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RING-CLOSING METATHESIS OF HETEROATOM-SUBSTITUTED DIENES

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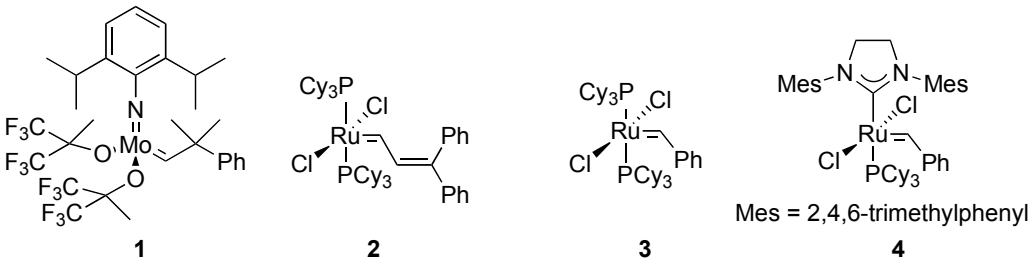
Abstract – The ring-closing metathesis (RCM) of dienes that contain at least one participating heteroatom-substituted olefin is reviewed (olefins substituted with O, N, S, P, Si, B, and halogen atoms will be considered). Efforts have been made to include as many relevant examples of RCM of heteroatom-substituted dienes as possible, but due to the increasing volume of research in this area, an exhaustive coverage is not intended. Attention has focussed on diene RCM reactions catalysed by ruthenium and molybdenum alkylidene complexes, although a brief discussion of some ring-closing reactions of titanium alkylidene species is provided. Other metathesis reactions such as enyne RCM, cross-metathesis and ROMP are not included.

The universal uptake of diene ring-closing metathesis (RCM) by synthetic organic chemists underscores the broad scope this method has as a reliable tool for carbon-carbon bond formation.[1] Thanks to the discovery of pre-catalysts (**4**) with high activity and good functional group compatibility (Figure 1),[2] diene RCM has evolved into one of the most general modern methods for the synthesis of carbocyclic and heterocyclic systems.[1,3-5] Moreover, RCM chemistry has found widespread application in total syntheses of complex natural products.[6] However, it was apparent in early studies that there were some olefin classes that were less amenable to the RCM process using the then available 1st generation ruthenium alkylidene pre-catalyst complexes (**2**) and (**3**). These dienes included sterically demanding systems and electron-rich olefins substituted at the α-position with heteroatoms e.g. enol ethers, enamines, vinyl sulfides and vinyl halides.[7] In certain cases these limitations were overcome by the use of the Schrock Mo-alkylidene complex (**1**), although the sensitivity of this more active complex discouraged some organic chemists from exploiting its application in RCM. The timely discovery of 2nd generation

This paper is dedicated to Professor Steven M. Weinreb on the occasion of his 65th birthday.

ruthenium alkylidene pre-catalysts such as **4**,[2,8] which exhibit generally good stability and functional group compatibility alongside excellent metathesis activity, opened the door to more general application of RCM in challenging diene systems.



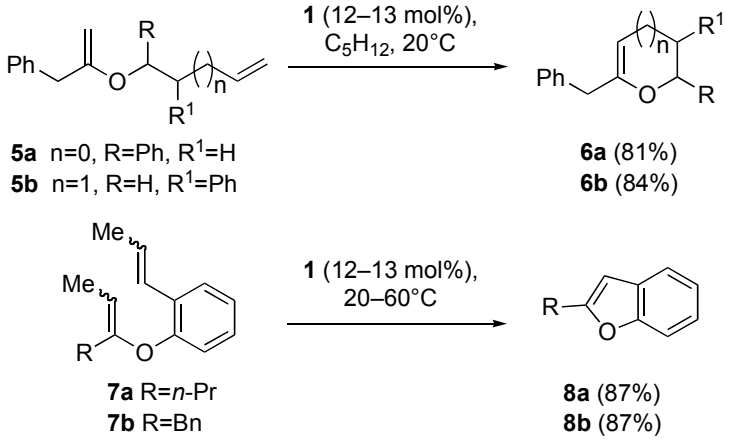
1 **2** **3** **4**

Figure 1. Metal alkylidene complexes commonly used for diene RCM.

RING-CLOSING METATHESIS OF VINYL ETHER-CONTAINING DIENES (ENOL ETHER–OLEFIN RCM)

Cyclic enol ethers are well recognised as synthetically useful precursors to a variety of cyclic ether-containing biologically active natural products, including carbohydrate derivatives.[9] In addition, the cyclic ether functionality is embedded within medicinally relevant heterocyclic ring systems such as benzofurans and benzopyrans. Not surprisingly therefore, the development of methods to prepare substituted cyclic enol ethers has proved to be an area of major interest to synthetic chemists. Indeed, a number of research groups recognised that RCM had considerable potential as a tool for the construction of cyclic enol ether-containing systems, offering relatively mild reaction conditions and good compatibility with the acid sensitive enol ether functionality.[4]

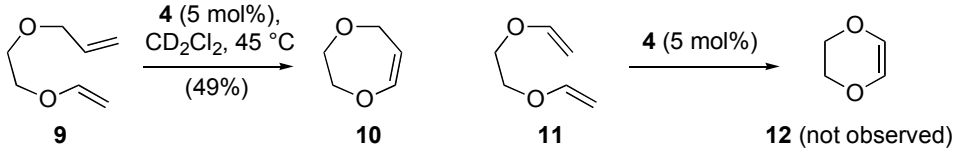
RCM to produce endocyclic enol ethers: The ensuing section will detail RCM reactions that give enol ethers where the enol oxygen atom is contained within the new ring being formed.



Scheme 1. Enol ether–olefin RCM using the Schrock catalyst (**1**).

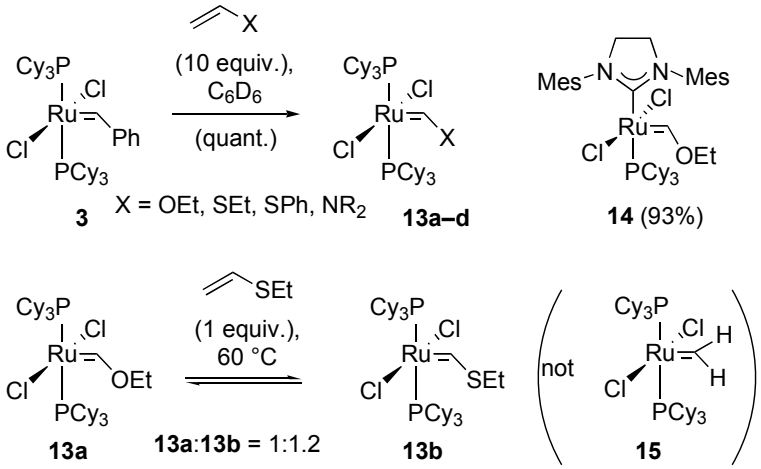
The first reported catalytic examples of RCM of acyclic enol ethers used the Schrock molybdenum catalyst (**1**), to afford five- and six-membered endo- and exocyclic enol ethers in high yields (Scheme

1).[10] It is interesting to note that in this early study, the ruthenium alkylidene (**2**) failed to provide any of the corresponding cyclic enol ether, and slow dimerisation of the mono-substituted olefin was noted. It was postulated that the carbene resulting from the metathesis with the terminal olefin did not react with the enol ether because of unfavourable steric or electronic effects. Indeed, it was later reported that the *bis*-triphenylphosphine analogue of complex (**2**) reacted with stoichiometric ethyl vinyl ether to give an unstable Fischer carbene, which decomposed through a bimolecular pathway giving 1,2-diethoxyethylene (50%).[11] No productive cross-metathesis was observed.



Scheme 2. Enol ether RCM using the 2nd generation ruthenium alkylidene (**4**).

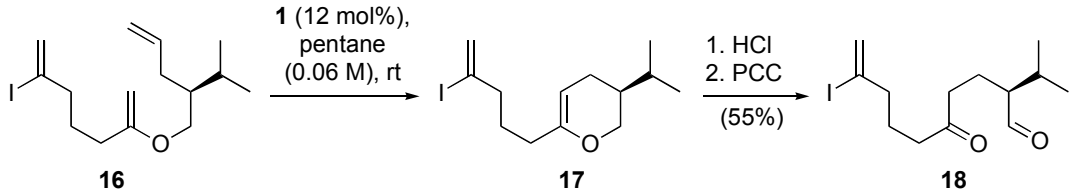
The Grubbs group subsequently showed that the 2nd generation catalyst (**4**) was capable of effecting RCM of vinyl ether substrate (**9**), albeit in moderate yield (Scheme 2).[12] The noted failure of the *bis*-vinyl ether (**11**) to give cyclisation product (**12**) was consistent with the notion that ruthenium Fischer carbene complexes derived from enol ethers did not provide a productive reaction manifold to cyclised products, or they at least showed diminished reactivity.



Scheme 3. Reactions of electron-rich olefins with ruthenium alkylidenes to give Fisher carbenes.

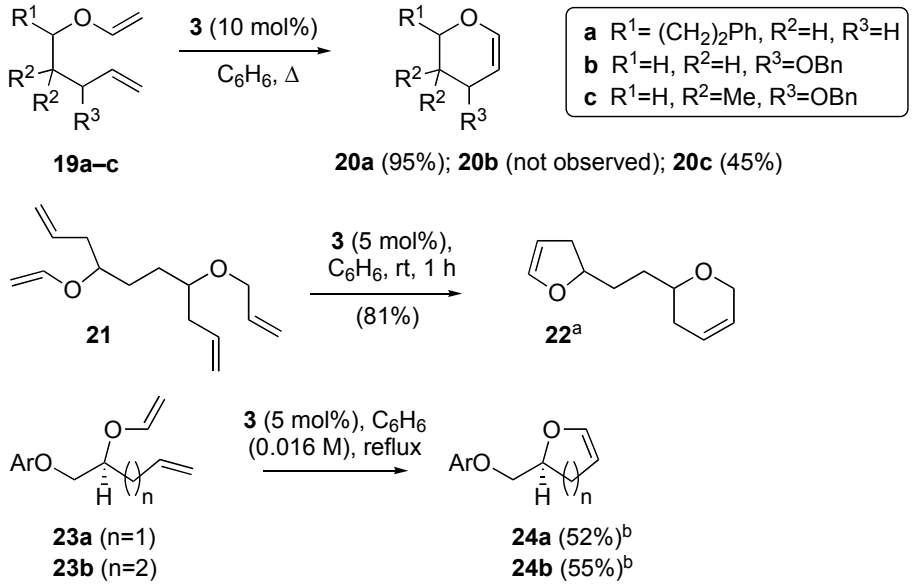
Further detailed investigations revealed that reactions of electron-rich olefins with complexes (**3**) and (**4**) led to the efficient formation of Fischer carbene complexes (**13a–d**) (Scheme 3).[7] In this study it was shown that these Fischer carbene complexes were significantly less active metathesis catalysts than (**3**) or (**4**), and that the Fischer carbene complexes (**14**) substituted with *N*-heterocyclic carbene ligands were more active than the corresponding *bis*-phosphines. Furthermore, stoichiometric reactions of the Fischer carbene complex (**13a**) with electron-rich olefins did not give di-functionalised olefins, a result which

was consistent with the unsuccessful attempted RCM of *bis*-enol ether (**12**).



Scheme 4. Enol ether–olefin RCM using the Schrock catalyst (**1**).

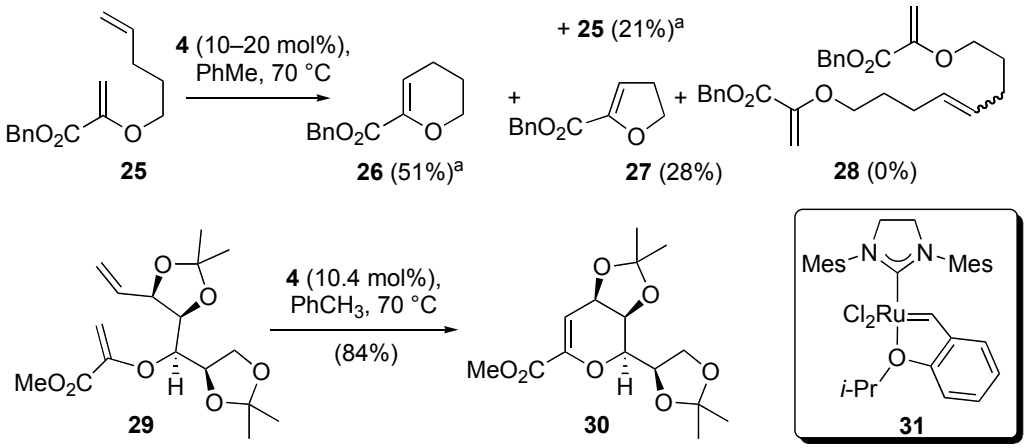
Hodgson and his coworkers also found ruthenium complex (**3**) to be ineffective for enol ether–ene RCM for the non-racemic triene (**16**) (Scheme 4),[13] instead promoting homometathesis of the mono-substituted alkene. Successful RCM occurred in the presence of molybdenum alkylidene (**1**), to afford a dihydropyran (**17**) that subsequently underwent hydrolysis and oxidation to the dicarbonyl compound (**18**). In a footnote, the authors noted that the then recently discovered 2nd generation ruthenium alkylidene complexes might be more effective for the enol ether-ene RCM. It is also noteworthy that the presence of an iodoolefin in the substrate did not adversely affect ring-closure of the diene system.



