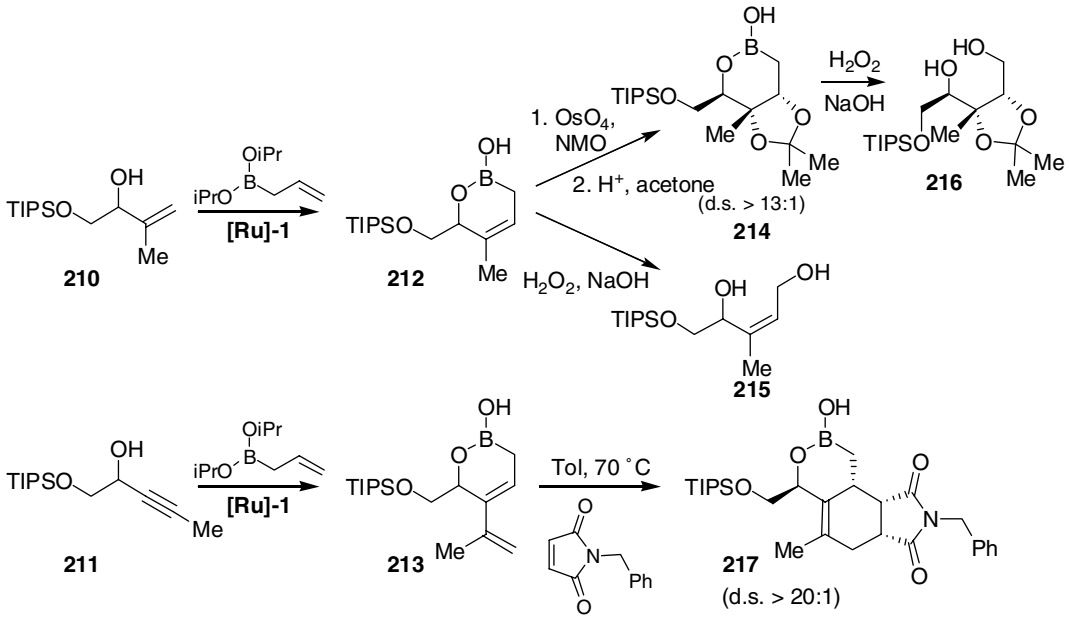
Scheme 61.



Scheme 62.



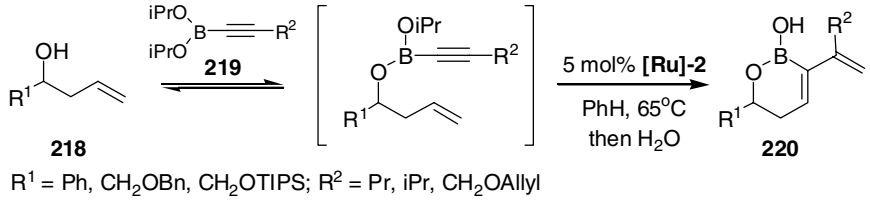
Scheme 63.



Scheme 64.

or transformed into protected pentaols whereas pentadienylboronic esters could be converted into fused polycyclic compounds by diastereoselective Diels–Alder reaction.

Extension of the boron-tethered strategy to the preparation of dialkenylboronic esters was also performed starting from alkynylboronic esters and using **[Ru]-2** as catalyst (Scheme 65) [71].



Scheme 65.

As shown in Scheme 66, the cyclic boronic acids were converted into enones **224** by oxidation, and into homoallenyl alcohols **225** by treatment with trioxane. The latter reaction provides a new convergent approach to the diastereoselective synthesis of trisubstituted allenes from homoallylic alcohols.

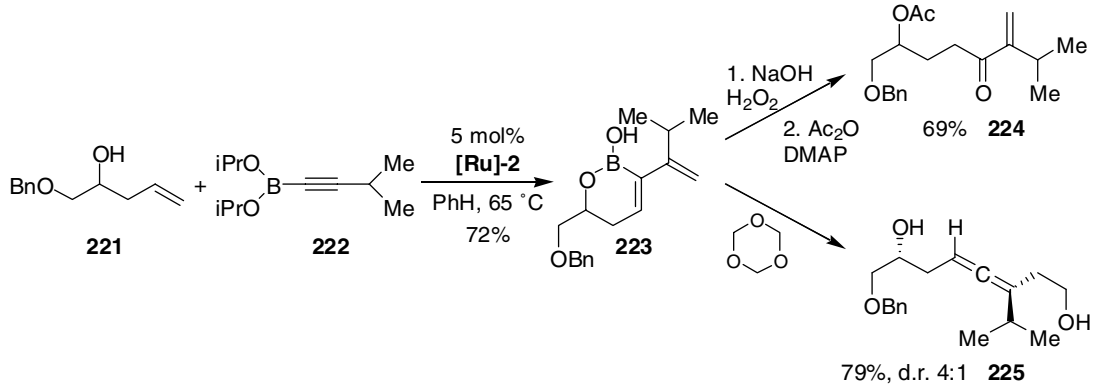
Ring-closing metathesis involving vinyl-boron species has also been exploited by Ashe et al. for the preparation of new ligands **226**, surrogates for cyclopentadiene, for early and late transition metals complexes **227** (Scheme 67) [72–74].

