Ring closing diene metathesis in organic synthesis

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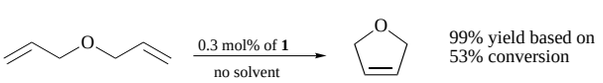
REVIEW PERKIN 1

Covering: up to July 1997

1 Introduction

1.1 Coverage

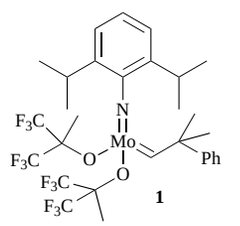
This review covers the literature from 1980 to the summer of 1997. It focuses on catalytic ring closing diene metathesis (RCM) reactions in which the substrates are low-molecular-weight non-polymeric organic molecules, although a few references are made to the polymeric systems which gave the original impetus for the development of metathesis catalysts. A simple example of the type of reaction involved is that shown in **Fig. 1**, which we have carried out using Schrocks' molybdenum-based catalyst **2**.[1]



The turnover number of 180 is typical for this catalyst.

Fig. 1

The bulk of this review is dedicated to ring closures catalysed by well-defined metal alkylidene complexes, in particular the Schrock molybdenum-based catalyst **1**[2] and Grubbs' ruthenium-based catalysts **2**[3] and **3**.[4] Other catalysts in less general use for RCM include the tungsten-based catalyst **4**,[5] developed in France, and the recently reported chiral molybdenum-based catalyst **5**,[6] among others. Reference is made in section 2 and elsewhere to catalytic systems produced *in situ*, in which the active catalytic species is not known with certainty.



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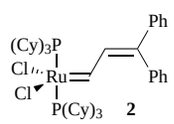

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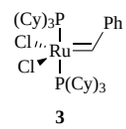

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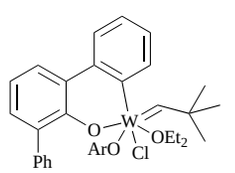
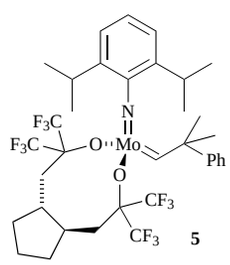


4, Ar = 2,6-diphenyl-C_6H_3



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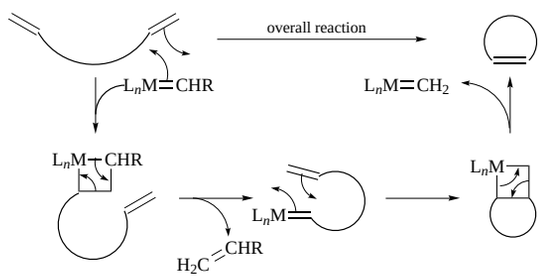
This review is dedicated exclusively to catalytic ring closing processes. Despite an isolated report of a cyclisation reaction catalysed by $(OC)_5Cr=C(Me)OEt$,[7] chromium- and titanium-mediated ring closures are referred to only in the Tables of section 4, and even this coverage is strictly limited to reactions catalytic in transition metal. The metal alkylidene complexes **1**–**5** of course catalyse polymerisation reactions as well as ring closures: most were designed to carry out polymerisations, particularly ring opening metathesis polymerisation or ROMP. During polymerisation the catalyst forms part of the living polymer chain, and may react with a carbon–carbon double bond further down the chain, excising part of the chain as a small cyclic molecule. In this way a cyclic dimer,[8,9] or less frequently a cyclic monomer[10] or trimer, may be formed: so-called 'bite-back' ring formation. Such cyclisations are presumed to occur after the bulk of the available monomer has been incorporated into the growing polymer,[9,10] and they are excluded from this review.

1.2 Mechanism and catalytic cycle

In the 'classical' metathesis systems produced by an *in situ* mixing of two or more organometallic species, the nature of the active catalyst is not confidently known. This makes it very difficult to obtain confirmatory evidence for any postulated reaction mechanism. In the bulk of the reactions covered by this review, the catalytic species is known to be a metal alkylidene. There is also some evidence for the involvement of metallacyclobutanes,[2] and the overall reaction mechanism involves, effectively, a series of alternating [2+2] cycloadditions and

cycloreversions between metal alkylidene and metallacyclobutane species (**Scheme 1**; here and later the formula $L_nM{=}CHR$ is used to represent a general metal alkylidene catalyst).[11] Several of the catalysts generated *in situ* are also believed to operate by this mechanism (see section 2.2 below). In the first turn of the catalytic cycle, the alkene by-product depends on the R group in the original catalyst, while in second and subsequent catalytic cycles it depends on the substrate. For terminal alkene substrates the reaction by-product is ethene, and a partial vacuum may be used to drive the reaction. Alkene substitution in both substrate and product can dramatically influence the reaction rate and outcome. In particular, several catalysts do not tolerate excessive steric hindrance (see sections 3 and 4 below).



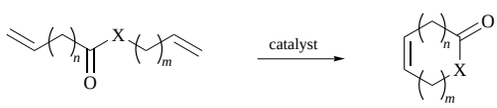
Scheme 1

A recent kinetic study has elucidated a detailed mechanism for the metathesis ring closure of diethyl diallylmalonate using $(Cy_3P)_2Cl_2Ru{=}CH_2$, a catalyst related to **2** and **3** but showing rather lower activity.[12] The advantage of this catalyst from a mechanistic viewpoint is that, provided a terminal alkene is used, all rounds of the catalytic cycle are identical, and ethene is the only by-product. The kinetic studies revealed that the generally postulated mechanism is only a minor contributor in the case studied. The major reaction pathway involves phosphine loss before metallacyclobutane formation (**Scheme 2**), with 14-electron complexes formed as catalytic intermediates. The investigators extended their mechanistic analysis to stereochemical considerations, but point out that care must be used in extending the results to other ruthenium alkylidene catalysts because the details are greatly affected by ligand variation. With this *caveat* in mind, the general mechanism presented in Scheme 1 seems adequate for understanding the reaction results in most cases.