Scheme 5. RCM reactions of vinyl ethers using the 1st generation Grubbs alkylidene complex (**3**). [a] Ref. 15; [b] Ref. 16

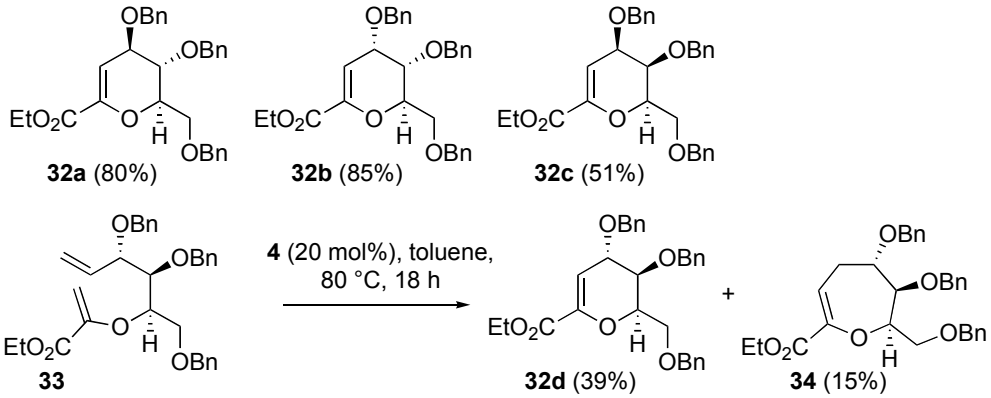
Despite discouraging results from the early attempts to achieve enol ether RCM using the Grubbs 1st generation ruthenium alkylidene (**3**), Sturino *et al.* demonstrated that this complex could effectively catalyse RCM of certain vinyl ether substrates such as **19a** to produce cyclic ether (**20a**) in excellent yields (Scheme 5).[14] However, substitution pattern in the chain tethering the olefin functionalities was found to play a dominant role in the success or failure of RCM. For example, alkoxy substituted diene (**19b**) failed to give the cyclised product (**20b**), whereas the *gem*-dimethyl analogue provided dihydropyran (**20c**) in moderate yield. The research teams of Mioskowski and Gurjar *et al.* also reported

success in the synthesis of dihydrofurans (**24a**) and dihydropyrans (**24b**) using the 1st generation ruthenium alkylidene (**3**) (Scheme 5).[15,16]



Scheme 6. RCM and olefin isomerisation-RCM of enol ethers. [a]GC yields.

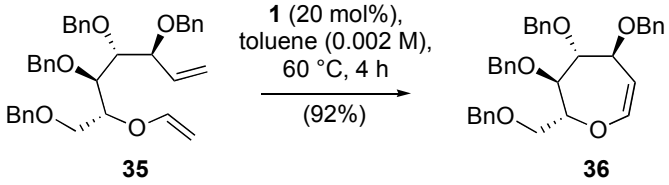
During a study of RCM reactions of olefins substituted with both electron-withdrawing (ester) and electron-donating (enol ether) substituents, Rutjes and co-workers observed unexpected product (**27**) in addition to the desired RCM product (**26**) (Scheme 6).[17] The undesired side reaction involved isomerisation of the terminal double bond to a disubstituted olefin prior to the cyclisation reaction, which was attributed to a different ruthenium species derived from **4**.[7,11,18] In accordance with other reports of enol ether RCM, the first generation Grubbs catalyst (**3**) did not induce the desired cyclisation and instead led to slow formation of homo-metathesis product (**28**), whereas the use of other metal carbene complexes (**1** or **31**) was ineffective or gave no advantage over **4** respectively. It was suspected that the olefin isomerisation process was sensitive to steric effects and this notion seemed to be supported by the smooth cyclisation of **29** to give the dihydropyran (**30**) without any isomerisation-RCM product. Further synthetic manipulation of **30** allowed the authors to complete a short formal synthesis of the natural product KDO.



Scheme 7. α-Alkoxyacrylate–ene metathesis and alkene homologation–RCM reactions.

In 2006, the Rutjes group published a detailed study of the α-alkoxyacrylate–ene metathesis reaction, leading to the formation of carbohydrate-derived dihydropyrans (**32a–d**) (Scheme 7).[19] Curiously, during the course of this study they observed the formation of a homologated product (**34**) in the *xylo*-series thought to be derived from methylene addition to the starting olefin (**33**) via a non-catalytic pathway, followed by RCM.

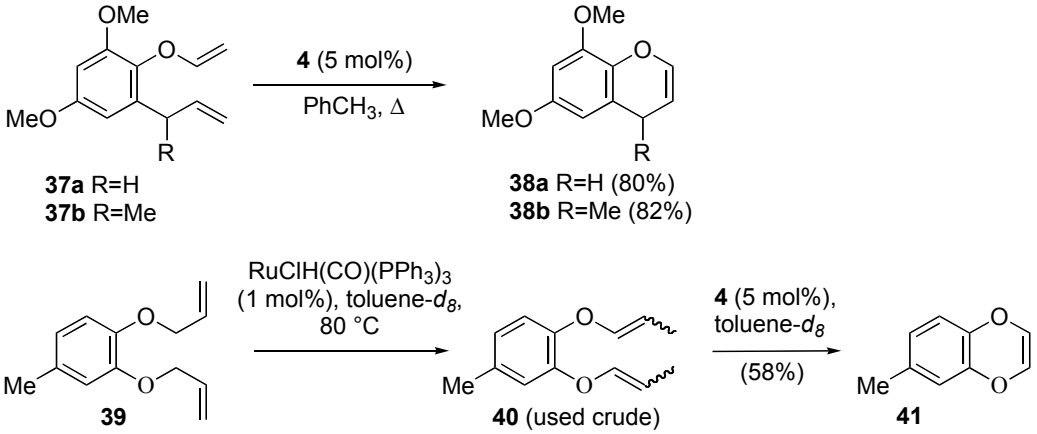
The ring-expansion of glycals to tetrahydrooxepines has been achieved using a three step procedure that culminated in RCM (Scheme 8).[20,21] In all of the reported examples superior yields were obtained using the Schrock catalyst compared to the 2nd generation ruthenium alkylidene (**4**).



35 **36**

Scheme 8. Oxepine formation by RCM.

The 2nd generation Grubbs catalyst (**4**) proved effective for RCM of five phenolic vinyl ethers (e.g. **37a,b**) to deliver 4*H*-chromenes (**38a,b**) in good to excellent yields (80–98%, Scheme 9).[22,23] The same authors went on to report a one-pot olefin isomerisation-RCM route to benzo[1,4]dioxins **41** and benzofurans, which avoided the sometimes troublesome vinylation of catechol or phenol derivatives.[18,24-27] The RCM of the *bis*-vinyl ether (**40**) is unusual because two electron-rich olefins are combined in a reaction which proceeds through a ruthenium Fischer carbene intermediate.



37a R=H
37b R=Me

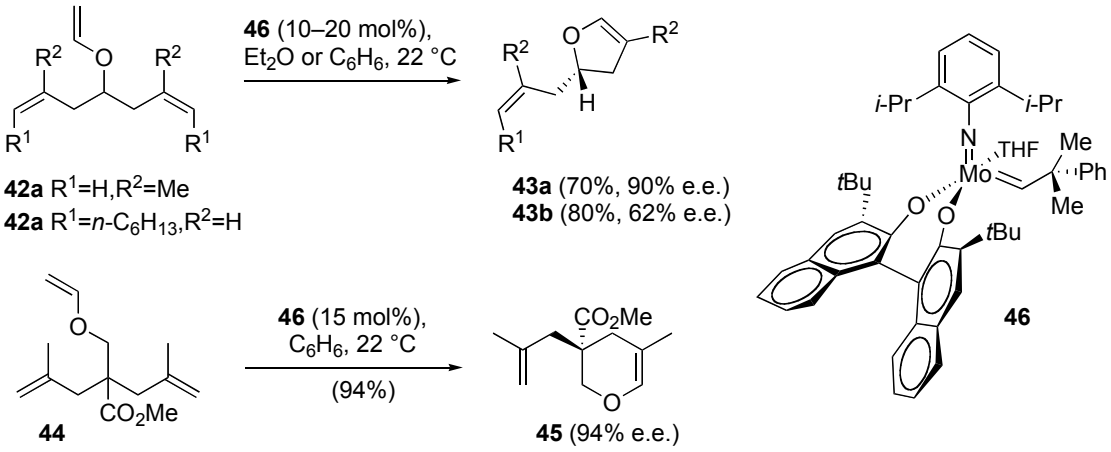
38a R=H (80%)
38b R=Me (82%)

39 **40** (used crude) **41**

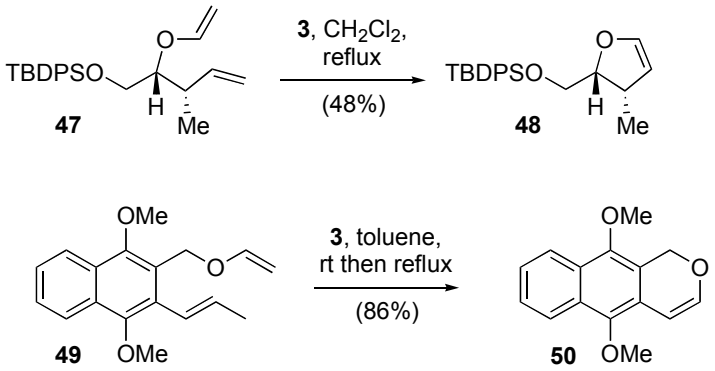
Scheme 9. RCM of phenolic vinyl ethers and olefin isomerisation–RCM of phenolic allyl ethers.

An exciting development in the field of ring-closing metathesis has been the discovery of desymmetrisation processes for achiral substrates using chiral metal alkylidene complexes.[28] Using this tactic, asymmetric enol ether-olefin RCM has been realised, providing dihydrofurans (**43**) and dihydropyrans (**45**) with high enantioselectivities using the molybdenum complex (**46**) (Scheme 10).[29] The mechanistic rationale describes a sequence where initial reaction occurs at the sterically less hindered enol ether alkene, followed by selective reaction with one of the diastereotopic alkenes. Chiral ruthenium

alkylidene complexes either displayed low reactivity or promoted ring-closure with modest enantioinduction for the reported examples.

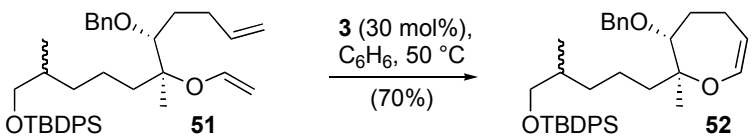


Scheme 10. Catalytic asymmetric enol ether–olefin RCM.



Scheme 11. Applications of enol ether–olefin RCM in total synthesis of antibiotics.