6.2. CM

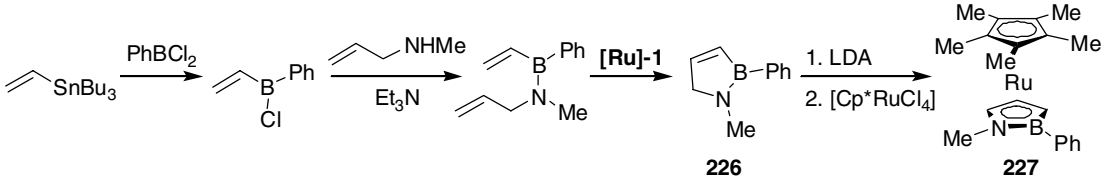
During their first in-depth study on olefin cross-metathesis, Grubbs et al. tested for the first time a vinylboronate as a CM partner [75]. As shown in Scheme 68, the pinacol-derived vinylboronate was found to react with a terminal olefin to furnish the desired cross-product in good yield and excellent *trans*-selectivity.

These conditions were later exploited by Danishefsky and co-workers as part of a macrocyclization strategy in the epothilone series (Scheme 69) [76].

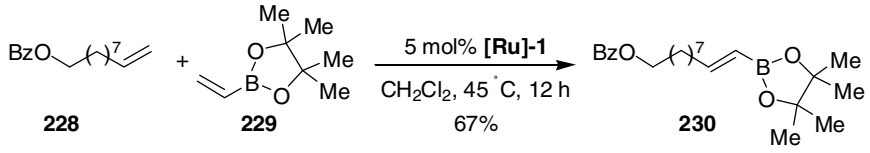
The usefullness and broad scope of CM as a powerful and versatile alternative to alkyne hydroboration for the synthesis of alkenyl pinacol boronates was further demonstrated by Grubbs et al. Using **[Ru]-2** as catalyst; styrenes, allylsilanes, alcohols and protected amines are good partners in the process [77]. The substituted vinyl boronates, e.g. **237**, **240**, **243** thus obtained can readily and stereoselectively be converted to vinyl bromides and iodides, using the halogenation procedures reported by Brown et al.



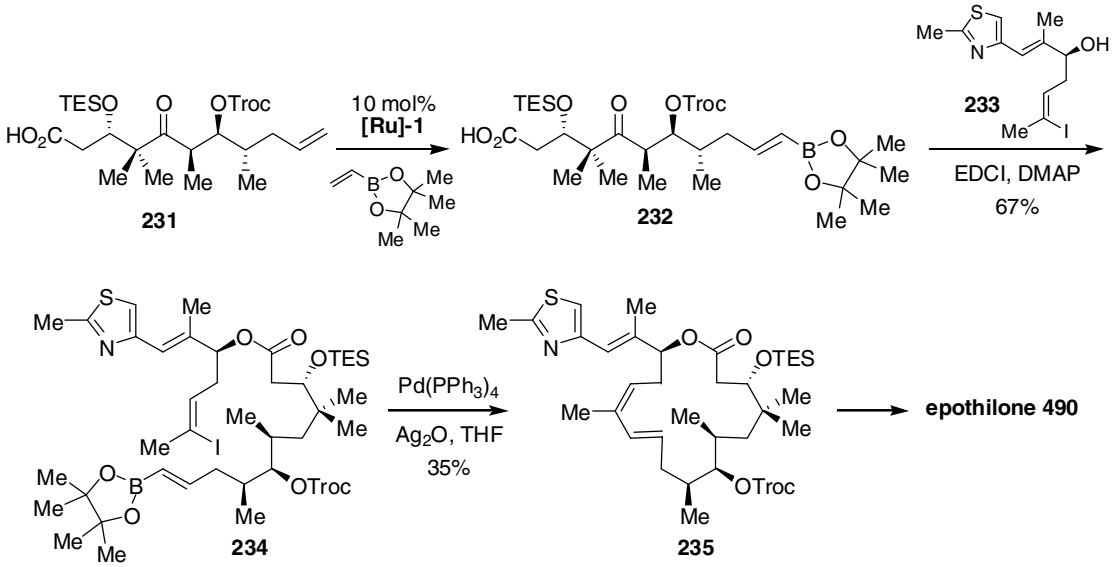
Scheme 66.