2 'Classical' catalysts in ring closing diene metathesis

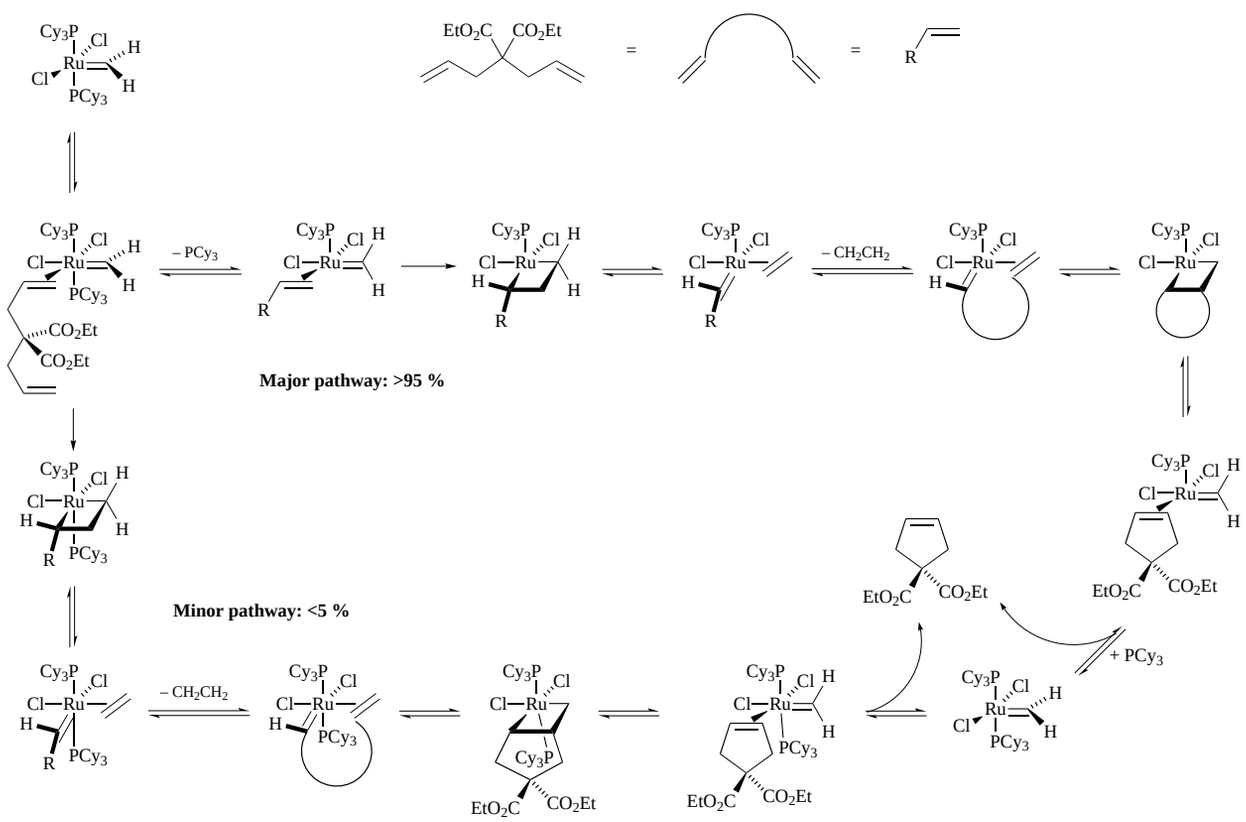
2.1 Early reports of RCM

The early examples of RCM naturally used 'classical' catalysts prepared *in situ* from poorly understood mixtures of organometallic reagents, usually including a tungsten chloride or oxychloride and an alkyl metal species. In a synthetic context they went almost unnoticed, and yields were generally low,[13–15] but the formation of 15- and 16-membered rings in 60–65% yield (albeit as *E*/*Z* mixtures) is certainly noteworthy.[16] Examples are collected in **Scheme 3**, which also includes a more recent result for comparison.[17] Recently, a Russian group has shown that WCl_6 with silane activators, including Ph_2SiH_2, can be used for RCM, giving cyclopent-3-enecarboxylic acid esters in up to 98% yield from the corresponding hepta-1,6-diene derivatives.[18]



Scheme 3

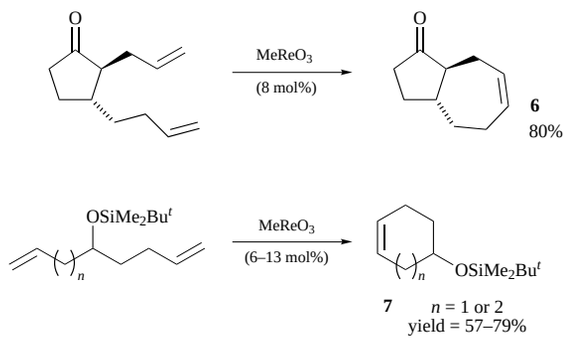
n	*m*	X	Catalyst and mol equiv. used	Yield (%)	Ref.
8	4	O	5 mol% WCl_6 + 5 mol% Me_4Sn	65	16
8	9	O	20 mol% WCl_4O + 24 mol% Cp_2TiCl_2	12	13, 14
7	6	CH_2	19 mol% Re_2O_7 + 11 mol% $SnBu^n_4$	12	15
8	4	O	4 mol% of **2**	79	17



Scheme 2

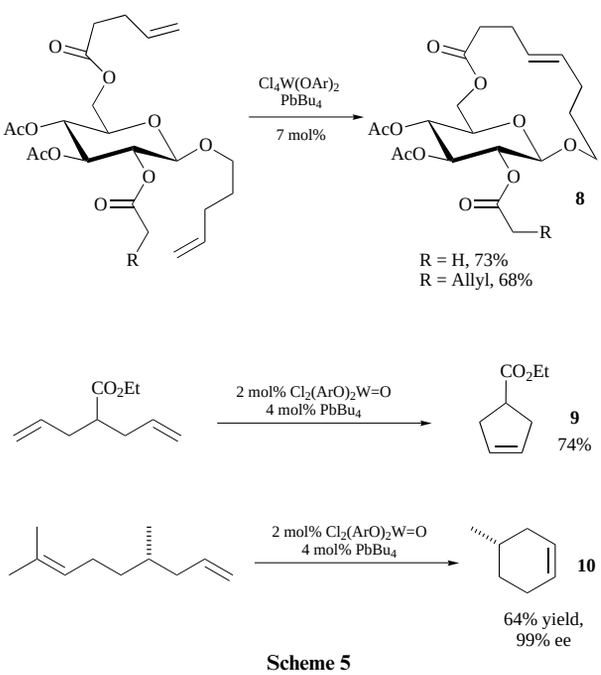
2.2 Developments from 'classical' systems

Two developments from the 'classical' catalysts seem noteworthy. One is the use of $MeReO_3$ as a catalyst for RCM.[19,20] This compound is stable and storable, and although it does not conform to the metal alkylidene model, seems an active and useful RCM catalyst. As yet, comparatively few examples of its use have been published. It shows good tolerance of ketones in the substrate, as shown by the synthesis of *trans*-fused bicyclic ketone **6** (**Scheme 4**). It can certainly be used to make six- and seven-membered carbocycles such as **7** (n = 1 or 2); beyond this, little is known. In three cases it fails where ruthenium alkylidene **2** succeeds, but the reasons for this are unclear.[20]



Scheme 4

The other recent development is the combination of a well-defined tungsten complex, either $Cl_4W(OAr)_2$[21] or $Cl_2(ArO)_2W{=}O$,[22] with a tetraalkyllead or tetraalkyltin activator. These systems show good functional group tolerance, as far as they have been tested, and have even been used successfully to make bridged bicyclic systems such as **8** (**Scheme 5**; see also Table 2, section 4). They have been used extensively to make a variety of five- and six-membered carbocycles including **9** and **10**. The active catalyst has been postulated to be a metal alkylidene, such as $Cl_2(ArO)_2W{=}CHMe$, when starting from $Cl_2(ArO)_2W{=}O$, but there is no direct evidence for this. Some of this work was carried out in the DuPont laboratories,[22] where catalysts **1**–**3** were felt to be unsuitable for industrial applications owing to the complexity and expense of their syntheses. More readily accessible catalyst systems should be widely welcomed in view of the difficulties encountered in preparing and handling some of the metal alkylidenes (*cf.* section 4.1).

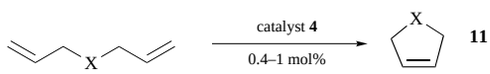


Scheme 5

3 Metal alkylidene catalysts: structures, scope and limitations in RCM

3.1 $W(OAr)(OAr)(=CHBu^t)(OEt_2)Cl$

$W(OAr)(OAr)(=CHBu^t)(OEt_2)Cl$, **4**, has been developed and applied by J.-M. Basset and co-workers.[23] To date, it has been shown to be remarkably tolerant of heteroatoms, including S, Si, P and Sn, but it has been tested only on a small range of other functional groups, and apparently only on five-membered ring systems (*e.g.* **11**, **Scheme 6**).[24,25] The catalyst is very sterically hindered, which is probably the reason for its success, but this limits its scope in ring closing reactions. Even with the systems that have been tested, the cyclisation fails if both alkenes are disubstituted, and the catalyst does not tolerate an allylic substituent, presumably for steric reasons. A less hindered catalyst is, unfortunately, likely to suffer problems of deactivation by coordination to the substrate, particularly when the substrate contains a sterically available sulfide or phosphine group.[23,26]



X = S, O, $SiMe_2$, PPh, yields 90–100%
X = $SiPh_2$, yield 8%

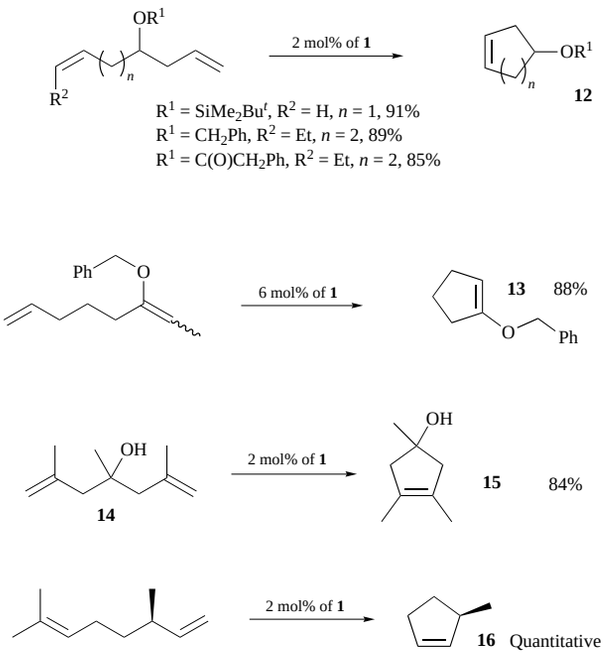
Scheme 6

3.2 $ArN{=}Mo(OR)_2{=}CH{-}CMe_2Ph$

$ArN{=}Mo(OR)_2{=}CH{-}CMe_2Ph$ [Ar = 2,6-$C_6H_3Pr^i_2$, R = $C(CF_3)_2Me$], **1**, was the first metal alkylidene complex reported to catalyse ring *closing* metathesis reactions, by the groups of Grubbs[27,28] and of Wagener[29] and Forbes[30] in 1992. In consequence, despite its drawbacks of sensitivity to oxygen and water and difficulty of storage (see section 4.1), many reports of applications in synthesis have followed. Its scope and limitations have been extensively investigated by the Grubbs group[27,28,31,32] and by others. Initially, only monocyclic systems were attempted, but recently more ambitious applications have been reported (see below and section 5). Although sensitive to hydroxy and several other functionalities, molybdenum alkylidene **1** probably shows the highest activity of any RCM catalyst so far reported, so it has remained popular among chemists having the equipment to make and store it. It is noteworthy that the corresponding tungsten catalyst $ArN{=}W(OR)_2{=}CH{-}CMe_2Ph$ [Ar = 2,6-$C_6H_3Pr^i_2$, R = $C(CF_3)_2Me$], although active and widely used for polymerisation, has only rarely been reported to carry out ring closure.[27,33]