A number of research teams have employed enol ether–olefin RCM catalysed by the 1st generation ruthenium complex (**3**) in natural product total syntheses. Williams and co-workers secured the key dihydrofuran (**48**) by RCM during their total synthesis of antibiotic lankacyclinol (Scheme 11).[30] In 2004, Van and De Kimpe reported the synthesis of pyranonaphthoquinone antibiotics using a highly efficient enol ether–olefin RCM (**49**→**50**) as the key step.[31]

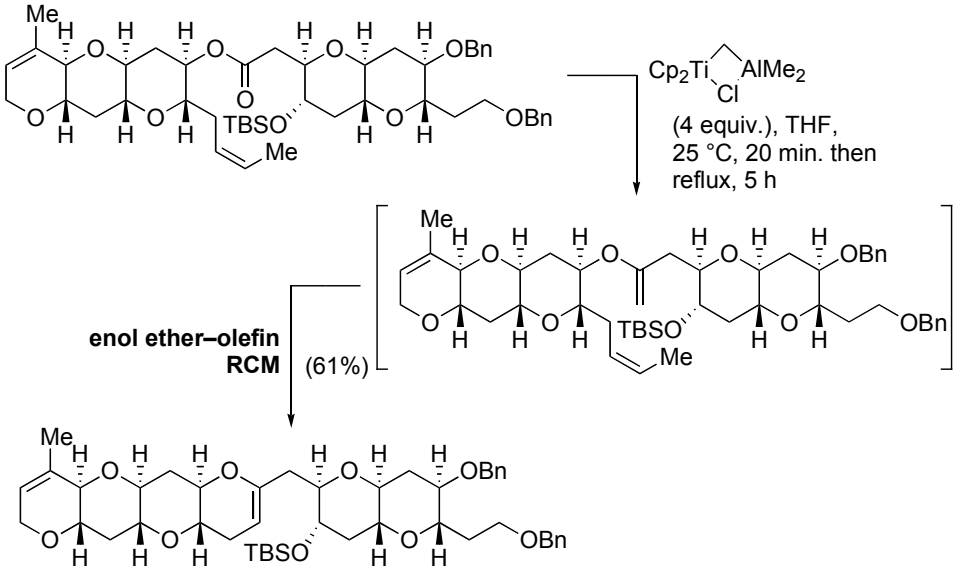


Scheme 12. Oxepene formation by enol ether-ene RCM.

In 2005, Taillier *et al.* reported a synthetic strategy towards the diterpenoid zoapatanol using enol ether-ene RCM to close an oxepine ring (Scheme 12).[32] A high loading of the 1st generation catalyst (**3**) (30 mol%) delivered the desired cyclic enol ether (**52**) in good yield. Unfortunately, the authors were not able to successfully instal the required β-oxygen functionality in order to complete the total synthesis by

this route. Zoapatanol was ultimately synthesised by an approach involving an intramolecular Horner–Wadsworth–Emmons olefination.

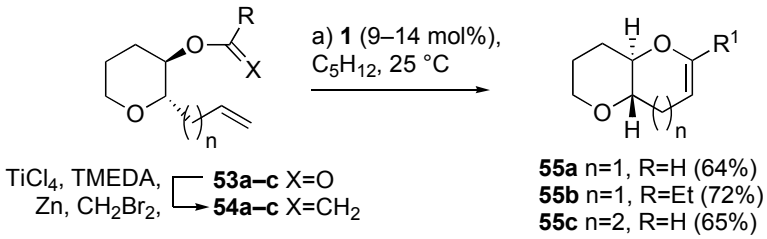
Ester–olefination followed by enol ether–olefin RCM: An attractive approach to cyclic enol ethers from enoates, consisting of carbonyl-olefination using stoichiometric titanium reagents and subsequent catalytic RCM, was highlighted by Grubbs and co-workers (Scheme 1).[10,33] This general approach, and related strategies, have been exploited by a number of research teams. For example, using Tebbe ($Cp_2TiCH_2ClAlMe_2$) or Petasis (Cp_2TiMe_2) reagents, Nicolaou and co-workers discovered one- and two-step approaches to complex fused cyclic enol ethers from alkenyl esters. It was proposed that the reaction pathway commenced by initial methylenation of the ester carbonyl group with subsequent alkene metathesis.[34] The stoichiometric approach was later employed to construct several of the ring systems embedded within the structure of the complex marine natural product maitotoxin (Scheme 13).[35] Oishi *et al*. made similar use of the Tebbe reagent during the synthesis of the I–M pentacyclic ring fragment of ciguatoxin CTX3C,[36] suggesting in a later publication that the reaction proceeded by an olefin metathesis–carbonyl olefination pathway rather than by enol ether–olefin RCM (see also Scheme 18).[37] This mechanistic rationale is consistent with the findings of Stille and Grubbs in their classic synthesis of capnellene using titanocene alkylidene complexes.[38]



Scheme 13. Formation of cyclic enol ethers from enoates using Tebbe reagent.

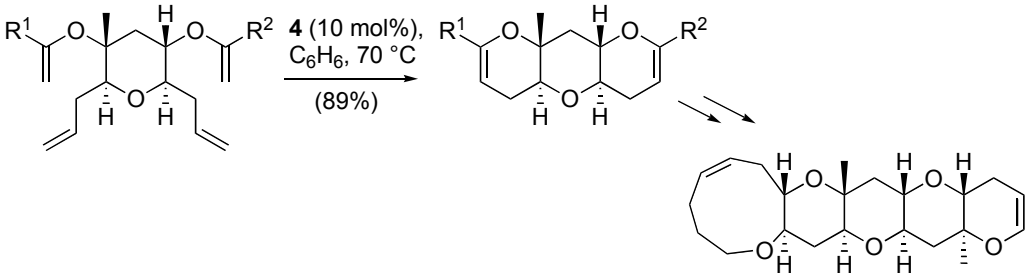
The research groups of Clark and Rainier have reported extensively on RCM reactions of enol ethers derived from olefination of esters in the context of fused-polyether syntheses (Schemes 14–18).[39] Clark's group found that RCM of monocyclic enol ethers (**54**) proceeded at room temperature using the Schrock catalyst, whereas the then available ruthenium catalyst (**3**) proved to be completely ineffective (Scheme 14).[40,41] An example of an eight-membered bicyclic enol ether was also reported to be formed in modest yield as a mixture with the seven-membered product and a macrocyclic diene. The formation of ring-contracted products by an olefin isomerisation–RCM sequence is now a well-recognised side

reaction when cyclisation is disfavoured.[18] To demonstrate the potential application of the methodology as a strategy for the synthesis of fused polyether toxins, enol ether products (**55**) were shown to undergo diastereoselective hydroboration. This could be carried out directly following RCM in order to avoid isolation of sensitive cyclic ethers.



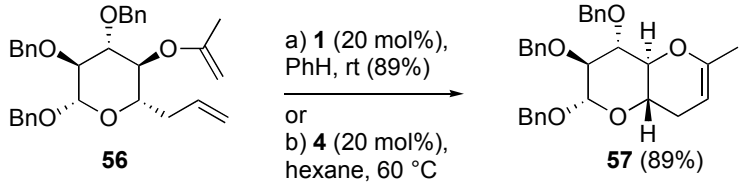
Scheme 14. Carbonyl-olefination followed by catalytic enol ether–olefin RCM as a route to fused polyethers.

Implementation of this strategy in a two-directional fashion facilitated the rapid assembly of the F–J ring system present in the gambieric acid marine ladder toxins (Scheme 15).[39,42,43]



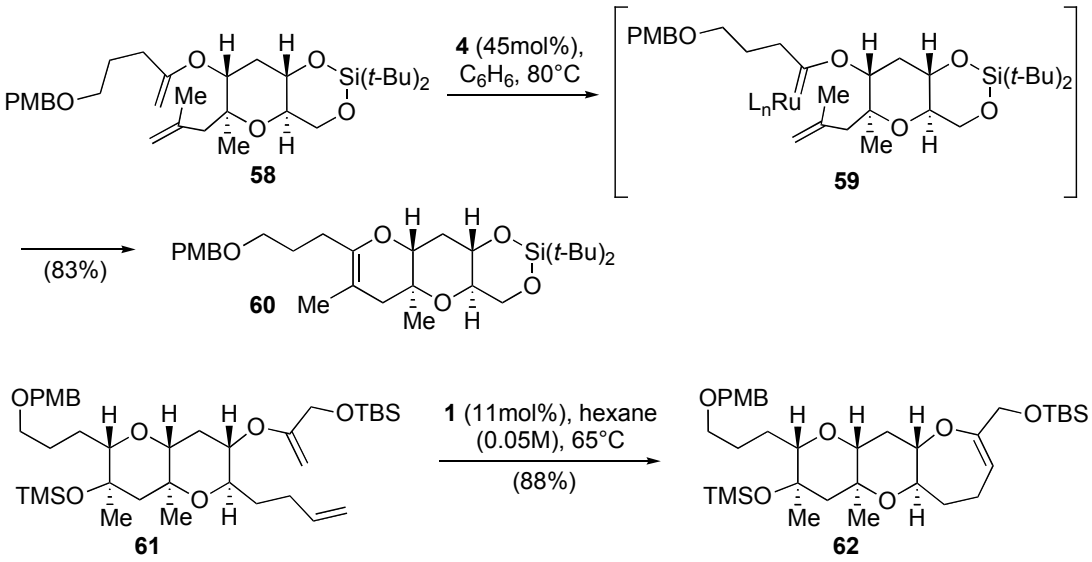
Scheme 15. Synthesis of the F–J model ring-system found in gambieric acid A.

Preliminary findings from the Rainier group showed that *C*-glycoside (**56**) underwent high yielding RCM to afford the fused dihydropyran system (**57**) using either 20 mol% of the ruthenium complex (**4**) or the molybdenum catalyst (**1**).[44] This methodology was applied in a formal synthesis of hemibrevetoxin B.[45]



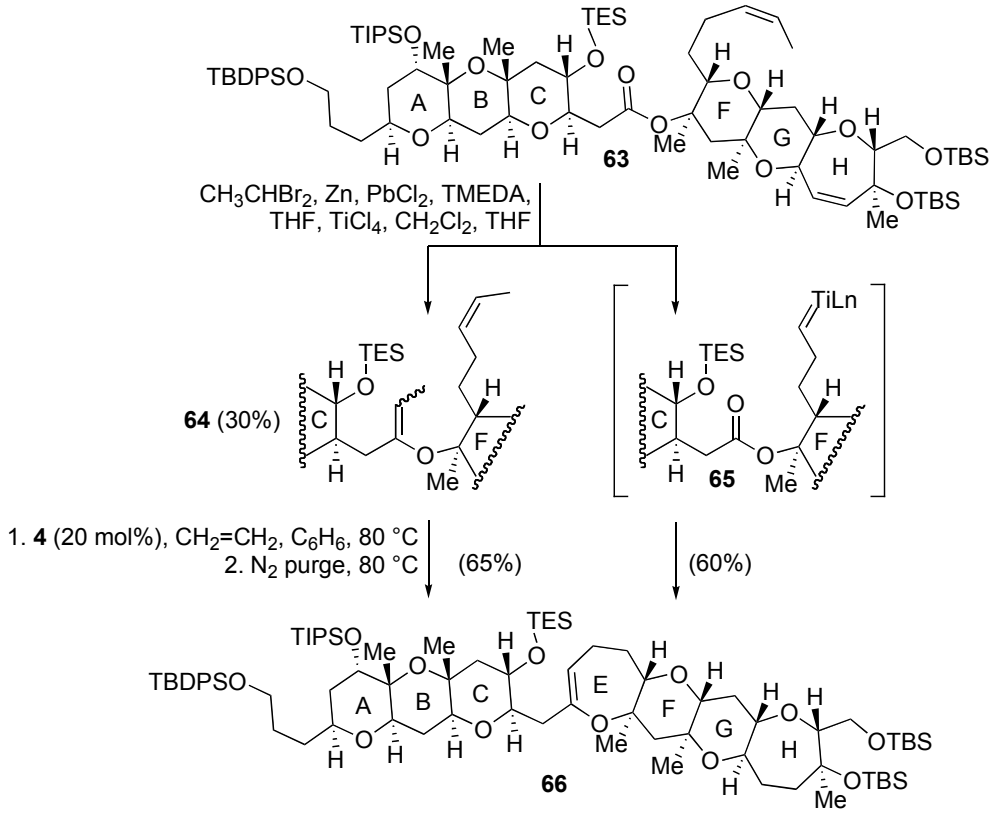
Scheme 16. RCM of *C*-glycoside (**56**) by Rainier and co-workers.

Rainier's group went on to apply enol ether–olefin RCM several times in an impressive total synthesis of the marine ladder toxin gambierol (Schemes 17 and 18).[46] Notable achievements included the closure of the tricyclic oxepine (**62**) and the formation of a tetrasubstituted enol ether (**60**) (Scheme 17). One point of mechanistic interest was the proposal that enol ether–olefin RCM of more sterically encumbered olefins such as **58** proceeds through less reactive Fischer carbene intermediates (**59**). This hypothesis was based upon the higher temperatures and high catalyst loadings needed to close these hindered systems.