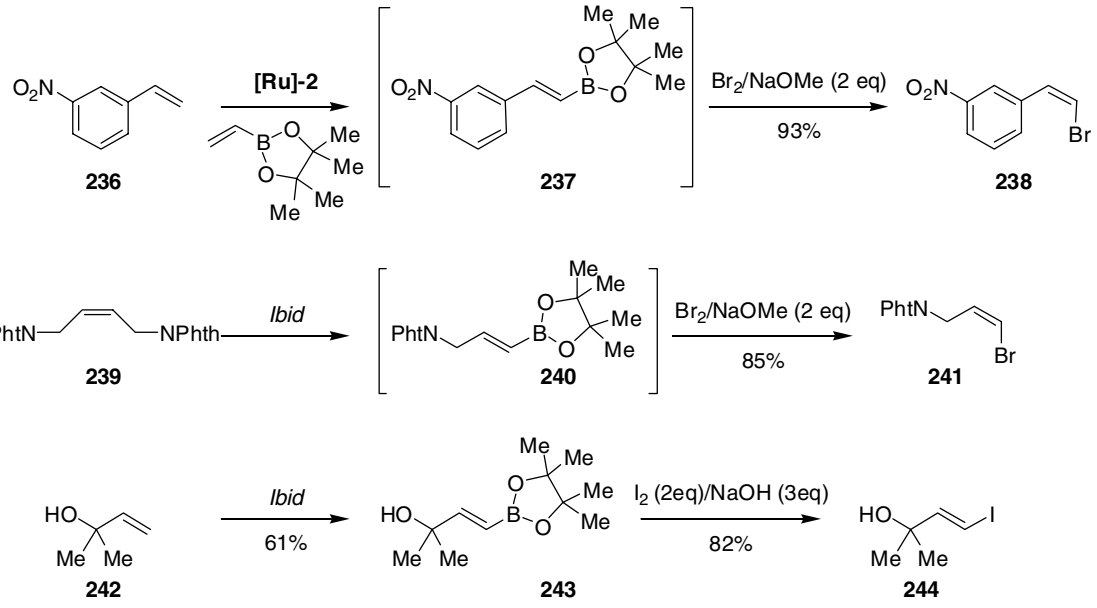
Scheme 67.



Scheme 68.



Scheme 69.



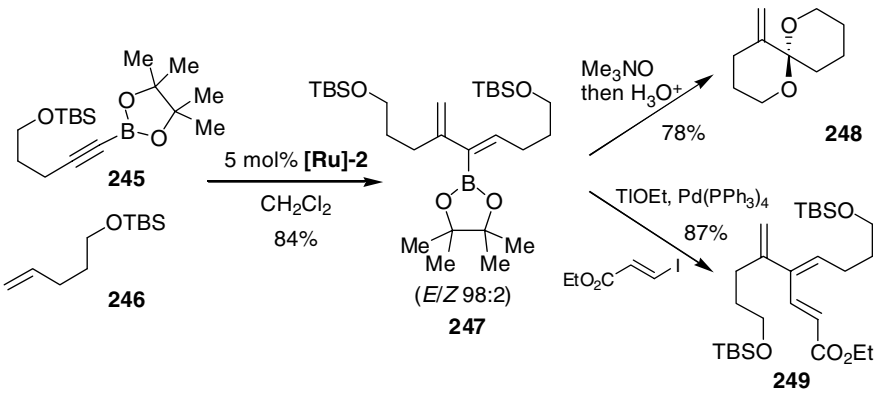
Scheme 70.

(Scheme 70) [78]. In agreement with Brown's observations, vinyl bromides, e.g. **238**, **241** could be formed in situ in very good yields and with inversion of stereochemistry while vinyl iodides, e.g. **244** were best obtained when purified vinyl boronates were used as starting materials, the original olefin stereochemistry being retained in this case.