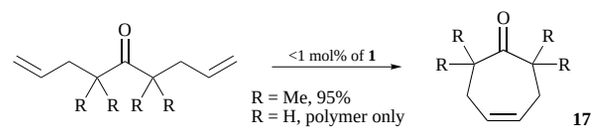
3.2.1 Monocyclic systems. Grubbs' group has shown[31] that catalyst **1** can be used to make simple five- and six-membered carbocycles with pendant ether (*e.g.* **12**, R^1 = Bn), silyl ether (*e.g.* **12**, R^1 = TBDMS), enol ether[32] (*e.g.* **13**) and ester [*e.g.* **12**, R^1 = C(O)Bn] groups (**Scheme 7**). In the unusual case of diene **14** even an alcohol was tolerated, but alcohol and carboxylic acid groups are not normally compatible with catalyst **1**. The double bond generated during the reaction is usually disubstituted in these examples, but tri- and even tetra-substituted (*e.g.* **15**) product double bonds have been reported; although the substrate double bonds are generally monosubstituted, di- or tri-substituted double bonds are metathesised by this catalyst. More recently Sita has shown that the catalyst is compatible with the formation of optically active carbocycle **16**.[34]

Forbes *et al*. showed that geminal disubstitution could assist in closing five- and seven-membered (*e.g.* **17**, R = Me, **Scheme 8**) carbocycles by the Thorpe–Ingold effect,[30] and failures to close simple seven-membered (*e.g.* **17**, R = H) and eight-membered rings lacking such a substitution pattern have been reported.[30,35] Even *gem* disubstitution does not guarantee successful ring closure, however, since Forbes' paper also reports the failure of catalyst **1** to close an 11-membered and two 5-membered carbocycles all with *gem* disubstitution. Curiously, one of the failures



Scheme 7

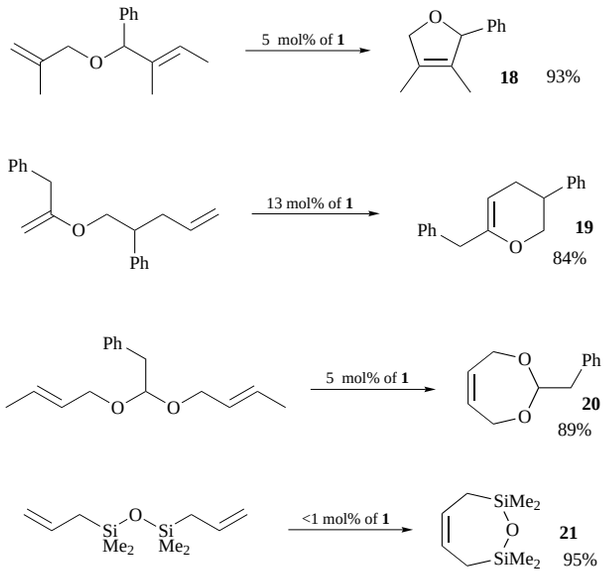
involved dimethyl diallylmalonate, the diethyl analogue of which was used as the substrate for the recent kinetic studies on ruthenium-based catalysts (see section 1.2). The kinetic study comments, however, that ring closure is comparatively slow with this substrate.[12]



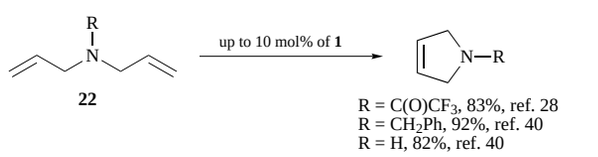
Scheme 8

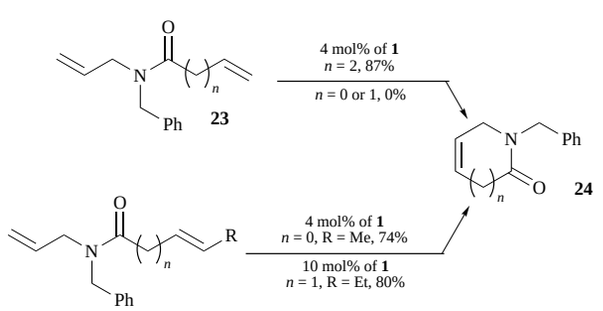
The most comprehensive studies on oxacycle formation using catalyst **1** are again those of Grubbs,[27] whose group has made five-, six- and seven-membered rings in good to excellent yields (*e.g.* **18**–**20**, **Scheme 9**). Recently the formation of a 16-ring lactone has also been reported, in the context of a total synthesis (see sections 3.2.2 and 5).[36] In addition to the functional groups (FGs) mentioned above, acetals (*e.g.* **20**) and bis-silyl ethers (*e.g.* **21**) are tolerated by the catalyst. Wagener suggests that the disubstitution of the silicon atoms probably assists ring closure to **21**.[30] Once again, as shown, the double bond formed during the reaction may be di-, tri- or tetra-substituted, while the double bonds metathesised by the catalyst may be mono-, di- or even tri-substituted.

The formation of nitrogen-containing rings by RCM has attracted considerable attention, not least because of their prevalence in naturally occurring systems. Again the initial work was carried out by Grubbs' group,[28] but this has been built on significantly since 1992, with over 30 different azacycles reported to have been made using molybdenum-based catalyst **1**. These include not only five-, six- and seven-membered rings but also 14-membered rings (see section 3.2.2), and a variety of bicyclic systems (see section 3.2.3). The original study demonstrated the tolerance of the catalyst for tertiary amines (*e.g.* **22**, R = Bn, **Scheme 10**) and tertiary amides (*e.g.* **22**, R = $COCF_3$);[28] this has since been extended to include secondary amides[37,38] and, despite a suggestion that it does not react with this catalyst,[39] the secondary amine diallylamine (**22**, R = H).[40] There are a few somewhat surprising failures, which may represent limitations on the use of the catalyst in the synthesis of γ- and δ-lactams: thus amide **23** (*n* = 2) cyclises readily in 87% yield to lactam **24**, (*n* = 2), while amides **23** (*n* = 1) and **23** (*n* = 0) do not cyclise at all.[28] The problem is



Scheme 9

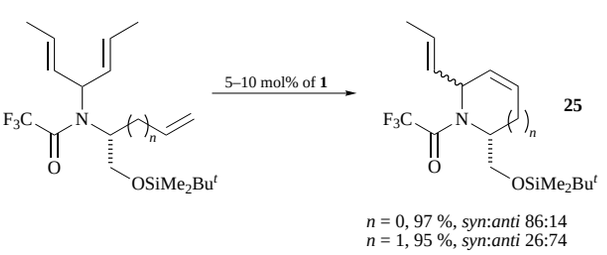




Scheme 10

easily overcome by using internal rather than terminal dienes, as shown, to give lactams **24** (*n* = 1) and **24** (*n* = 0) in 80 and 74% yields respectively.