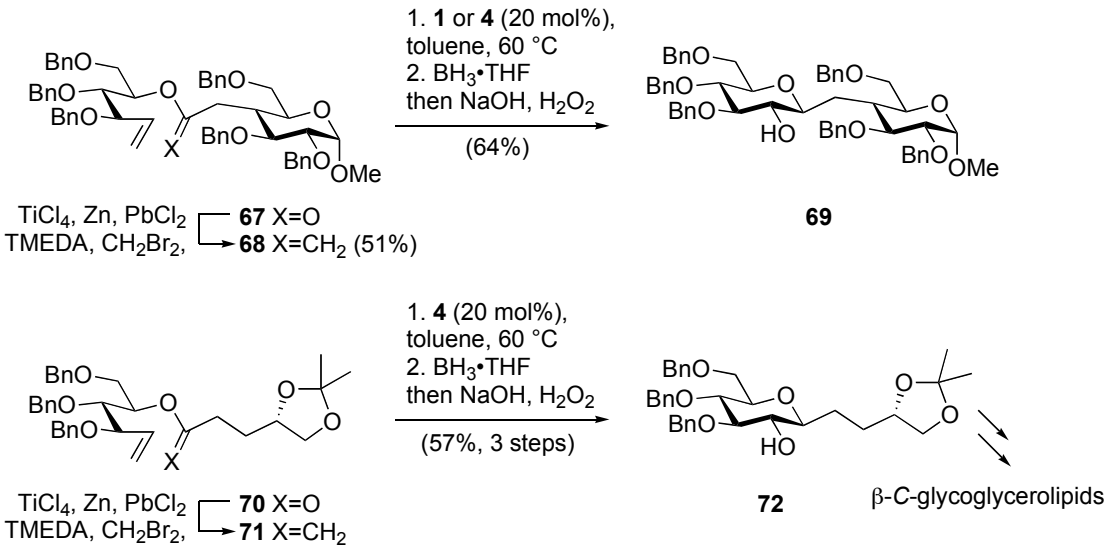
Scheme 17. Applications of enol ether–ene RCM to the synthesis of the F–H ring system of gambierol

Following coupling of the major fragments, Rainier's group employed a titanium alkylidene mediated cascade sequence to close the E-ring of the polyether toxin (Scheme 18).[46-48] A key feature in the success of the ring closure reaction in this complex setting was the use of a substituted titanium alkylidene reagent, rather than the methylidene reagent. It was proposed that these types of cyclisation reactions using Takai–Utimoto reagents actually proceed through an intramolecular carbonyl olefination pathway rather than by diene RCM.[47,48]



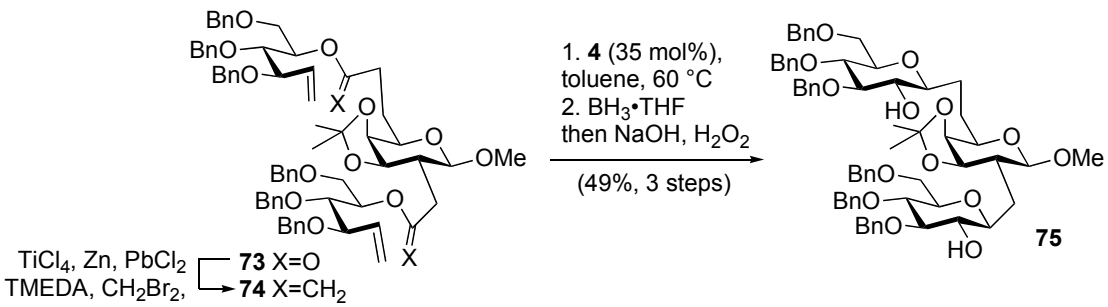
Scheme 18. Synthesis of a key intermediate en route to gambierol employing titanium alkylidene and ruthenium alkylidene complexes.

The Rainier group were able to increase the overal efficiency of the cyclisation to give the oxepine (**66**) through RCM of the acyclic enol ether byproduct (**64**) using the Grubbs 2nd generation complex (**4**) (Scheme 18).[46b] Using the ruthenium catalysed metathesis, oxepine (**66**) was obtained in a decent yield along with 20% of the corresponding dihydropyran from olefin isomerisation-RCM. Interestingly, this cyclisation required an ethylene atmosphere to convert **64** into a terminal olefin by cross-metathesis prior to cyclisation.



Scheme 19. Strategies for the synthesis of *C*-glycosides using RCM.

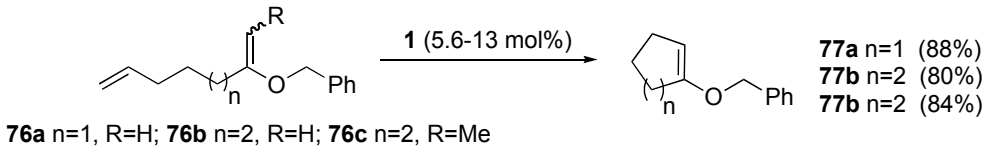
Postema realised elegant syntheses of various *C*-di- tri- and tetra-saccharides and *C*-glycosides using enol ether–olefin RCM–hydroboration sequences (Scheme 19).[49-56] The 1st generation catalyst (**3**) was found to deliver RCM products, but only when used in stoichiometric amount.[50] The optimised route to (1→6)-β-*C*-disaccharides (**69**) and β-*C*-glycosides (**72**) from the esters (**67**) and (**70**) commenced with olefination using a large excess of the Takai–Utimoto reagent to give enol ethers (**68**) and (**71**). Ring-closure of the resulting enol ethers was effected using either Schrock or Grubbs 2nd generation catalysts to provide glycals, which underwent stereoselective hydroboration or hydrogenation (not shown). Due to the sensitivity of *C*-glycal intermediates, in some cases hydroboration was carried out by direct addition of the borane to the RCM reaction mixture, leading to improved overall yields for the one-pot process.



Scheme 20. Synthesis of *C*-trisaccharides.

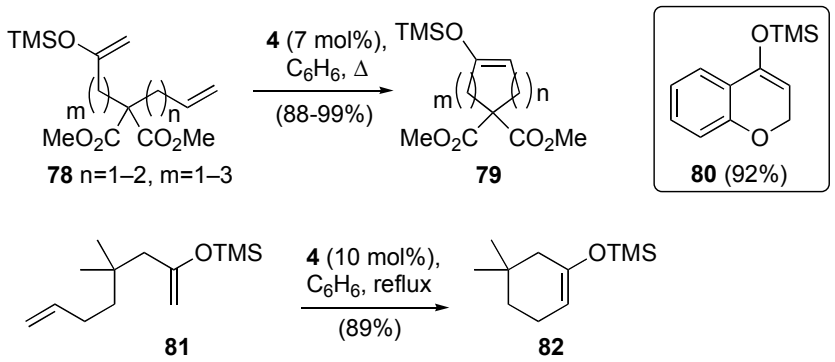
The *C*-glycoside strategy was evolved further to make use of double and triple enol ether–olefin RCM to prepare *C*-trisaccharides (e.g. **75**) and *C*-tetrasaccharides in good yields (Scheme 20).[55,57]

RCM to produce exocyclic enol derivatives: In the ensuing section, RCM reactions that give enol derivatives where the enol oxygen atom is exocyclic to the new ring being formed will be reviewed. An early report of this transformation by Grubbs and co-workers using the molybdenum alkylidene (**1**), indicated that five and six-membered exocyclic enol ethers (**77**) could be synthesised in high yields (Scheme 21).[10]



Scheme 21. Formation of exocyclic enol ethers by RCM.

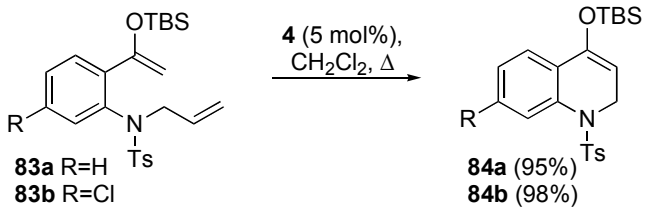
The regioselective formation of cyclic enol silyl ethers from unsymmetrical ketones by using classical enolisation–silylation methods often presents a significant challenge in organic synthesis. Okada and co-workers have presented an alternative approach to the regioselective synthesis of cyclic enol silyl ethers (**79**) using intramolecular RCM reactions (Scheme 22).[58] Catalyst (**4**) promoted RCM of a variety of acyclic enol ethers (**78**) to furnish five- to seven-membered rings in good to excellent yields under dilute conditions in benzene. Olefin migration was noted as a significant side reaction when 1st generation complex (**3**) was employed in CH_2Cl_2, and to some extent when using catalyst (**4**) in CH_2Cl_2 for certain reactions.



Scheme 22. RCM approaches to enol silyl ethers.

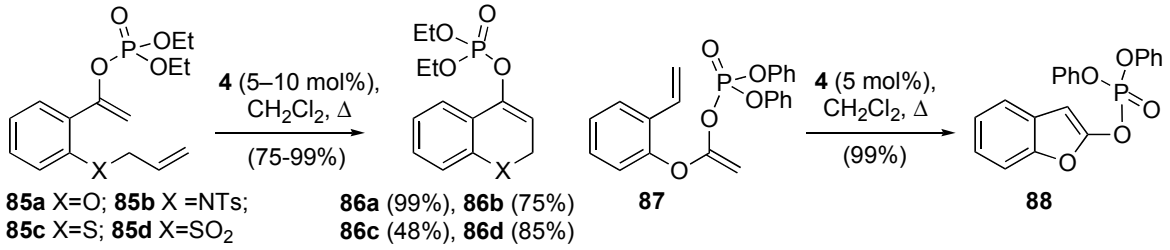
By contrast, Aggarwal's group were initially unable to effect the efficient RCM of trimethylsilyl enol ethers under similar conditions,[59] instead observing isomerisation of the alkyl olefin. The critical difference in their results apparently originated from a lack of geminal substituents in the diene linking chain, or some other conformational constraint that favoured cyclisation. This seemed to be corroborated by the efficient RCM of *gem* dimethyl substrate (**81**) (Scheme 22). A mechanistic rationale was presented, which balanced the rate of ring-closure of the alkylidene carbene against reversible formation of an

unstable Fischer carbene complex. The Aggarwal group were also able to demonstrate RCM of methyl enol ethers and TBDMS enol ethers in moderate yields.



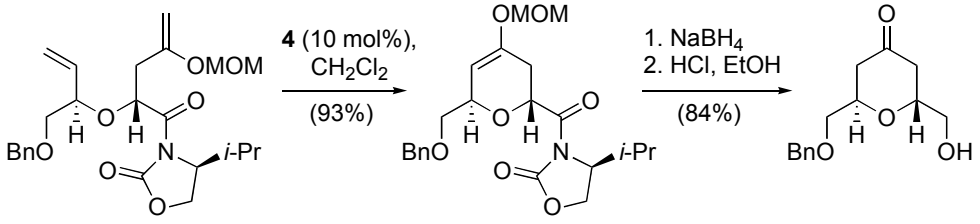
Scheme 23. Enol ether olefin metathesis by Arisawa and co-workers.

At around the same time Arisawa and co-workers reported examples of enol ether-ene metathesis to produce 4-siloxy-1,2-dihydroquinolines (**84a,b**) in excellent yields using complex (**4**) in CH_2Cl_2 (Scheme 23).[60-62] They found that solvent degassing was not essential for efficient RCM, and that increasing the concentration up to 0.1 M was not detrimental to the yield of **84a**. Methyl enol ethers were also found to cyclise under similar conditions. Having succeeded in developing an efficient synthesis of quinoline building blocks, this methodology was applied to the synthesis of fragments of the anti-malarial compounds quinine, chloroquine and a PPMP-quinine hybrid.



Scheme 24. RCM to afford cyclic enol phosphates.

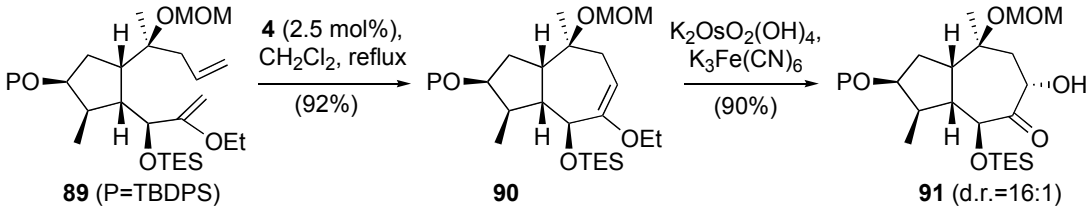
Hanson and co-workers described the first examples of RCM reactions of enol phosphates (**85**) and (**87**), derived from methyl ketone and acetate derivatives respectively, to afford heterocyclic enol phosphates (**86**) and (**88**) (Scheme 24).[63] The enol phosphate moiety has been recognized as a robust and versatile substrate for metal-catalysed cross coupling reactions, and the potential to generate such intermediates regioselectively by RCM should prove to be of future value.