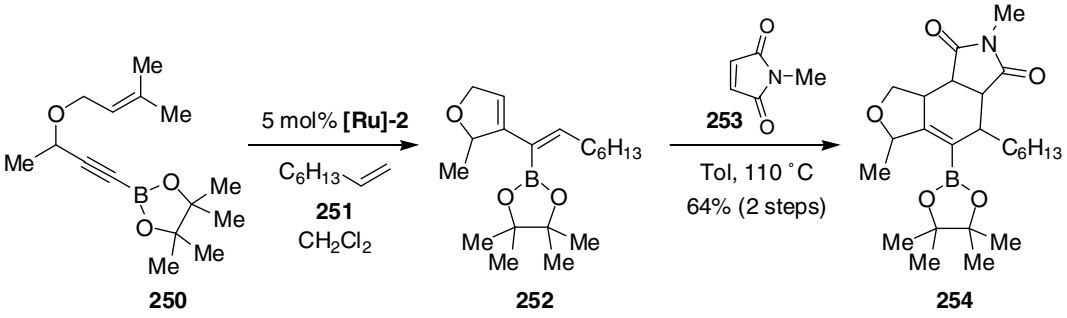
Regio- and stereoselective enyne cross-metathesis reactions between borylated alkynes and terminal alkenes were recently used to prepare functionalized vinyl boronates **247** in high chemical yields and regioselectivity [79]. The resulting vinylboronates were either converted into a cross-conjugated triene **249** under typical Suzuki coupling conditions or into a spiroketal **248** by oxidation (Scheme 71).

A spectacular tandem RCM/CM followed by a Diels–Alder reaction with *N*-methylmaleimide was also performed demonstrating the high regio- and stereoselective nature of the key cross-enyne metathesis (Scheme 72). The stereoselectivity of the Diels-reaction was not indicated [79].

As shown in the above section, the combination of CM/RCM of alkynyl boronates and olefins and Diels–Alder reaction leads to useful synthetic intermediates. As alkynyl boronates themselves are readily prepared (Scheme 61), the



Scheme 71.



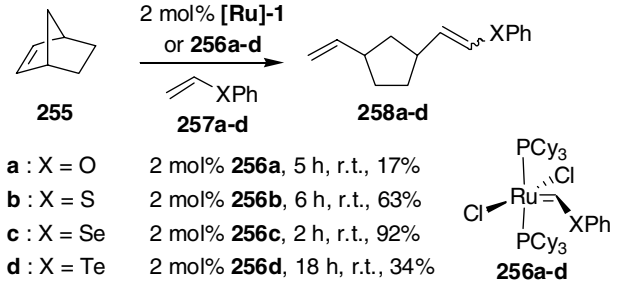
Scheme 72.

overall sequence constitutes a particularly interesting method for preparing functionalized, complex molecules.

7. Sulfur/selenium/tellurium-substituted olefins

7.1. Vinyl chalcogenides

Despite the potential of vinyl sulfides and selenides as synthetic intermediates, we are aware of only two reports dealing with their preparation by metathesis. ROM/CM experiments involving norbornene and phenylvinyl sulfide, selenide or telluride were carried out (Scheme 73). First, Fischer-type carbenes **256a**–**d**, prepared by reaction of **[Ru]-1** with the corresponding vinyl chalcogenides were used. As shown in Scheme 73 the best results were obtained



Scheme 73.

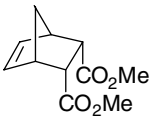
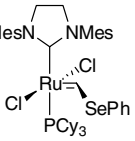
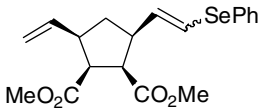
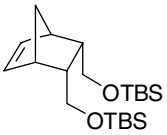
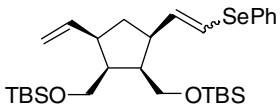
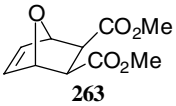
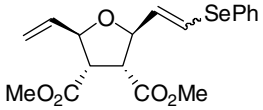
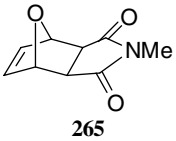
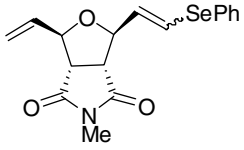
using the selenium-containing carbene **256c** as catalyst and the corresponding vinyl selenide. The reaction could also be performed using **[Ru]-1**, provided that precatalyst and vinyl chalcogenide were mixed before addition of the norbornene. Failure to do so led to substantial polymerisation of norbornene. The reason for this behaviour is unclear [80].