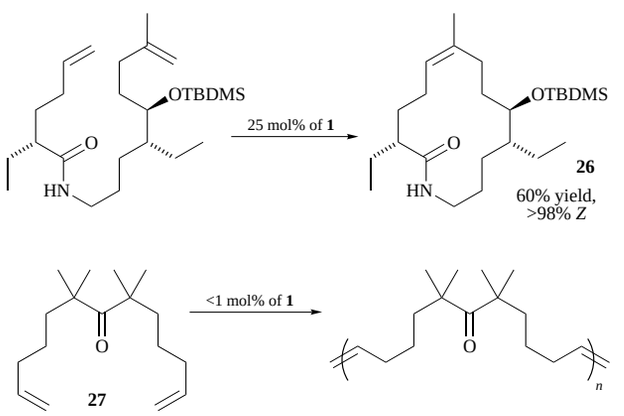
In an interesting development, Blechert has shown how steric effects can be harnessed to make the catalyst diastereoselective, albeit in a rather specialised system.[41] Generally the published syntheses of azacycles use monosubstituted alkenes in the substrates, and make disubstituted cycloalkene products, but some trisubstituted cycloalkene products have also been reported. Blechert uses the substitution pattern of the substrate to ensure that the catalyst reacts first with a terminal alkene, and then selects, in a diastereoselective fashion, between two disubstituted alkenes to close the ring in amide **25** (**Scheme 11**).



Scheme 11

Molybdenum alkylidene **1** seems to be the catalyst of choice for sulfur-containing compounds.[42] The catalyst gives good yields of five- and six-membered rings containing either sulfides or disulfides,[40] unless steric hindrance is excessive. In the demanding case of a tetrathiafulvalene substrate, however, the cyclisation reaction failed completely.[42] Only a few thiacycles have been synthesised, chiefly based on 2,5-dihydrothiophene,[43] its disulfide analogue, and the 3-methyl substituted variants.

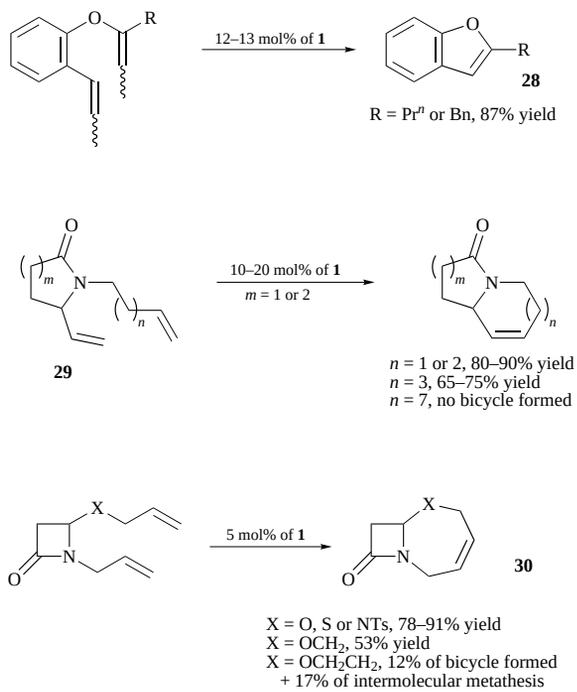
3.2.2 Medium and large ring closure. Very few reports have appeared of successful attempts at 'difficult' ring closures using catalyst **1**. As discussed below, a nine-membered ring has been made, fused to a β-lactam, but in only 12% yield.[44] Ten-membered rings have been produced by 'back-biting' from polymers[9] (see section 1.1 above), and 14-membered lactams (*e.g.* **26**, **Scheme 12**)[37,38] and 16-membered lactones (similar to structure **74** below)[36] have been produced in synthetic contexts. As described in the next section, attempts to form 11- and 12-membered rings as parts of bicyclic systems have all failed. An attempt to form an 11-membered ring from ketone **27** also gave only polymeric products of intermolecular metathesis; this reaction was performed in the absence of solvent, and might have been helped by working at high dilution.[30]



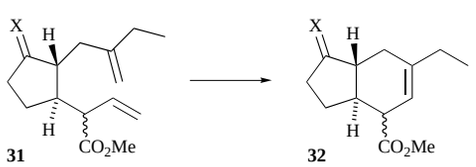
Scheme 12

3.2.3 Bicyclic systems. Several investigations have been made into the feasibility of making fused bicyclic systems by RCM using molybdenum-based catalyst **1**. Grubbs showed that this method can be used to make benzofurans (*e.g.* **28**, **Scheme 13**), by building the furan ring onto a suitably substituted benzene.[32] In these cases trisubstituted cycloalkenes were made from di- and tri-substituted alkenes in the starting dienes. There is also one report of an eight-membered ring being built onto a benzene ring in a similar fashion.[45] Martin and co-workers have extensively investigated annulation onto a lactam: five-, six-, seven- and eight-membered rings may be made in this way by RCM (*e.g.* from **29**, $n = 0$–3), and the pre-existing ring may be a γ- or a δ-lactam (*e.g.* **29**, $m = 1$ or 2).[46,47] Their attempts to make a 12-membered ring in the same way (from **29**, $m = 1$, $n = 7$) resulted only in intermolecular metathesis. This methodology was later used in their synthetic approaches to manzamine A (see section 5.1 below). Barrett and Gibson have extended this to show how seven- and eight-membered rings, and even (in low yield) nine-membered rings, may be built onto a β-lactam to give bicyclic systems **30**.[44,48] The newly-formed ring in these bicycles may contain a second heteroatom, which may be oxygen, nitrogen or even sulfur (**30**, X = O, NTs or S). In all of the bicyclic β-, γ- and δ-lactams produced in this way, the nitrogen atom was at the ring junction, so stereochemistry of the fused rings was not an issue. In virtually all compounds, the substrates contained only terminal alkenes, and the products disubstituted cycloalkenes.

The issue of ring junction stereochemistry has been addressed in part by Hölder and Blechert, who have demonstrated the formation of a *trans*-fused 6,5-ring system (**32**, X = OCH_2CH_2O, **Scheme 14**) in excellent yield using the Schrock catalyst **1**.[49] These results should be compared with the investigations into ring junction stereochemistry using ruthenium alkylidenes **2** and **3**, which are discussed in sections 3.3 and 3.4 below. The work of Hölder and Blechert also reveals a little-known incompatability between the catalyst **1** and certain ketones: ketone **31**, X = O was converted into *exo*-alkene **32**, X = CH_2 to the extent of two thirds of the catalyst. This problem was overcome by conversion of the ketone to acetal **31**, X = OCH_2CH_2O, which proved a better substrate for RCM. Since the catalyst is frequently used at <5 mol%, it is perhaps hardly surprising that this methylenation has not been reported elsewhere, but it may be more prevalent in reactions with ketones than is currently realised, and may well cause unnecessarily low yields in some cases.

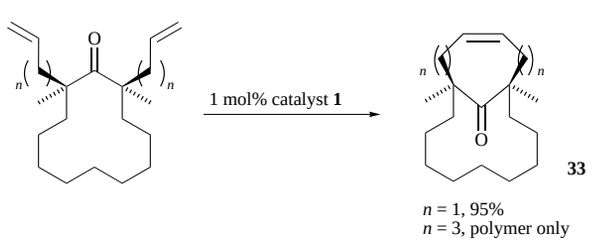


Scheme 13



Scheme 14

Only one report of attempts to make bridged bicyclic systems by RCM using the Schrock catalyst **1** has appeared to date: synthesis of the [9.4.1] ring system in ketone **33**, $n = 1$ was successful, but attempted formation of a related [9.8.1] system gave only the polymeric product of intermolecular metathesis (**Scheme 15**).[30]

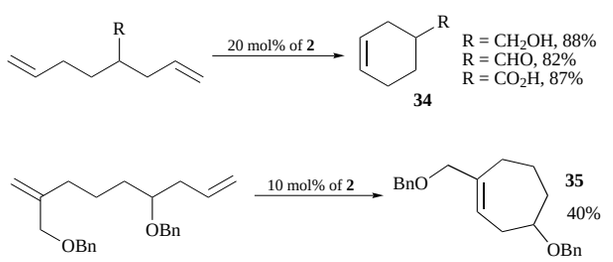


Scheme 15

3.3 $(Cy_3P)_2Cl_2Ru{=}CH{-}CH{=}CPh_2$

$(Cy_3P)_2Cl_2Ru{=}CH{-}CH{=}CPh_2$, **2**, was reported to catalyse ring closing metathesis in 1993, again by Grubbs *et al.*[50] It is significantly easier to make and handle than complex **1** (see section 4.1), and has therefore proved popular among synthetic organic chemists despite its apparently lower overall activity. It has significantly wider functional group tolerance than molybdenum alkylidene **1**, although there are a few functionalities which it does not tolerate (see section 4.3). For these reasons there have been many reports of its use in a large variety of systems following the original wide-ranging report of Grubbs.