Scheme 25. Stereoselective synthesis of tetrahydropyranones.

The Crimmins group have devised an asymmetric entry into 2,6-*cis* and 2,6-*trans* disubstituted tetrahydropyranones via an exocyclic enol ether intermediate prepared by RCM (Scheme 25).[64] Although the enol ether was hydrolysed to give a ketone in the reported examples, the researchers noted that the

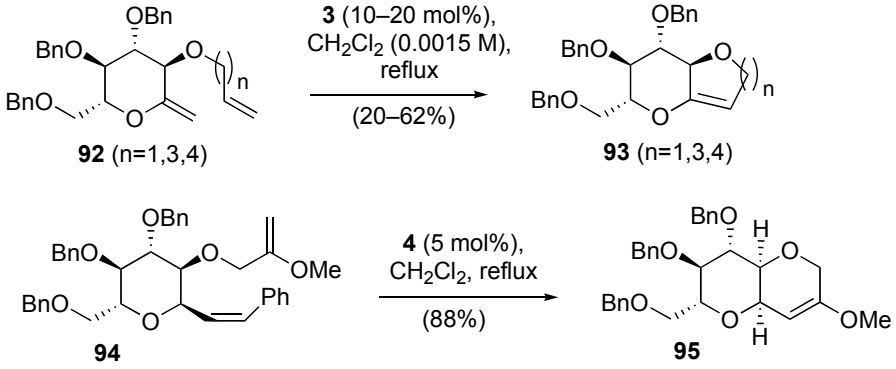
regiospecific incorporation of the enol ether presented opportunities for further selective functionalisation.



89 (P=TBDPS) **90** **91** (d.r.=16:1)

Scheme 26. Enol ether-ene RCM applied to the total synthesis of trilobolide.

Ley and co-workers demonstrated the utility of the enol ether-ene RCM as a means to access unsymmetrically substituted ketones in their total synthesis of trilobolide and related natural products (Scheme 26).[65] The low catalyst loading, high yielding RCM and highly stereoselective oxidation of the enol ether (**90**), combined to achieve the highly efficient assembly and functionalisation of the cycloheptane ring.



92 (n=1,3,4) **93** (n=1,3,4)

94 **95**

Scheme 27. Synthesis of bicyclic carbohydrate derivatives.

Examples of enol ether-ene RCM reactions to produce carbohydrate-derived bicyclic systems have been reported, where the ether is exocyclic with respect to the ring being formed. Under high dilution conditions *C*-glycosylidene derivatives (**92**) gave fused bicyclic products (**93**) in low to moderate yields (Scheme 27).[66] Using the *N*-heterocyclic carbene complex (**4**), *C*-glycoside (**94**) underwent RCM to afford the methyl enol ether (**95**) in high yield.[67]

RING-CLOSING METATHESIS OF VINYL AMINE-CONTAINING DIENES

Kinderman and co-workers reported the first successful catalytic ring-closing metathesis reactions of olefinic enamides in the presence of the ruthenium-based catalysts (**3**) or (**4**) to provide the five- and six-membered cyclic enamides in good yields (Table 1).[68] In general, it was observed that use of the 2nd generation catalyst (**4**) in DCE at very high dilution (17.5 μM) provided the highest yields. However, the corresponding reactions to create seven-membered rings were not successful, instead leading to six-membered ring formation via an olefin-isomerisation–RCM pathway.

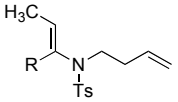
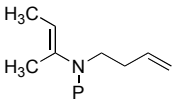
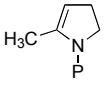
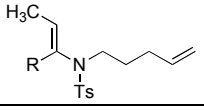
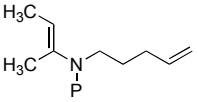
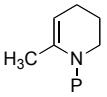
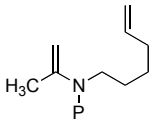
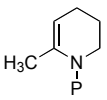
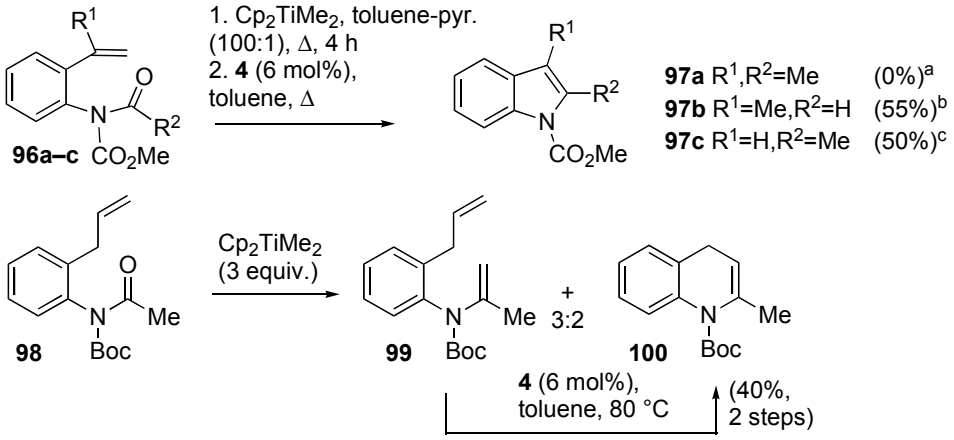
Entry	Enamides	Products	Yield
1			R = H (84%) R = Me (86%)
2			P = Bz (63%) P = CO_2Et (62%)
3			R = H (80%) R = Me (75%)
4			P = Bz (93%) P = CO_2Et (57%)
5			P = Ts (62%) P = Bz (24%) P = CO_2Et (34%)

Table 1. RCM of olefinic enamides.

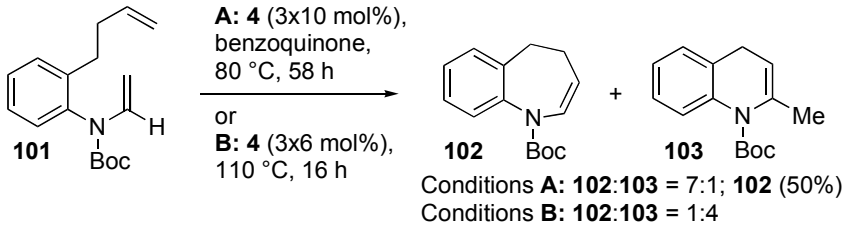
The carbonyl olefination–RCM routes to cyclic enol ethers discussed in the previous section have been extended to benzo-fused nitrogen heterocycles by Bennasar *et al.* (Scheme 28).[69,70] Amide olefination using dimethyltitanocene in the presence of pyridine gave the sensitive enamides, along with some cyclised material (**97c**) and (**100**) in some cases. Cyclisation under the olefination conditions was evident where the amide was more sterically hindered, and was attributed to an olefin metathesis–carbonyl olefination pathway by the authors. Treatment of the acyclic enamides, or the mixture of acyclic enamide and cyclic product, with the 2nd generation alkylidene complex led to satisfactory overall yields of the cyclised products in most cases, an exception being when both enamide and olefin were sterically encumbered (e.g. **96a**, R^1,R^2 = Me).



Scheme 28. Synthesis of benzo-fused *N*-heterocycles by amide olefination followed by RCM. [a] Acyclic enamide formed in 45%; [b] Olefination (61%), RCM (90%); [c] 6:1 mixture of the acyclic enamide and **97c** formed under olefination conditions.

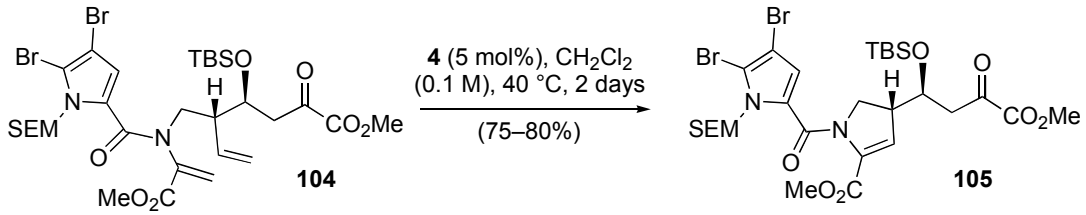
Using the protocol described, five- six- and seven-membered products (**97**), (**100**) and (**102**) were obtained in moderate overall yields for the two step process, although in the later case, the olefin

isomerisation–RCM manifold gave varying amounts of ring-contracted products (Scheme 29). Addition of benzoquinone, recently reported as a scavenger for Ru-H species in RCM reactions,[71] was found to reduce the amounts of unwanted isomerisation–RCM product formed in some reactions.

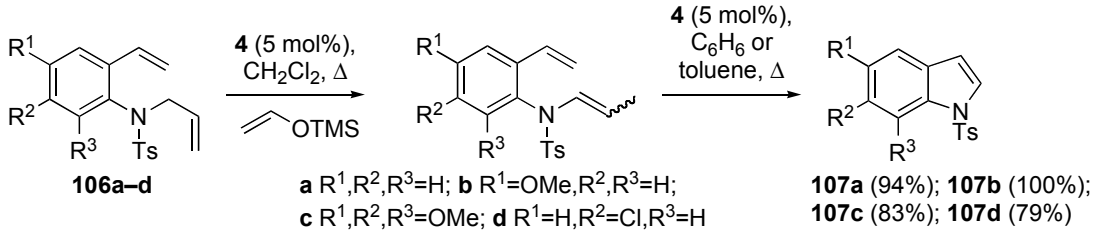


Scheme 29. RCM of benzo-fused enamides in presence and absence of benzoquinone.

In the course of synthetic studies towards palau'amine Katz and Overman investigated the enamide–olefin RCM reaction to secure the intermediate dihydropyrrole (**105**) (Scheme 30).[72] The key ring closure proceded in good yield in the presence of a diversity of funtionality, underscoring the excellent functional group tolerance of the ruthenium alkylidene catalysts.



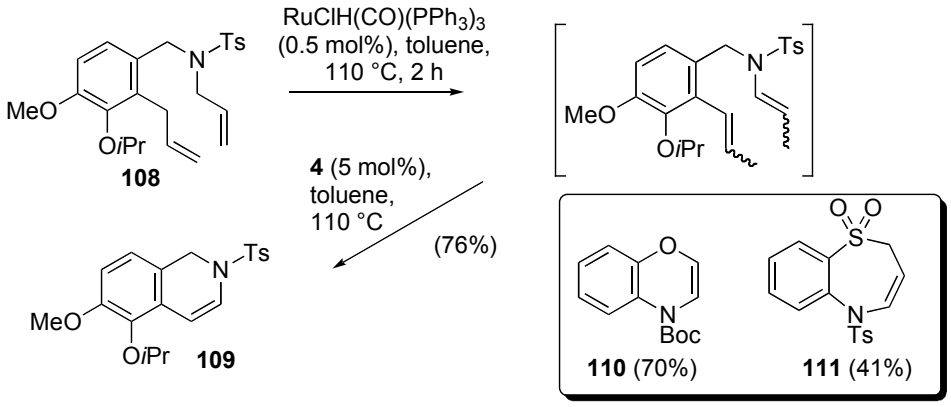
Scheme 30. Enamide–olefin RCM applied in the synthesis of a 4,5-dihydropyrrole-2-carboxylate.



Scheme 31. Ruthenium-catalysed synthesis of indoles.

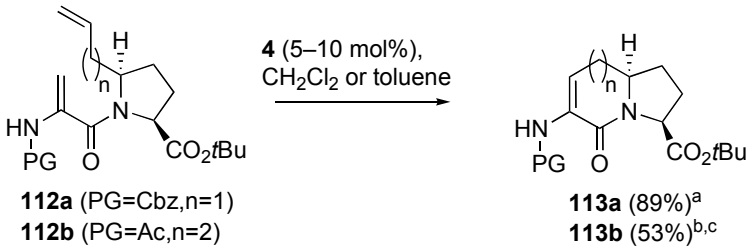
Arisawa and co-workers introduced a novel synthesis of indoles by exploiting the olefin isomerisation–RCM pathway that had been observed by a number of research groups (Scheme 31).[60,73] *N*-Allyl sulfonamides (**106a–d**) underwent isomerisation to the *N*-sulfonyl enamines using the Grubbs complex (**4**) and 1 equivalent of vinyloxytrimethylsilane. The resulting enamines were isolated in crude form, then redissolved in benzene or toluene and heated in the presence of Grubbs catalyst (**4**) to provide indoles (**107a–d**) in good to excellent yields. It was proposed that exposure of **4** to trimethylsilylvinyl ether produced a new ruthenium complex that isomerised the double bonds but was incapable of inducing the RCM of the enamide product.