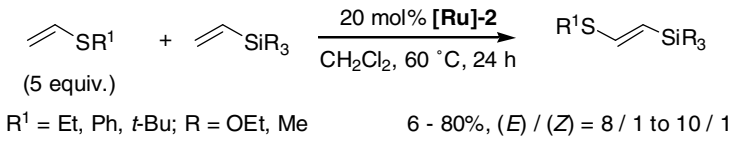
The method was then applied to the preparation of a series of selenium-containing cyclopentene and tetrahydrofurans in high yield (Table 1). Using the more reactive catalyst **267** was necessary for the less reactive *endo*-5,6-disubstituted norbornenes **259** and **261**. In all cases a low-to-moderate *E*/*Z* stereoselectivity (favouring the *E* isomer) was observed during the CM step.

In ROM/CM experiments, a major problem is the competing ROMP. A particularly interesting feature of the ROM/CM sequence using phenyl vinyl selenide as CM partner is the quasi-absence of polymerized **255**. This selectivity ROM/CM vs. ROMP gradually diminished when switching to the vinyl sulfide, then the vinyl ether. In control experiments using styrene, 1-hexene or allyltrimethylsilane, no CM was observed and nearly quantitative yields of polymerized **255** were obtained.

In 2004, Marciniec et al. reported a cross-metathesis beween vinyl sulfides and vinyl silanes (Scheme 74) [81]. Satisfactory results were obtained only using vinyltriethoxysilane and *t*-butyl vinyl sulfide as substrates and **[Ru]-2** as catalyst.

Table 1
ROM/CM of strained bicyclic olefins with phenyl vinyl selenide

Substrate	Catalyst	Product	Yield (%)	*E*/*Z*
 **259**	 **267**	 **260**	96	55/45
 **261**	**267**	 **262**	91	58/42
 **263**	**256c**	 **264**	99	84/16
 **265**	**256c**	 **266**	82	72/28



Scheme 74.

7.2. Vinyl sulfones and sulfoxides

As compared to vinyl chalcogenides, metathesis of vinyl sulfones has been more extensively studied [82]. Cross-metathesis of vinyl sulfones with terminal olefins has been shown to work well using **[Ru]-2** or **[Ru]-5** and analogues, affording exclusively *E*-isomers [83]. **[Ru]-1** is not an efficient catalyst for CM, leading to self-metathesis of the electron-rich reaction partner and the very active **[Mo]** catalyst seems not to be compatible with the sulfone functional group. Cross-coupling experiments involving geminal disubstituted olefins or α-substituted vinyl sulfones were unsuccessful (Table 2). The method was used by Martin et al. for the preparation of glycoconjugate mimetics (Scheme 75) [59].

Surprisingly, to the best of our knowledge, no example of RCM of vinylic sulfones has been described.

Vinyl sulfoxides do not undergo CM reactions [82] and there seems to be only one reported example of RCM involving a terminal vinylsulfoxide. In this work, one equivalent of **[Ru]-1** had to be used for the reaction to proceed in good (79%) yield [84]. Sulfoxides are known to complex and deactivate Grubbs-type carbenes which probably explains these disappointing results.

7.3. Vinylic sulfonates, sulfonamides [85]

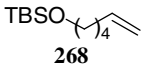
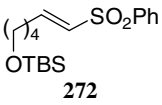
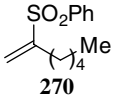
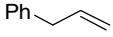
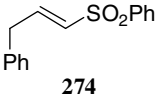
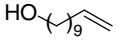
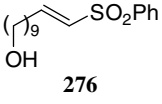
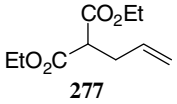
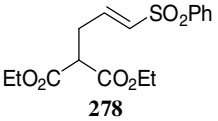
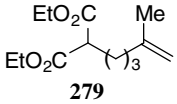
RCM of vinylic sulfamates proceeds in good to excellent yield using **[Ru]-1** and **[Ru]-2**, to afford 5- to 7-membered sultones [86,87]. Similarly, vinylic sulfonamides are converted to 5- to 7-membered sultams (Scheme 76) [88].

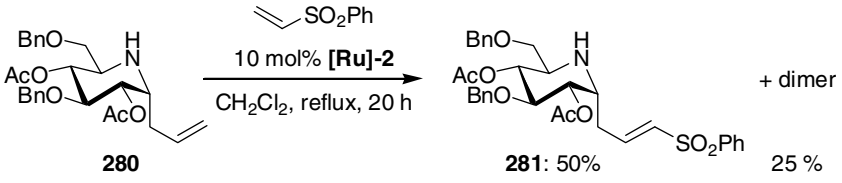
Diels–Alder reaction of the latter with cyclopentadiene produced functionalized norbornenes that were further polymerized by ROMP (Scheme 77) [89].