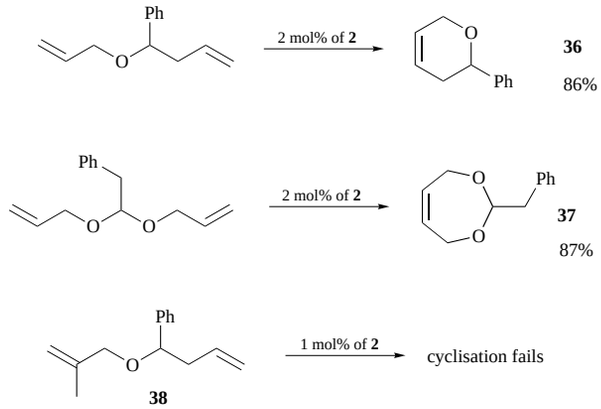
3.3.1 Monocyclic systems. Grubbs' original paper described the synthesis, in very good yields, of a few five- and six-membered carbocycles having not only pendant silyl ethers, but also alcohol (**34**, R = CH_2OH), aldehyde (**34**, R = CHO) and carboxylic acid (**34**, R = CO_2H) functional groups (**Scheme 16**).[50] This represented a range of functionalities totally incompatible with catalyst **1**, and therefore opened up a wide range of new potential substrates. Very few reports of monocyclic carbocycle formation have followed. It seems that ring size and substitution are critical: Maier *et al*. showed that ruthenium alkylidene **2** was superior to the molybdenum-based catalyst **1** for making cycloheptene **35** having a trisubstituted double bond.[35] The yield of this reaction was not good (40%) even with catalyst **2**, and many other five-, six- and seven-membered carbocycles have been made in higher yields as part of bicyclic systems using this catalyst (see section 3.3.3 below). Similarly, Grubbs and co-workers found that the triethylsilyl ether of 4-methyldeca-1,9-dien-4-ol was not converted to the corresponding cyclooctene by ruthenium alkylidene **2** despite the geminal disubstitution, although several bicyclic analogues were available (section 3.3.3).[51]



Scheme 16

Grubbs' original paper describes the synthesis of a few five-, six- and seven-membered oxygen-containing rings using ruthenium alkylidene **2**, which included ether (*e.g.* **36**) and acetal (**37**) functionalities (**Scheme 17**).[50] Similar cyclisations have since been reported by the groups of Hoveyda,[52] Mori[53] and Lee.[40] In all cases the alkene generated by the ring closure was disubstituted: indeed an attempt by Kinoshita and Mori to achieve ring closure from 1,1-disubstituted alkene **38** failed completely.[53] This appears to be a serious limitation on the use of this catalyst, although Grubbs reports that such cyclisations can be achieved, at elevated temperatures.[50] Another limitation on the use of ruthenium alkylidene **2** is the report by Grubbs *et al*. that enol ethers are not cyclised by this catalyst, but undergo a slow dimerisation instead.[32] Recently Fürstner and Langemann have investigated the application of ruthenium-based catalyst **2** to the synthesis of macrolactones; these results are discussed in section 3.3.2 below.

The area of azacycle synthesis has again attracted much attention, with at least 45 published examples (including bi- and poly-cyclic systems). These range from simple molecules such as *N*-Boc-2,5-dihydropyrrole[50] to complex polycyclic peptides containing very large rings.[54] Grubbs' original study concentrated almost exclusively on tertiary amides and carbamates having no other functional groups (*e.g.* **39**, **Scheme 18**),[50] but it has since been shown that ruthenium alkylidene **2** is compatible with secondary amides and carbamates (*e.g.* **40**),[55] with sulfonamides (*e.g.* **41**),[53] and with many other functionalities including most ethers (*e.g.* **42**, $R^1 \neq H$) as well as free alcohols (*e.g.* **42**, $R^1 = H$; **43**),[56–58] and a ferrocenyl group (**44**).[59] The presence of esters does not usually cause problems: thus ester **45** was produced in good yield as shown, although a homologous cyclopentene derivative could not be formed using this method.[60] Catalyst **2** is clearly incompatible with free amines, either secondary or tertiary; the presence of a secondary amine has been shown to poison the catalyst.[40] This problem can usually be overcome by protecting the amine as a carbamate, or more simply by protonating the amine: ammonium salts such as **46** are suitable substrates for catalyst **2**.[50]

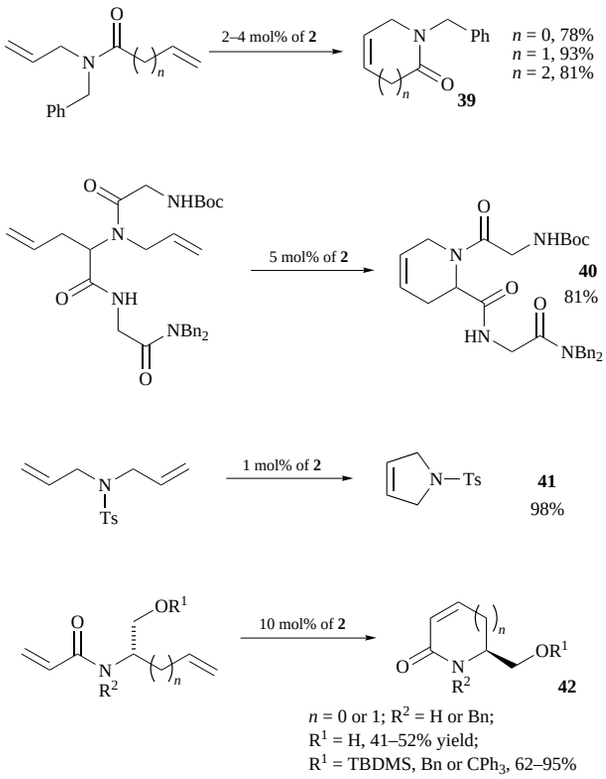


Scheme 17

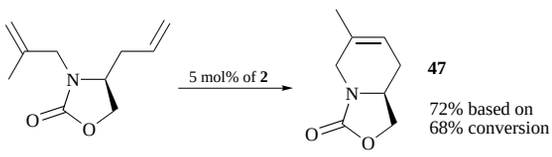
Five-, six-, seven- and even eight-membered nitrogen-containing rings can be produced in reasonable to excellent yields as shown in the above examples, although conformational assistance may be required for the successful formation of eight-membered rings (see section 3.3.3) and yields are sometimes lower for seven- and eight-membered rings.[51] The formation of azacyclopentene derivatives has also occasionally proved problematical, possibly for steric reasons (*cf.* **45** and its homologue).[55,56,60] Larger rings have also been made (see section 3.3.2). The diene produced during the reaction is usually disubstituted, and the substrate generally has two terminal alkenes. The (bicyclic) trisubstituted alkene **47** (**Scheme 19**) has been produced, but only 68% conversion of starting material could be achieved.[58] α,β-Unsaturated amides are metathesised efficiently by ruthenium alkylidene **2** to give α,β-unsaturated lactams such as **42**.[58] As several of these examples show, the ruthenium-based catalyst **2** is compatible with the synthesis of optically active cycloalkene derivatives such as **42**, **44** and **47**.

In an interesting series of experiments, Kinoshita and Mori demonstrated that *N*-allyl-*N*-prop-2-ynylsulfonamides and their homologues are metathesised to dienes.[53] The efficiency of the metathesis depends largely on the other substituent of the alkyne, with electron-donating groups favouring the cyclisation: thus cyclisations of **48** to **49** are particularly high-yielding (**Scheme 20**). The mechanism of the reaction presumably involves reaction of the catalyst first with the alkyne to give a metallacyclobutene, followed by regeneration of a ruthenium alkylidene and reaction with the alkene unit. This is outlined in **Scheme 21**. Consequently, the first round of the catalytic cycle is likely to give a different product from subsequent rounds, so that the minimum quantity of catalyst consistent with maximum conversion should be used. This is of course desirable in all cases for 'atom economy', but is particularly critical in these reactions. This technique of ene–yne metathesis was later used in their total synthesis of (−)-stemoamide (see section 5.1).