A similar strategy was realised by van Otterlo and his co-workers to afford 1,2-dihydroisoquinoline (**109**), 3,4-dihydro-2*H*-1,4-benzoxazine (**110**) and a 1,5-benzothiazepine (**111**) (Scheme 32).[26,27] A ruthenium (II) hydride species was employed for the isomerisation of **108**, and upon consumption of the starting material, the metathesis catalyst (**4**) was added.

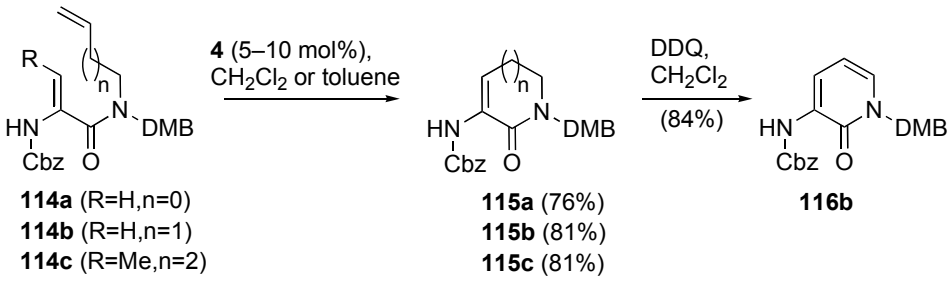


Scheme 32. One-pot olefin isomerisation–RCM approach to *N*-heterocycles.

Enamide–olefin RCM has also been achieved to generate systems where the nitrogen group is exocyclic with respect to the ring undergoing closure (Schemes 33 and 34). Manzoni *et al.* found that the *bis*-phosphine complex (**3**) did not induce efficient ring-closure of **112a** to give bicyclic enamide (**113a**), whereas the desired product was produced in high yield using the *N*-heterocyclic carbene complex (**4**).[74] A seven-membered product (**113b**) was also obtained in moderate yield from RCM of **112b**.



Scheme 33. RCM to give exocyclic enamides. [a] CH_2Cl_2 (0.04 M), 20 °C, 5 h; [b] toluene (0.004 M), 100 °C, 72 h; [c] Some of the six membered product (n=1, 14%) was observed.



Scheme 34. Synthesis of 3-amino-2-pyridones.

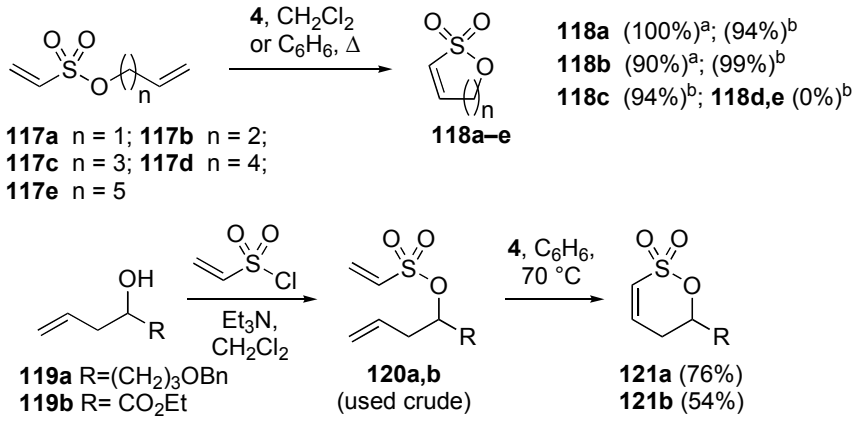
Nan's group prepared five-, six- and seven-membered cyclic enamides by RCM in generally good yields (Scheme 34).[75,76] Dihydropyridone products (**115b**) could be dehydrogenated to give a small library of

3-amino-2-pyridones (e.g. **116b**), whist caprolactams (**115c**) were of interest for incorporation into biologically active natural products and related analogues.[76]

RING-CLOSING METATHESIS OF VINYL SULFIDE-, SULFONATE-, SULFONAMIDE-CONTAINING DIENES

The preparation of sulfur heterocycles by RCM has been recently reviewed.[3] It has been reported that the electron-pair donor ability of sulfur (II) compounds may adversely affect the metathesis reaction using ruthenium alkylidene complexes, and RCM of sulfides using the 1st generation ruthenium catalysts (**2**) or (**3**) proceeded in moderate yields at best. However, the 2nd generation catalyst (**4**), molybdenum alkylidene (**1**) and a tungsten alkylidene have shown promise as more proficient catalysts for RCM of sulfide-linked dienes.[3,77] Stable Fischer carbene complexes have been prepared from metathesis of vinyl thioethers with ruthenium alkylidene complexes, and shown to be less active metathesis catalysts than the corresponding carbon-substituted analogues.[7] Furthermore, efforts to effect cross metathesis of these Fischer carbenes resulted in degenerate metatheses, and no ruthenium methylidene complexes were observed.

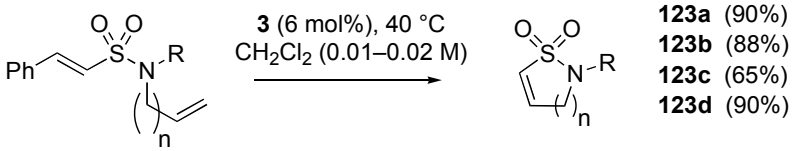
RCM of dienes linked by sulfonyl groups has turned out to be a more generally applicable process using ruthenium alkylidene pre-catalysts.[3] Significant successes have been realised for substrates containing vinylic sulfonyl moieties, even using the less active 1st generation catalyst (**3**). The research groups of Metz and Cossy have both shown that vinylic sulfonates undergo successful RCM to provide cyclic sulfonates (sultones) in the presence of the ruthenium catalysts (**3**) or (**4**) (Scheme 35).[78,79] Under the metathesis conditions in the presence of the 2nd generation Grubbs catalyst (**4**), the vinylsulfonates (**117a–c**) smoothly cyclised to provide the sultones (**118a–c**) in excellent yields, whereas no eight-membered or larger ring products were obtained.



Scheme 35. Synthesis of sultones by RCM. [a] REF 79: **4** (5 mol%), C_6H_6 (0.01 M), 70 ºC, [b] REF 78: **4** (0.8–3 mol%), CH_2Cl_2 (0.001–0.015 M), reflux.

Additionally, Cossy and co-workers have conducted RCM on substituted sulfonates (**120a,b**) to form substituted sultones (**121a,b**) (Scheme 35).[79] In contrast to the acylic vinylsulfonates (**117a–e**) derived from 1° alcohols, which were found to be quite stable, acyclic sulfonates of 2° alcohols (**120a,b**) were considerably more fragile and were used directly in RCM reactions.

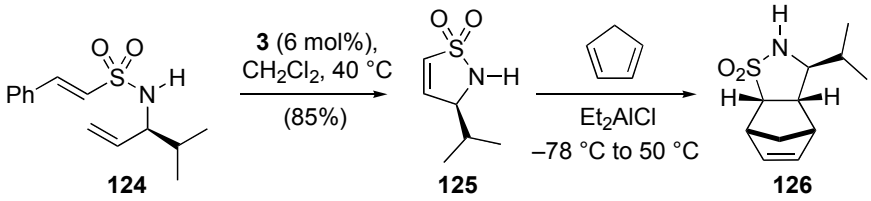
Prior to the reported RCM of sultones, Hanson's group had shown that the sulfonamide moiety is compatible with RCM using the 1st generation Grubbs catalyst (**3**) through the synthesis of cyclic vinylsulfonamides (sultams) (**123a–d**) in good to excellent yields (Scheme 36).[80] The rates of metathesis using **1** were moderate using the less active *bis*-phosphine complexes (24 h), although all reactions proceeded cleanly.



122a n=1, R=H; **122b** n=1, R=Bn;
122c n=2, R=Bn; **122d** n=1, R=(*S*)-CH(CH$_2$*i*-Pr)(CO$_2$Me)

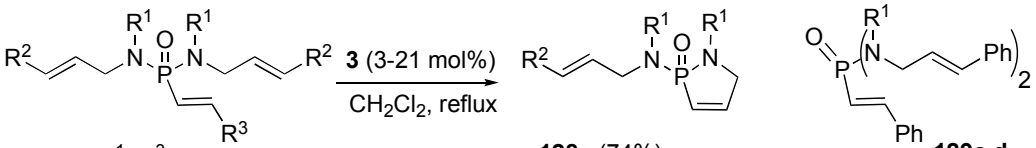
Scheme 36. RCM of vinylsulfamides.

As part of their investigations of ROMP routes towards oligomeric sulfonamides, Hanson's group prepared the monomeric unit (**126**) (Scheme 37).[81] The bicyclic sultam (**126**) was conveniently prepared in two steps (RCM and Diels-Alder reactions) from the valine-derived vinylsulfonamide (**124**) using the 1st generation Grubbs catalyst (**1**).



Scheme 37. Synthesis of ROMP monomers using a RCM/Diels-Alder sequence.

RING-CLOSING METATHESIS OF DIENES SUBSTITUTED WITH A PHOSPHORUS ATOM ON ONE OF THE REACTING DOUBLE BONDS



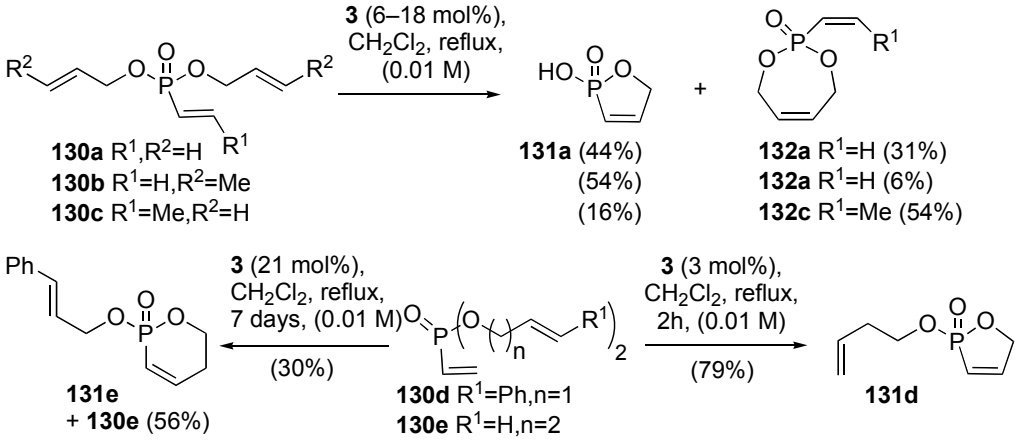
127a R^1–R^3 = H
127b R^1=Me,R^2,R^3=H
127c R^1,R^3 = H,R^2=Ph
127d R^1=Me,R^2=Ph,R^3=H
127e R^1,R^3=Me,R^2=H

128a (74%)
128b (76%)
128c (68%) + **129c** (17%)
128d (13%) + **127d** (60%) + **129d** (12%)
128e (87%)

129c,d

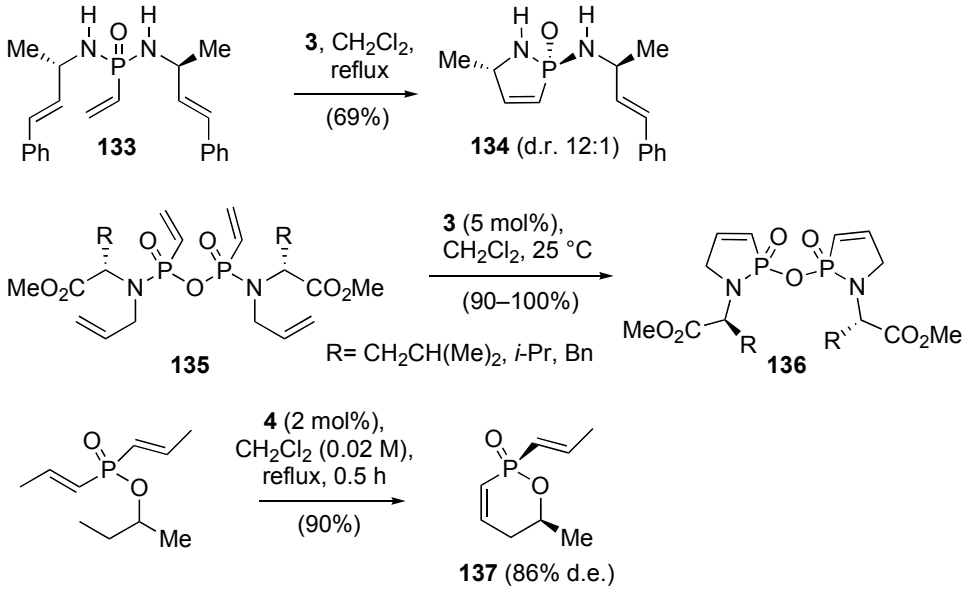
Scheme 38. RCM of vinylphosphonamides.