8. Vinyl halides and pseudohalides

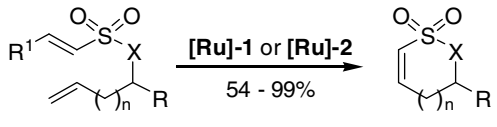
Vinyl halides and pseudohalides (e.g. enol phosphates or sulfonates) are well known versatile intermediates for the creation of new C–C bonds via transition metals-catalyzed

Table 2
CM of vinyl sulfones

Olefin	Sulfone	Catalyst	Product	Yield (%)
 **268**	 **269**	**[Ru]-1**	–	Dimer
		[Mo]		No reaction
		[Ru]-2	 **272**	85
	 **270**	**271** (see Scheme 59)		90
		[Ru]-3	–	0
 **273**	**269**	**[Ru]-2**	 **274**	68
		271		86
 **275**	**269**	**271**	 **276**	96
 **277**	**269**	**[Ru]-2**	 **278**	74
 **279**	**260**	**[Ru]-3**	–	0



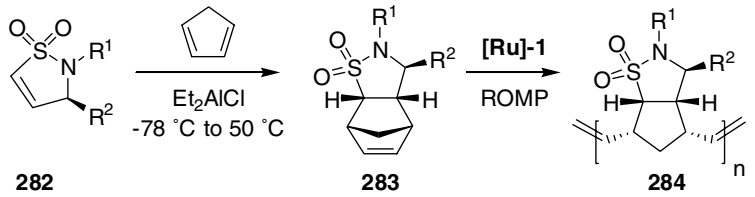
Scheme 75.



Scheme 76.

coupling reactions. Their preparation, however, except in simple cases is not straightforward. Metathesis, if applicable, would be the ideal method to prepare complex vinylic halides or pseudohalides starting from simpler, more readily available members of this family of compounds. At this point, several questions are raised:

- Are the Fisher-type, halide- (pseudohalide)-containing metal carbenes possibly formed during the metathesis initiation or propagation steps sufficiently stable or reactive for an acceptable catalyst turnover [90]?
- If formed, will the intermediate metallocyclobutane intermediate cyclorevert to afford the metathesis product or could other pathways be favoured?



Scheme 77.

8.1. Vinyl halides

8.1.1. Fluorides

RCM of fluorovinyl-containing dienes has been used in several instances for the preparation of fluorinated carbo- or heterocycles. In all reported examples, **[Ru]-2** was used, affording high yields of 5-, 6- and 7-membered rings, some representative examples being shown in Table 3.

Brown et al. made the general observation that RCM involving fluoro-olefins are slower than those using their non-fluorinated [91] counterpart as substrates while Haufe et al. noted that certain fluorinated dienes (e.g. **291**, Table 3), did not lead to productive RCM in contrast to similar, non-fluorinated dienic systems [92].

We are not aware of any successful, ROMP or CM ene-yne metathesis involving fluorinated olefins or alkynes.

8.1.2. Vinyl chlorides, bromides and iodides

From the synthetic viewpoint, metathesis leading to complex vinyl bromides or iodides would be very interesting. Unfortunately, attempts reported so far to synthesize these compounds by RCM of dienes (containing vinyl bromides) or enynes (containing 1-bromoalkynes) have been unsuccessful [93,94]. In the case of dienes, a possible explanation is that the Grubbs precatalyst reacts first with the vinyl bromide functionality, leading to an unreactive Fisher-type carbene [94]. Initial attempts to perform CM involving vinyl chlorides [7] or tandem dieneyne RCM involving 1-chloroalkynes [93], using several catalysts, were unsuccessful. More recently, however, RCM of dienes containing vinyl chloride moieties could be achieved [94,95]. In particular, using **[Ru]-2**, Weinreb et al. demonstrated that 5- to 7-membered carbo- (**294**) or heterocycles (**296**, **298**)