Attempts to make thiacycles using RCM and ruthenium alkylidene **2** have revealed a further limitation on its use: it appears in general to be incompatible with sulfides in the substrate. Like the incompatability with amines, this may be due to coordination of the substrate onto the ruthenium centre; we are currently investigating the compatability of catalyst **2** with



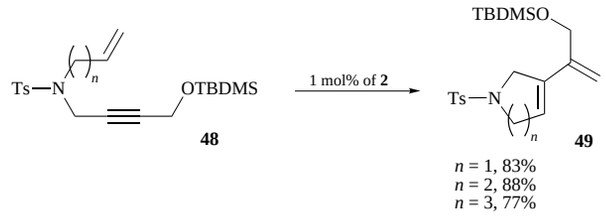
Scheme 18



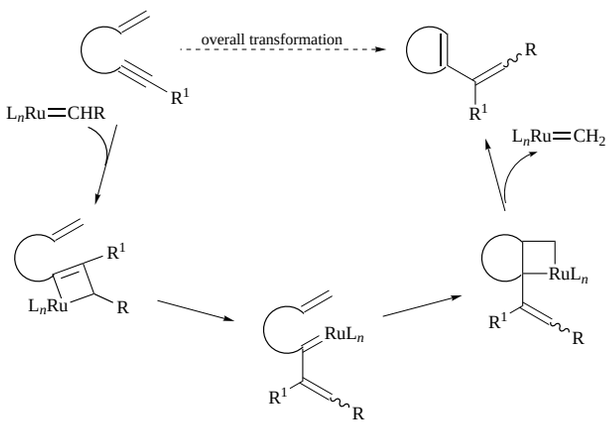
Scheme 19

higher oxidation states of sulfur.[61] There is a single report of the ring closure of diallyl sulfide to 2,5-dihydrothiophene in 29% yield,[40] but all other attempts at ring closure of sulfides and disulfides using catalyst **2** have failed.[40,42]

3.3.2 Medium and large ring closure. The only study on the formation of medium and large rings by RCM was carried out

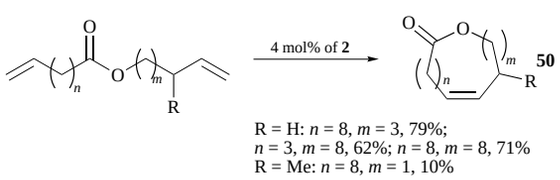


Scheme 20



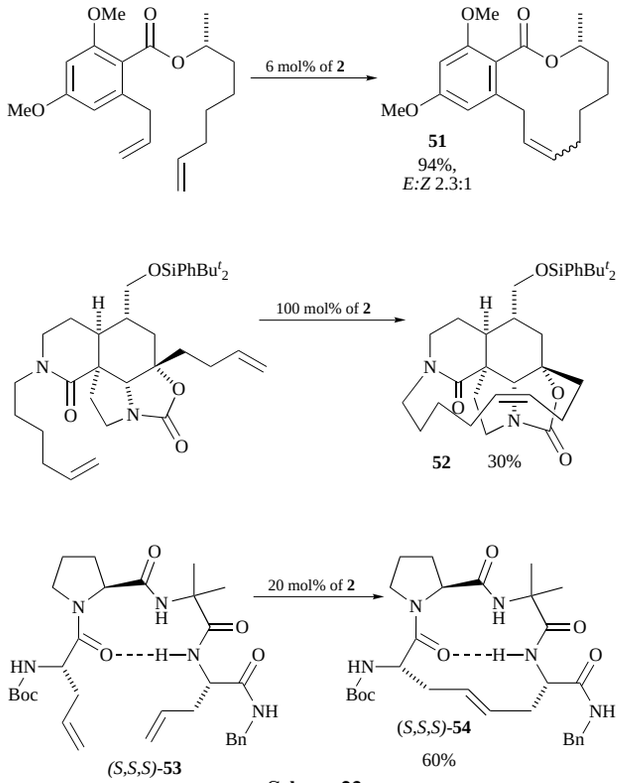
Scheme 21

by Fürstner and Langemann, who investigated the closure of macrolactones **50** using ruthenium alkylidene **2** (**Scheme 22**).[17] They found that 14-, 16- and 21-membered lactones could be cyclised in 60–80% yields. The steric requirements of the ruthenium catalyst are again evident, however: an allylic substituent, even only a methyl group, dramatically lowers the yield of the ring closure. The lactones are almost invariably produced as *E*/*Z* mixtures, but the *E*:*Z* ratio varies from 31:69, through 46:54, to 96:4, depending on ring size and substitution pattern.

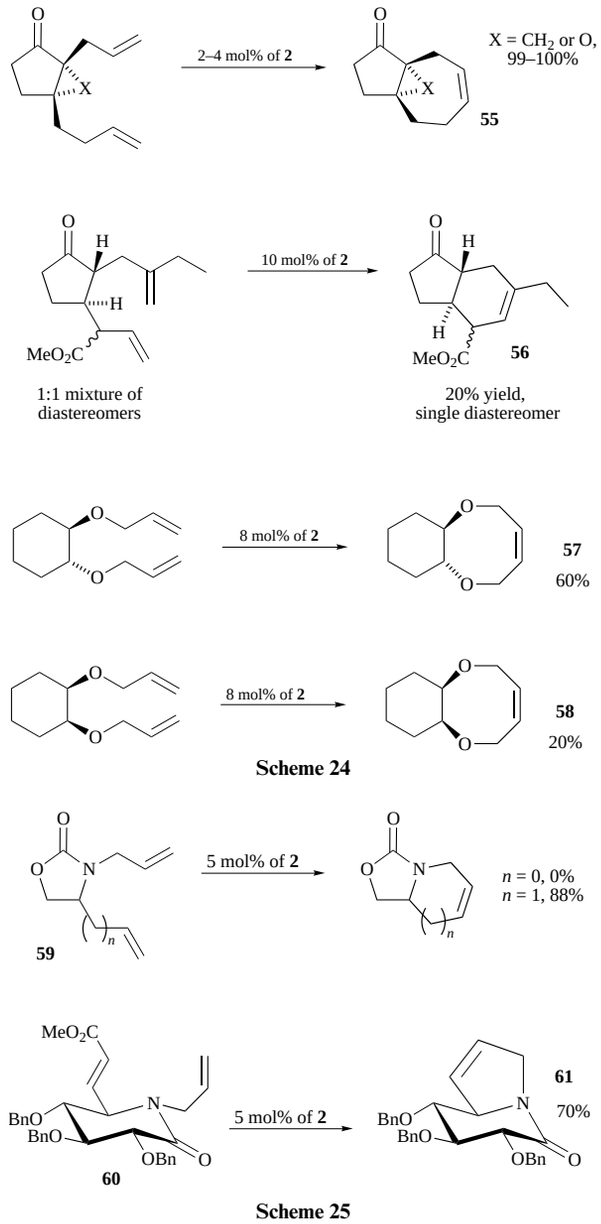


Scheme 22

Several larger rings have been synthesised, using ruthenium alkylidene **2**, as part of bi- and poly-cyclic systems. Fürstner and Kindler, during their synthesis of lasiodiplodin, used RCM to create 12-membered lactone **51** in excellent yield (**Scheme 23**).[62] The *E*/*Z* selectivity was poor, but this was unimportant since the double bond was subsequently removed by catalytic hydrogenation. Pandit and co-workers have used catalyst **2** to close large bridging rings in their synthetic studies on manzamine A. In one case (**52**), the reaction proceded in only 30% yield but gave exclusively the *Z* alkene;[63] in the other case no detailed results are given.[64,65] The need for a favourable substrate conformation has been illustrated by Grubbs and co-workers who synthesised an unnatural cyclic tripeptide using RCM. From a mixture of four diastereomeric substrates, only one (*S*,*S*,*S*-**53**) cyclised.[55] The product **54** was later isolated in 60% yield starting from isomerically pure *S*,*S*,*S*-**53**. NMR spectroscopic evidence shows that only the *E* alkene was produced in this case.[60] Despite the presence of intramolecular hydrogen bonding, designed to hold the molecule into a suitable conformation to cyclise, three isomers clearly did not adopt suitable conformations. Perhaps the most impressive example, and certainly the largest, of a polycyclic system produced by RCM is the synthesis by Clark and Ghadiri of a polycyclic peptide (see section 5.3 below).[54]