Hanson's team have also made significant contributions to the synthesis of *P*-heterocycles through application of RCM, and they recently reviewed this topic.[3] Cyclisation of vinylphosphonamides using the 1st generation Grubbs catalyst (**3**) was shown to generally afford five-membered heterocycles (**128**) in good yields (Scheme 38).[82] In some cases (**127c,d**), benzylidene exchange with the electron-poor vinylphosphonamide gave **129c,d** as significant side-products.



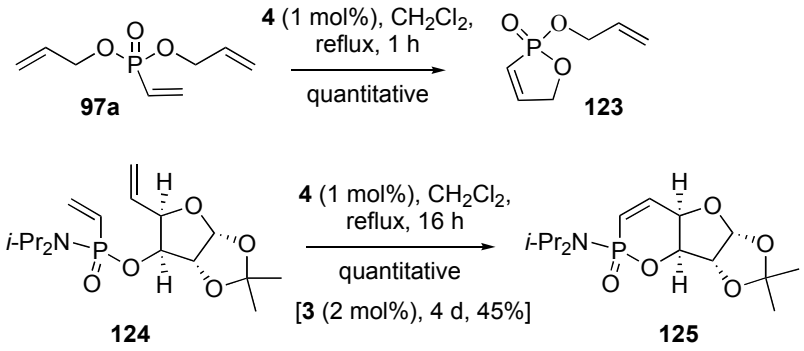
Scheme 39. RCM of vinylphosphonates.

RCM reactions of vinylphosphonates were also examined, and mixtures of products were obtained depending on substitution pattern of the starting trienes (Scheme 39).[82] None of the *O*-allylphosphonates (**130a–c**) gave the expected RCM products from reactions involving the vinyl phosphonate olefin, instead leading to cyclised *O*-deallylated product (**131a**). Hanson observed in a footnote that "cleavage of the allyloxy group occurred during chromatographic purification on silica gel" to give a de-allylated phosphonate (**131a**). However, it is concievable that the deallylation side reaction was due to the Ru-catalysed isomerisation-cleavage pathway later identified.[18]



Scheme 40. Synthesis of *P*-chiral heterocycles.

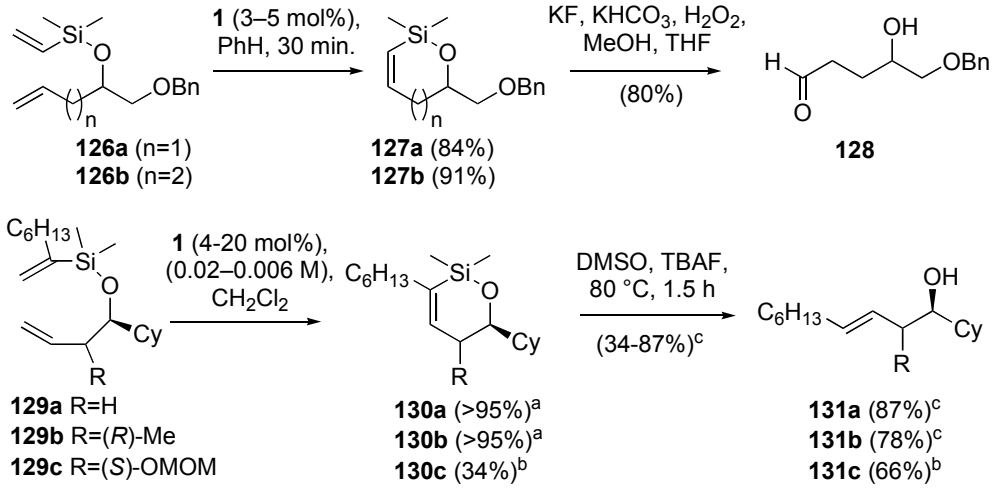
Desymmetrisation of pseudo-C_2-symmetric vinylphosphonamides (**133**) was investigated and a number of *P*-chiral five- and six-membered cyclic phosphonamides (e.g. **134**) were obtained with diastereoselectivities from 1:1 up to 15:1 (Scheme 40).[83] X-Ray crystallographic analysis allowed the relative stereochemistry of one of the major diastereoisomers (**134**) to be determined. The same group also reported RCM of *P*-chiral amino acid-derived phosphonamidic anhydrides (**135**), which proceeded in excellent yields using the 1st generation ruthenium complex (**3**) (Scheme 40).[84] Dunne *et al*. investigated the diastereoselective synthesis of *P*-stereogenic phosphinates (**137**) from trienes, with diastereoisomeric excesses of up to 86% d.e.[85]



Scheme 41. RCM of vinylphosphonamides in the presence of the 2nd generation Grubbs catalyst.

Subsequent reports from van Boom and co-workers concerning the RCM of phosphonates and phosphonamides showed the 2nd generation ruthenium complex (**4**) gave significantly enhanced performance in comparison to ruthenium complex (**3**) (Scheme 41).[86] Under the reduced reaction times and lower catalyst loadings required, phosphonate (**138**) underwent smooth cyclisation in quantitative yield using **4** without any of the *O*-deallylation previously observed by Hanson *et al*. using **3**.

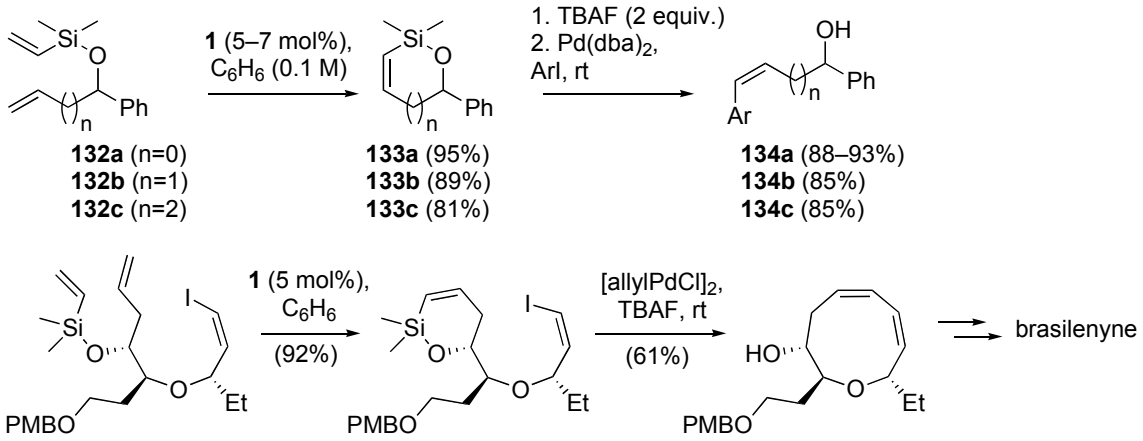
RING-CLOSING METATHESIS OF VINYL SILANE-CONTAINING DIENES



Scheme 42. RCM of vinylsilyloxy dienes and post-RCM modification. [a] Percentage conversions; [b] Isolated yields; [c] Isolated yields over two steps.

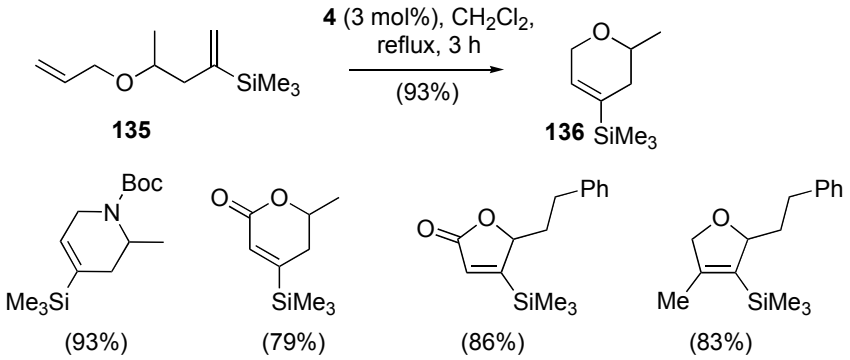
Temporary silicon tethers have been used extensively in organic chemistry as a means to facilitate numerous reactions, and to confer stereo- and regioselectivity upon a given process.[87] Chang and Grubbs were able to demonstrate the potential of silicon tethered RCM through the efficient cyclisation of two vinylsilyloxy dienes using the molybdenum catalyst (**1**) (Scheme 42).[88] It was noted by the authors that the ruthenium complex (**3**) was less effective due to the greater sensitivity of this catalyst to steric congestion of the reacting olefin. In fact, silyl substitution has been used as a strategy to protect olefins from participation in metathesis.[89] Cyclic vinylsilyl ether (**127a**) was oxidatively cleaved to give γ-hydroxyaldehyde (**128**), which can be considered as a homo-aldol product.

The synthetic utility of the silicon-tethered RCM was also recognised in a report by Ahmed *et al.* (Scheme 42).[90] RCM was effective using the Schrock catalyst (**1**), although high catalyst loading (20 mol%) and substrate dilution (0.006 M) were required for the conversion of diene (**129c**). Protodesilylation of the vinylsilanes (**130**) gave the enantiomerically enriched homoallylic alcohols (**131a–c**) with an *E*-configured disubstituted olefin. Subsequently, the same research team described how implimentation of the RCM-protodesilylation protocol facilitated a stereocontrolled synthesis of glycosphingolipids.[91]



Scheme 43. RCM and subsequent metal-catalysed cross coupling reactions of vinyl silanes.

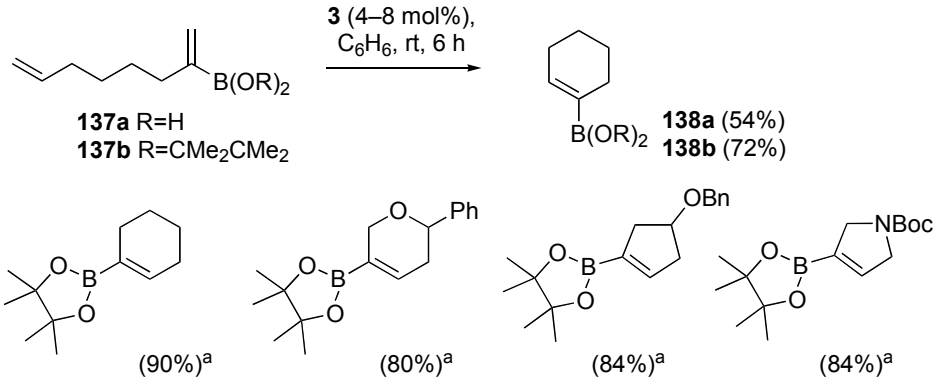
Denmark *et al.* applied RCM to the synthesis of six- and seven-membered cyclic vinylsilyl ethers (**133**), which were found to be effective substrates for stereospecific Pd-catalysed cross-coupling reactions to give *Z*-configured olefins (**134**) (Scheme 43).[92] They later went on to exploit this methodology during a total synthesis of (+)-brasilenyne.[93-95]



Scheme 44. RCM of trimethylsilyl substituted dienes.

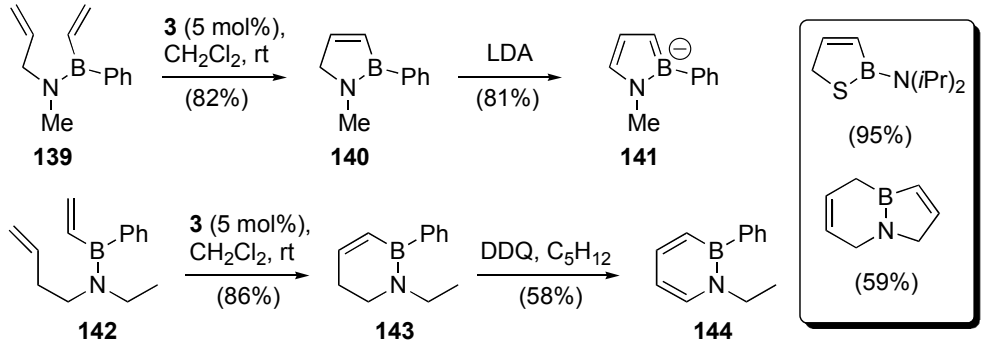
Schuman and Gouverneur have applied the RCM of vinylsilanes to the preparation of a series of trimethylsilyl substituted carbocycles and heterocycles (Scheme 44).[96] Whilst the ruthenium catalyst (**3**) displayed insufficient activity, RCM of diene (**135**) using the *N*-heterocyclic carbene complex **(4)** provided the carbocycle (**136**) in excellent yield. Substrates containing a variety of functionality in the diene-linking chain all cyclised in good to excellent yields to give cyclic ethers, α,β-unsaturated γ- and δ-lactones and a protected amine.