Table 3
RCM of vinyl fluorides

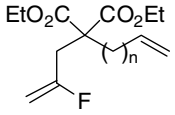
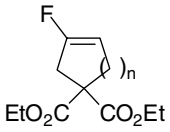
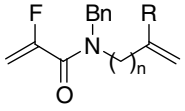
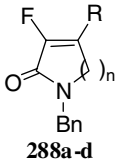
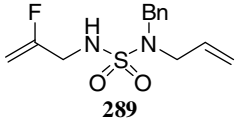
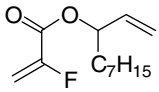
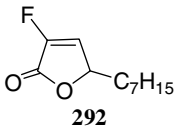
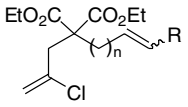
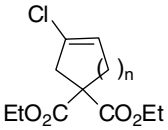
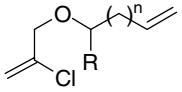
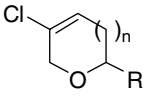
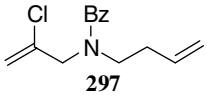
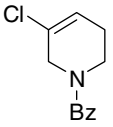
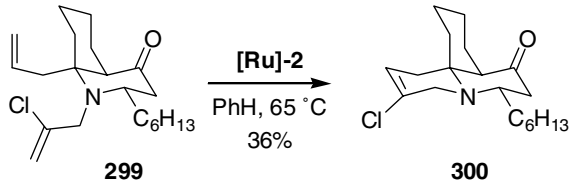
Diene		Conditions	Product	Yield (%)	Reference
 **285a-c**	**a**: $n = 1$ **b**: $n = 2$ **c**: $n = 3$	2 mol% **[Ru]-2**, Tol, 80 °C, 4 h	 **286a-c**	0 73 77	[91]
 **287a-d**	**a**: $n = 1$, R = H **b**: $n = 2$, R = H **c**: $n = 3$, 4 R = H **d**: $n = 1$, R = Me	2 mol% **[Ru]-2**, Tol, 80 °C,10 min. 2 mol% **[Ru]-2**, Tol, 80 °C, 2 h. 2 mol% **[Ru]-2**, Tol, 80 °C, 4 h. 2 mol% **[Ru]-2**, Tol, 80 °C, 8 h.	 **288a-d**	79 89 0 46	[92]
 **289**		2 mol% **[Ru]-2**, CH_2Cl_2, 40 °C, 7 h.	 **290**	79	[91]
 **291**		**[Ru]-2**	 **292**	0	[92]

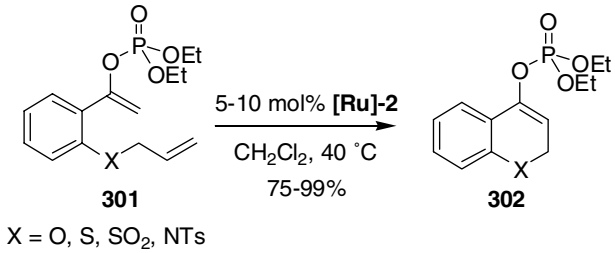
Table 4
RCM of vinyl chlorides

Diene		Conditions	Product	Yield (%)	Reference
 **293 a-e**	**a**: $n = 1$ R = H **b**: $n = 1$ R = Me **c**: $n = 2$ R = H **d**: $n = 2$ R = Me **e**: $n = 3$ R = H	10 mol% **[Ru]-2**, PhH, 65 °C, 4–10 h	 **294 a-e**	85 96 99 98 92	[94]
 **295 a-c**	**a**: $n = 1$, R = $PhCH_2$ **b**: $n = 2$, R = $Ph(CH_2)_2$ **c**: $n = 3$ R = $Ph(CH_2)_2$		 **296 a-c**	84 88 0	
 **297**			 **298**	90	

could be obtained in high yields by RCM of vinyl chlorides (Table 4). As pointed out by these authors, following the development of active palladium catalysts by Fu's group [96], vinyl chlorides have become valuable substrates for Suzuki–Miyaura or Negishi couplings.



Scheme 78.



Scheme 79.

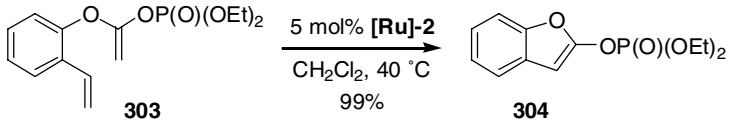
Recently, vinyl chloride RCM was used for the preparation of an intermediate in an approach to cylindricin B total synthesis (Scheme 78) [97].

8.2. Vinyl pseudohalides

Hanson et al. recently reported the preparation of cyclic enol phosphates from simpler, acyclic precursors (Scheme 79) [98]. The reaction was easy to perform and was even successful using ketene ketals phosphates (Scheme 80). In terms of synthetic potential the method is a nice alternative to the difficult vinyl halide metathesis.