Scheme 23



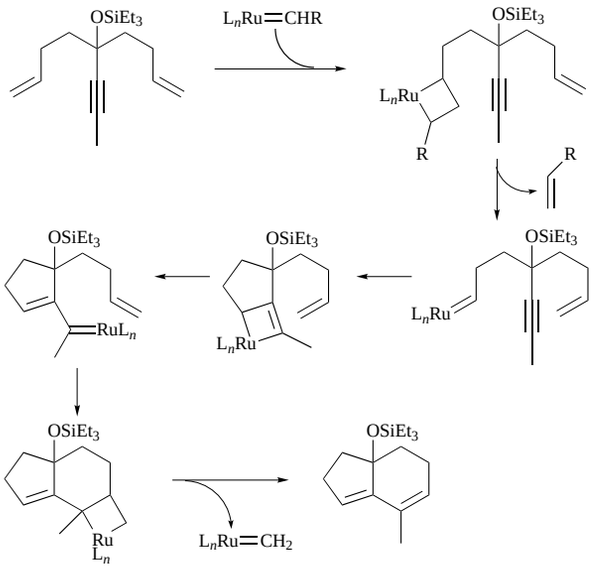
Scheme 24

Scheme 25

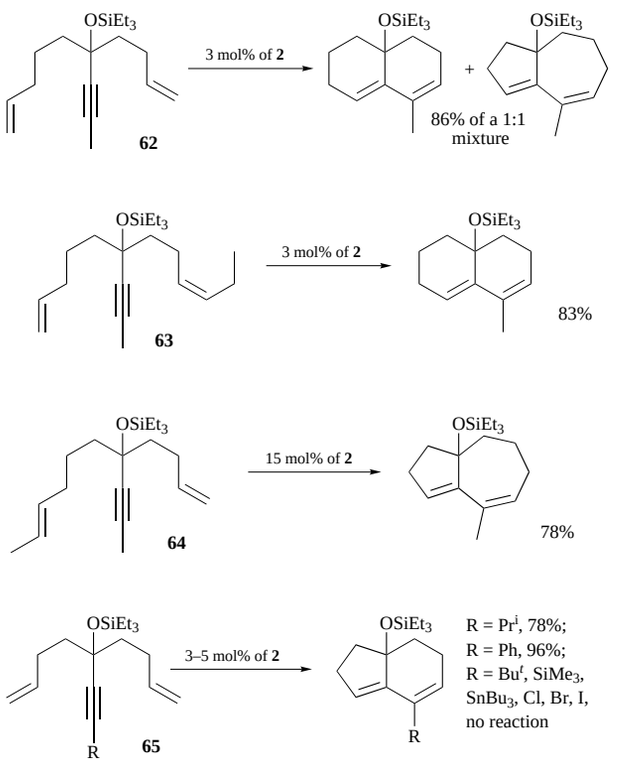
3.3.3 Bicyclic and polycyclic systems. The bicyclic and polycyclic systems (including those in the above paragraph) which have been synthesised using ruthenium alkylidene **2** demonstrate the range of structures accessible by RCM and the diversity of its applications. It is difficult to generalise in this area, but some conclusions can be drawn. A low-energy substrate conformation in which the two alkenes are in fairly close proximity is clearly useful, and perhaps essential. The existence of such a conformation is of course affected by the stereochemistry of the ring junction as well as by the size of the developing ring. Thus Blechert and co-workers were able to produce *cis*-fused [5.3.1.0] systems **55** in 99–100% yields, and the corresponding compound having a double bond at the ring junction in 94% yield (**Scheme 24**).[20] *trans*-Fused [4.3.0] systems (*e.g.* **56**) proved much more difficult, however, with ruthenium catalyst **2** giving only low yields at elevated temperatures (*cf.* section 3.2.2 above).[49] This will probably have been aggravated by the difficulty of forming a trisubstituted alkene using catalyst **2**. By contrast, Grubbs' group has shown that *trans* ring fusion is highly beneficial for the synthesis of [6.4.0] systems: *trans*-fused systems such as **57** could be produced in 60–75% yield whereas the corresponding *cis*-fused systems such as **58** gave only 20–33% yields.[51] For a [6.4.0] system in which the six-membered ring was aromatic, a yield of 59% was obtained. Pandit and co-workers have investigated the synthesis of [6.3.0] systems with an amide nitrogen at the ring junction: the yield has not been reported but is apparently low (see section 5 below).[64,65] In all of these cases the double bond produced was disubstituted.

The difficulty of forming certain cyclopentene derivatives is illustrated in the area of bicyclic systems by the failure of ruthenium alkylidene **2** to cyclise carbamate **59** ($n = 0$),[56] whereas the homologue **59** ($n = 1$) undergoes RCM in very good yield under similar conditions (**Scheme 25**).[58] By contrast, the sugar-derived dihydropyrrole **61** was synthesised in good yield from diene **60**.[66] This result is particularly interesting as an ester group is cleaved from azasugar **60** during metathesis: the by-product of the ring closure is methyl acrylate. Although, as mentioned above, there are other reports of α,β-unsaturated amides and esters undergoing metathesis, this is apparently the only case in which the carbonyl is removed by RCM. The formation of medium and large rings as parts of bi- and poly-cyclic systems using ruthenium alkylidene **2** is discussed in section 3.3.2 above.

Ene–yne metathesis has also been used for synthesising bicyclic systems. The earlier work of Kinoshita and Mori was recently extended to include the annulation of a 4-azacycloheptene onto a γ-lactam (*cf.* sections 3.4.3 and 5 below).[67] The majority of the work in this area, however, has been carried out by Grubbs.[68,69] This group has shown how a dienyne may be metathesised to give a bicyclic compound in which both rings are unsaturated. Unlike the systems of Kinoshita and Mori, it appears that the catalyst reacts first with one of the alkenes, then closes onto the alkyne. The second ring is formed by regeneration of a ruthenium alkylidene followed by intramolecular reaction with the second alkene. This is shown in **Scheme 26**. In this way [4.3.0], [5.3.0], [4.4.0] and [5.4.0] ring systems have been generated, depending on the lengths of the tethers connecting the unsaturated units. Steric hindrance can be used to discriminate between two possible ring systems: the catalyst will metathesise first the less hindered alkene. Thus the unsubstituted diene **62** gives a mixture of [4.4.0] and [5.3.0] ring systems, whereas monosubstituted dienes **63** and **64** each give a single product (**Scheme 27**). An ether tether can successfully be incorporated, but the reaction fails if the alkyne substituent is



Scheme 26



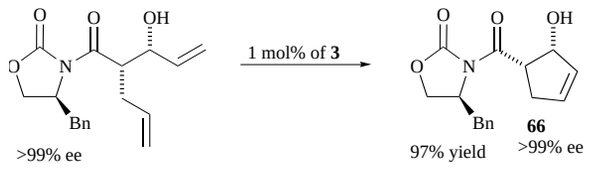
Scheme 27

too bulky or too electronegative: dienynes **65** (R = Pr^i or Ph) are cyclised as shown, but the cyclisation of dienyne **65** fails when R = Bu^t, Me_3Si, Bu_3Sn, or a halogen.[69] In general, this is a powerful and high-yielding reaction.

3.4 $(Cy_3P)_2Cl_2Ru$=CHPh

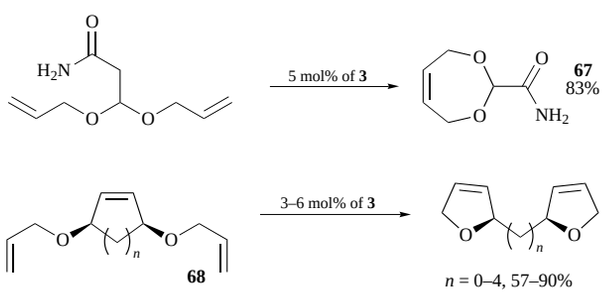
$(Cy_3P)_2Cl_2Ru$=CHPh, **3**, is among the newest of the known catalysts for RCM. Although its synthesis was reported in 1995,[4] applications to RCM are limited to 1996–7, but within this period a surprisingly large number of uses has appeared. Most of these relate to the synthesis of heterocyclic systems. The catalyst appears to be straightforward to make, reasonably stable for storage, and comparatively easy to use (*cf.* section 4.1).

3.4.1 Monocyclic systems. Apparently only two carbocycles in monocyclic systems have been made using ruthenium benzylidene **3**. Both involve the formation of substituted cyclopentenes. The successful and high-yielding synthesis of cyclopentene derivative **66** (**Scheme 28**) demonstrates the compatibility of the catalyst **3** with free alcohols as well as with carbonyl groups in the substrate, and also the suitability of benzylidene **3** for making optically active compounds: the starting diene is of course the product of an asymmetric aldol reaction.[70]



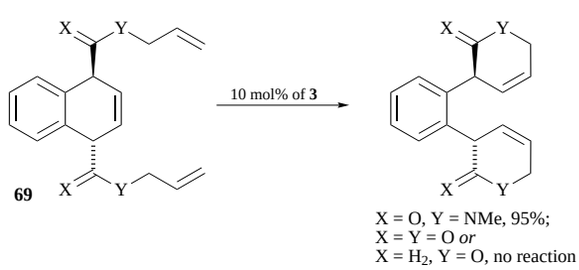
Scheme 28

Most of the oxacycles which have been made using ruthenium benzylidene **3** are medium and large ring lactones (see section 3.4.2). There is a single report of the synthesis of a seven-membered unsaturated acetal bearing a pendant primary amide (**67**) (**Scheme 29**).[44] In addition, Grubbs and co-workers have demonstrated the potential of benzylidene complex **3** for the sequential opening of one unsaturated ring and closure of two more within the same molecule. This tandem ring-opening–ring-closing process was expected to be assisted by starting from a small, strained cycloalkene, but in fact the original ring may be any size from four- to eight-membered (**68**, n = 0–4).[71]