RING-CLOSING METATHESIS OF VINYL BORONATE-CONTAINING DIENES



Scheme 45. Alkenylboronate–olefin RCM. [a] **3** (5–10 mol%) in C_6H_6 (0.004–0.05 M), rt.

Alkenylboronic esters and acids are well known to be versatile substrates for palladium-catalyzed coupling reactions,[97,98] prompting Renaud and co-workers to develop a regioselective method for their synthesis by RCM of acyclic dienylboronates (Scheme 45).[99] Cyclisation was initially demonstrated to proceed in moderate yield from the boronic acid (**137a**) using the 1st generation ruthenium benzylidene complex (**3**). Subsequently, boronic esters were shown to be useful substrates, affording five-, six- and seven-membered carbocyclic and heterocyclic alkenylboronates in high yields. High dilution was required in some cases when cyclisation rates were slow in order to minimise homo-metathesis of the unfunctionalised olefin.

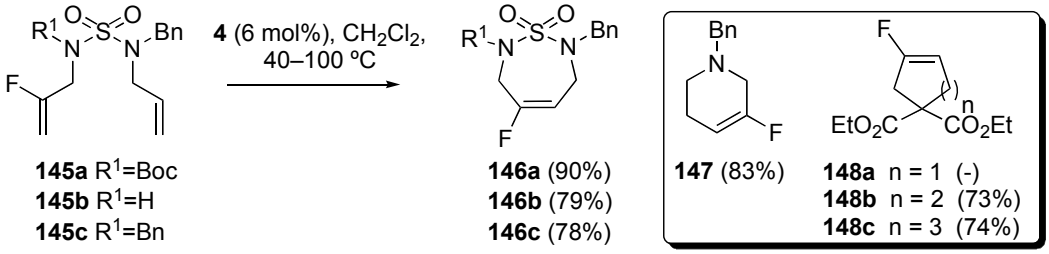


Scheme 46. Synthesis of boron-containing heterocycles.

An interesting series of *B–N* and *B–S* heteroaromatic compounds have been synthesised in good to excellent yields using vinylborane–olefin RCM as key steps (Scheme 46).[100] Following deprotonation of **140**, the resulting heterocyclic Cp analogue (**141**) was used to prepare a ruthenium sandwich complex. Oxidation of **143** using DDQ gave the aromatic azaboracycle (**144**).

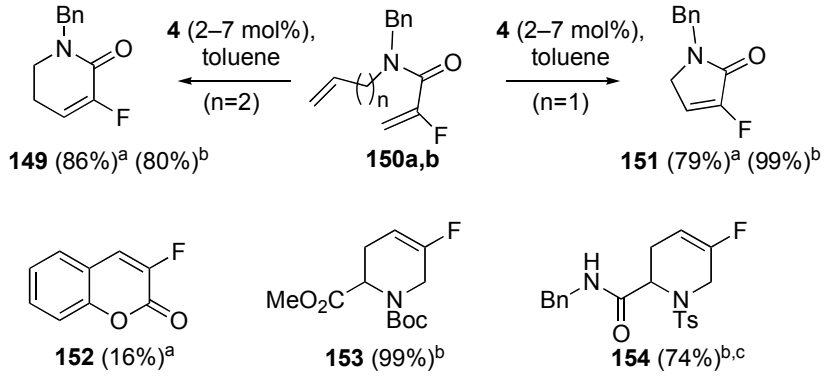
VINYL HALIDE–OLEFIN RING-CLOSING METATHESIS

One attraction of the RCM process is that it can enable the regioselective synthesis of unsymmetricaly substituted cyclic olefins under mild conditions and as new catalysts have been developed, the range of tolerated functional groups has expanded. Despite the advances in catalyst performance achieved through the development of **4**, reports from Grubbs indicated that the cross-metathesis of halides with mono-substituted olefins did not proceed to any significant extent.[12] One explanation for the lack of olefin cross-metathesis was the formation of a Fisher type carbene that was either unstable or failed to participate in productive metathesis. It is interesting to note that the Grubbs group showed that 1,1-difluoroethylene underwent metathesis with **4** to give the difluorocarbene complex ($Ru{=}CF_2$), the corresponding methylidene complex ($Ru{=}CH_2$), styrene and tetrafluorethylene.[101] No alkene cross-metathesis products were observed (i.e. $PhCH{=}CF_2$), and the difluorocarbene complex was shown to be a poor catalyst for ROMP relative to **4**. Dissociation of the Cy_3P ligand was thought to be an issue, and experimental corroboration was provided through NMR studies. Interestingly, some improvement in ROMP activity could be achieved through addition of HCl to aid phosphine dissociation. Although Grubbs reported that attempted RCM on vinyl halides had been unsuccessful using the 1st generation ruthenium alkylidene catalysts (**3**),[102] the discovery of more reactive *N*-heterocyclic carbene complexes such as **4** prompted several groups, including those of Weinreb, Rutjes, Haufe and ourselves, to re-investigate this transformation.



Scheme 47. RCM reactions of fluoro-olefins.

Vinyl fluoride–olefin RCM: Our own interest in halo-olefin RCM arose from the desire to introduce fluoride as an isosteric replacement for hydroxyl groups in cyclic sulfamide protease inhibitors.[103] During these studies, it emerged that ring-closing metathesis of vinyl fluoride-containing dienes could provide an efficient regiocontrolled approach to carbocyclic and heterocyclic fluoro-olefins (Scheme 47).[104] We showed that RCM of fluoro-olefins proceeded efficiently to give certain six- and seven-membered cyclic vinyl fluorides. Surprisingly however, we were not able to induce cyclisation to give five-membered vinyl fluorides. We attributed this failure to a kinetic barrier, impeding formation of the metallocyclobutane intermediate in this less reactive diene system.



Scheme 48. RCM of fluoro-olefins. [a] ~0.5 M, Ref. 107; [b] ~0.01 M, Refs. 105 and 106; [c] μw 100 °C.

At around the same time the groups of Haufe and Rutjes were also investigating RCM of fluoroolefins using Ru-complex (**4**), achieving some notable successes using α-fluoroacrylic acid derivatives to give five and six-membered cyclic products (Scheme 48).[105-107] The Rutjes group found that it was important to add the complex (**4**) portionwise over the course of the reaction, otherwise catalyst decomposition and decreased yields resulted.[105] Although vinyl fluoride–olefin RCM presents new opportunities for the synthesis of fluorinated heterocycles and carbocycles, the process is apparently less general than classical diene RCM using the commonly employed catalyst systems. To highlight some of the current limitations, a number of the substrates that failed to undergo cyclisation are depicted in Figure 2.

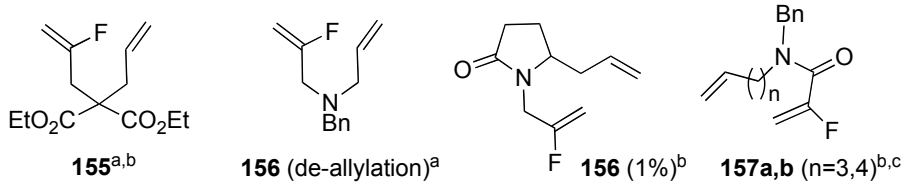
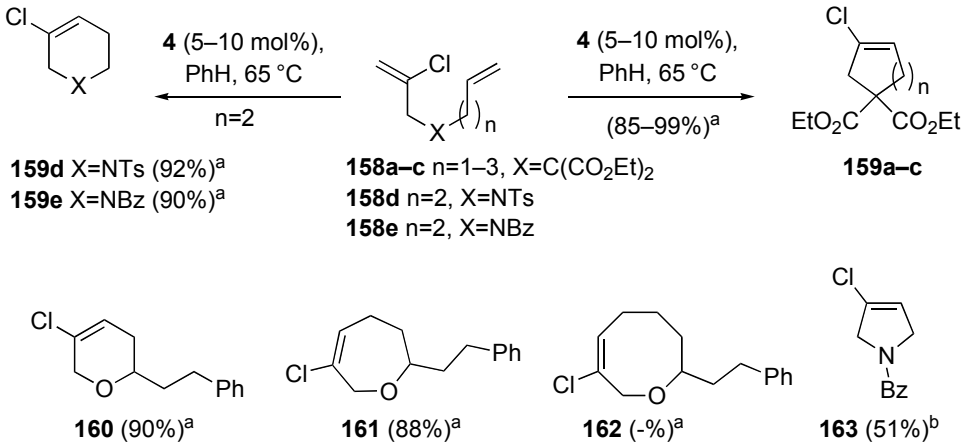


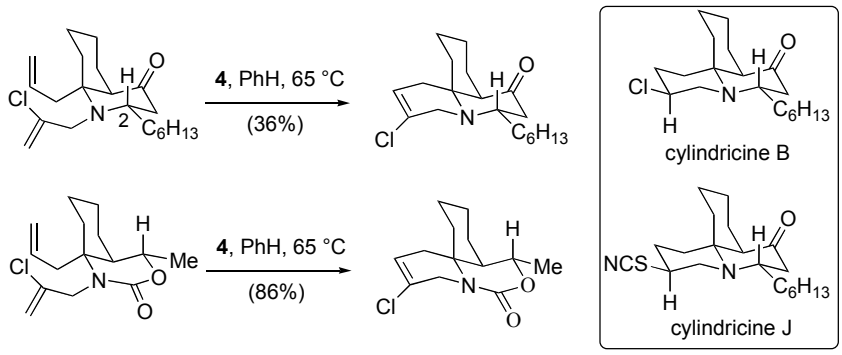
Figure 2. Substrates that failed to undergo efficient RCM. [a] Ref. 103; [b] Ref. 107; [c] Refs. 105 and 106

Vinyl chloride–olefin RCM: Weinreb and Chao published the first examples of halo-olefin RCM using the 2nd generation Grubbs catalyst (**4**), which provided a new route to regiodefined cyclic vinyl chlorides that would otherwise be difficult to access (Scheme 49).[108,109] Their work demonstrated that the reaction had significant scope for the synthesis of heterocyclic and carbocyclic systems (**159a–e**), (**160**) and (**161**), with a range of ring sizes accessible, including five-membered systems, in excellent yields. Attempted formation of an eight-membered cyclic ether (**162**) resulted in the recovery of a complex mixture of unidentified products. The Rutjes group also reported some selected examples of vinyl chloride-olefin RCM, including the formation of the dihydropyrrole (**163**) using either complex (**4**) or the Grubbs–Hoveyda complex (**31**).[106]



Scheme 49. RCM reactions of vinyl chlorides. [a] Refs. 108 and 109; [b] Ref. 106.

Recently, the Weinreb group went on to apply the vinyl chloride RCM reaction as a key step in their studies towards the synthesis of the marine alkaloids cylindricines B and J (Scheme 50).[110] Exposure of two dienes to the 2nd generation Grubbs catalyst (**4**) effected cyclisation in unoptimized yields of 36% and 86%. Pending confirmation of the configuration of the C2 stereogenic centre, the authors hope to manipulate vinyl chloride functionality to permit the total synthesis of the natural products.



Scheme 50. Formation of the tricyclic pyridoquinoline framework of cylindricine B and J.

CONCLUSIONS

The synthesis of cyclic heteroatom-substituted olefins by diene RCM has advanced at a tremendous rate over the last decade, and now many examples of these transformations are known including applications in the synthesis of complex targets. Many of the advances have been possible due the discovery of highly selective and active ruthenium-based olefin metathesis catalysts, although the Schrock type systems have also played a major role in this field. Investigation of RCM in these heteroatom-substituted systems has also led to an increased understanding of potential side reactions such as olefin isomerisation, and mechanisms for catalyst decomposition. Several of the heteroatom-substituted olefin classes that were originally reported not to participate in RCM have now succumbed to cyclisation, although limitations still remain. To the best of our knowledge, there are no reported examples of RCM to afford synthetically important vinyl iodides or bromides. Relatively high catalyst loadings are still required for many substrates, and these will need to be reduced for practical applications. It therefore seems that there are still exciting challenges in the field of catalyst development, and plenty of opportunities for new applications of the diene RCM reaction in heteroatom-substituted systems.

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