9. Discussion/conclusion

Within a short period of only a few years, organic chemists' understanding of olefin and alkyne metathesis has progressed to a level that allows the use of this powerful reaction for the preparation of many, structurally diverse complex molecules. In most cases, the substitution pattern of metathesis substrates encompasses hydrogen or substituents linked by a C–C bond (e.g, alkyl or aryl residues, carbonyl groups, etc.). As a result, during the metathesis process, alkenes, dienes or alkynes bearing H or C-substituents are obtained that are only moderately susceptible to further chemical transformation. In contrast, using hetero-



Scheme 80.

atom-substituted olefins and alkynes as substrates might lead (depending on the substitution pattern) to highly versatile synthetic intermediates.

In the present survey, we have attempted to put together the (often scattered) examples of metathesis involving heteroatom-substituted unsaturated species and several trends emerge from the available data. Metathesis of vinyl or alkynyl silanes in its various versions is now widely used for the synthesis of complex molecules. When alkoxy vinyl or alkynyl silanes are used, the metathesis products can be further functionalized by desilylation (to alcohols) or can participate in Pd-catalyzed coupling reactions as described by Denmark. After initial disappointing results, the advent of more active catalysis such as **[Ru]-2** has made possible metathesis reactions involving enol ethers or silylenol ethers. Numerous examples of diene or and enyne metatheses (RCM, CM) have been reported. The elaborated vinyl ethers thus obtained can be functionalized in a regioselective/stereoselective fashion to give alcohols, ketones or hydroxyketones. CM of vinyl ethers and alkynes affords reactive 1-alkoxy butadienes that readily take part in Diels–Alder reactions. Enamines and ynamines as well as vinyl or alkynyl phosphonates or phosphine oxides are good metathesis substrates and participate in RCM, cascade RCM and CM reactions. Enyne metathesis gives rise to *N*-substituted butadienes that can further react in cycloadditions.

Vinyl and alkynyl boronates appear to be potentially extremely useful substrates for metathesis as they provide a ready access to complex boronates that would otherwise be difficult to prepare. All versions of boron-substituted olefin and alkyne metathesis have been described. The resulting molecules can be further functionalized using the rich boron chemistry: Pd-catalyzed cross-coupling, conversion to vinylic bromides and iodides or oxidation to ketones have been described [99].

Curiously, despite their potential interest in radical chemistry, there seems to be only one example of preparing sulfides and selenides via metathesis. Finally, certain vinyl halides participate in metathesis reactions: vinyl fluoride RCM has been used for the preparation of fluorine-containing molecules. Although this may be useful in particular in medicinal chemistry, the products of vinyl fluoride metathesis have a very limited interest as synthetic intermediates. Vinyl chlorides also undergo RCM, albeit less easily than fluorides and are potentially useful as reactive partners in Fu's modified Pd-coupling reactions. Until now, it has not been possible to prepare directly complex vinyl bromides and iodides by metathesis. However, indirect access to these compounds is provided by the vinylboronate metathesis method mentioned earlier [100]. In contrast, enol phosphates, that are very good reactants in Pd-catalyzed couplings can be readily obtained by RCM of enol phosphates and even ketene ketal phosphates.

From the mechanistic viewpoint, a matter of debate is the participation (or lack of participation) of catalytic intermediates possessing a Fisher-carbene character which might explain the generally decreased metathetic activity of olefins and alkynes with electrodonating substituents. Whether this limitation can be overcome by using new types of metal carbenes specifically designed for electron-rich systems remains to be established.

Overall, olefin and alkyne metathesis is rapidly progressing from a very useful method for forming olefins, alkynes and conjugated dienes to a powerful new procedure for accessing a wide variety of useful synthetic intermediates. Regarding C–C bond formation, boronates currently appear to be the most versatile metathesis substrates. Although vinyl chlorides offer some interest as synthetic intermediates for Pd-catalyzed coupling reactions, further efforts to make vinyl bromides/iodides as well as vinyl sulfides/selenides accessible by metathesis are clearly needed. The same holds true for vinyl or alkynyl stannanes whose metathetic behaviour has been only briefly evaluated by Grubbs (with negative results) [93]. This would allow a ready access to useful intermediates for radical chemistry uses.

Finally, although the development of new generation of catalysts has allowed the scope of RCM to be extended, there is still plenty of scope for improvement. In particular, high loadings of (relatively costly) catalysts are often required for the metathesis reaction to go to completion. In the near future, further developments of the olefin/alkyne metathesis can be anticipated and these will directly be linked to the availability of more active catalysts with increased stability and turnover.

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