Scheme 29

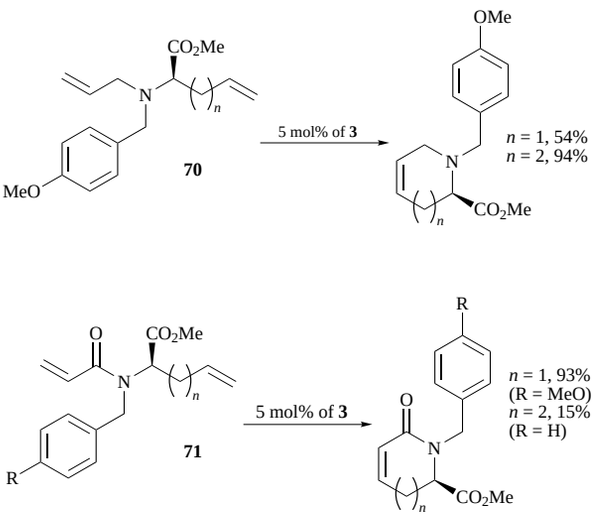
The tandem ring-opening–ring-closing approach has also been applied in the synthesis of azacycles using ruthenium benzylidene **3**.[71] Curiously, although the bis-amide **69** (X = O, Y = NMe) was metathesised in excellent yield, the corresponding bis-ester (**69**, X = Y = O) and bis-ether (**69**, X = H_2, Y = O) were not suitable substrates for benzylidene **3** and failed to ring-open (**Scheme 30**). This is attributed to conformational differences between the amide and the oxacycles. Blechert and co-workers tested ruthenium benzylidene **3** for their stereoselective ring closure of amides and carbamates (*cf.* section 3.2.1).[41] The catalyst showed little or no stereoselectivity in forming six-membered azacycles, in contrast to molybdenum alkylidene **1**. Unexpectedly, the catalysts showed opposite stereoselectivity in forming five-membered azacycle **25** (n = 0): as shown above the molybdenum catalyst gives a *syn*:*anti* ratio of 86:14 (97% yield), whereas with ruthenium benzylidene **3** the *syn*:*anti* ratio is 8:92 (98% yield based on 62% conversion).



Scheme 30

Rutjes and Schoemaker have investigated the formation of monocyclic nitrogen-containing compounds using ruthenium benzylidene **3**.[72] They investigated amines, amides and one

carbamate derivative, in the context of six- to eight-membered rings. All their diene substrates, being α-amino acid derivatives, contained a pendant ester group; other functional groups tolerated by benzylidene catalyst **3** in these systems included a ferrocenyl group. The success of the ring closing reaction in these cases seems to depend heavily on ring size and substitution pattern, and on the position of the double bond, as well as on functional group. In some cases tertiary amines (*e.g.* **70**), and in other cases tertiary amides (*e.g.* **71**), gave better yields; generalisations are almost impossible, but it is clear that secondary amines or amides give very poor yields, and attempts to make eight-membered rings (*e.g.* **70** or **71**, $n = 3$) by RCM failed (**Scheme 31**).

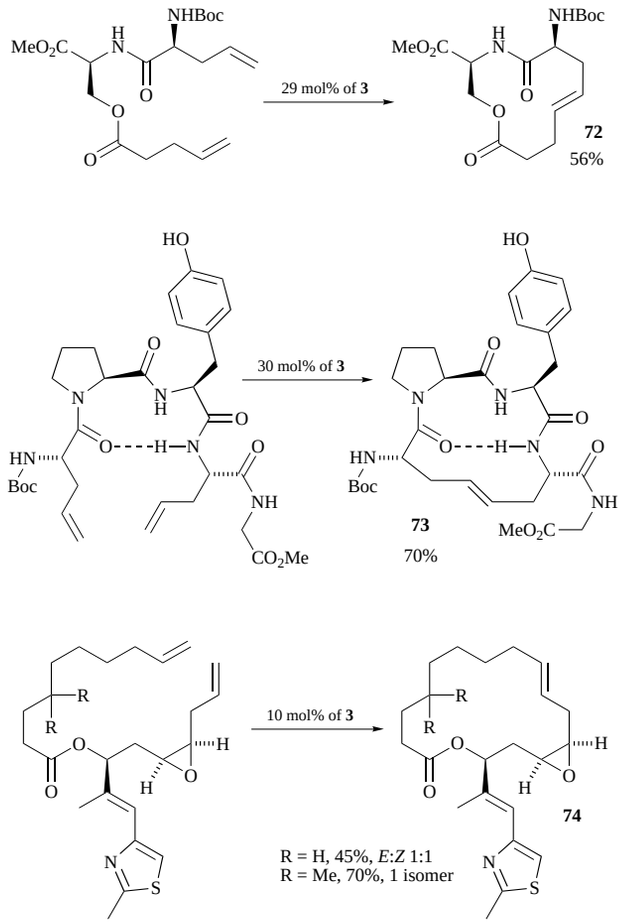


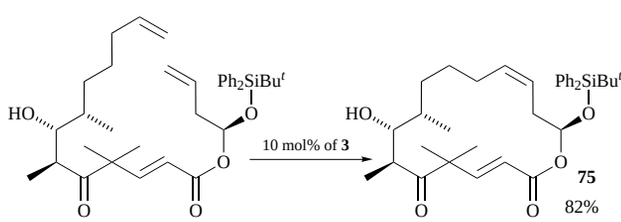
Scheme 31

It appears that sulfides are only moderately compatible with ruthenium benzylidene **3**: a single report exists of ring closure (to a bicyclic system and in only 22% yield) in the presence of a sulfide,[48] while other researchers have failed in their attempts to make cyclic sulfides using this catalyst.[73]

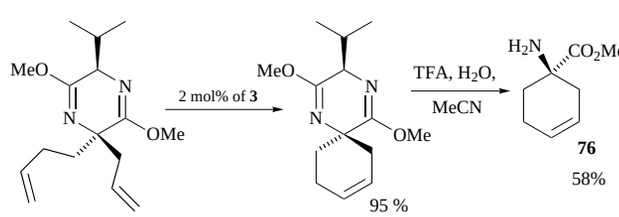
3.4.2 Medium and large ring closure. Surprisingly many examples of large ring closure using ruthenium benzylidene **3** have been published. Twelve-membered (**72**, **Scheme 32**)[60] and sixteen-membered lactones have been made in moderate to good yields; and fourteen-membered (*e.g.* **73**)[60] and larger rings have been made as parts of bi- or poly-cyclic systems (see section 3.4.3). In the case of the 14-membered polyamides such as **73**, ring formation is assisted by pre-organisation of the substrate with hydrogen bonding (*cf.* section 3.3.2 above). No fewer than 14 subtly different 16-membered lactones have been synthesised by the groups of Danishefsky[36,74] and Nicolaou[75–77] in their approaches to the epothilone group of natural products. The successful formation of these lactones demonstrates the compatibility of ruthenium benzylidene **3** with epoxides (*e.g.* **74**)[36] and free alcohols (*e.g.* **75**)[75] as well as with various silyl ethers in the substrate; they also demonstrate that ruthenium benzylidene **3** will metathesise terminal alkenes while leaving intact internal di- or tri-substituted alkenes (*e.g.* **74**, **75**) elsewhere in the molecule. The product $E:Z$ ratio in these lactones varies from apparently all-*E* (*e.g.* **74**, R = Me) through approximately 1:1 (*e.g.* **74**, R = H), to apparently all-*Z* (*e.g.* **75**) presumably for conformational reasons.

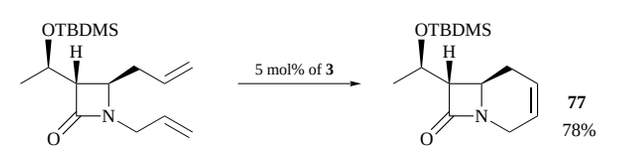
3.4.3 Bicyclic and polycyclic systems. In what appears to be the only known application of RCM to the construction of spirocyclic systems, Hammer and Undheim have published an elegant synthesis of some conformationally restricted α-amino acid esters (*e.g.* **76**) which would otherwise be very difficult to prepare in optically active form (**Scheme 33**).[78] The newly formed ring may be five-, six- or seven-membered, but

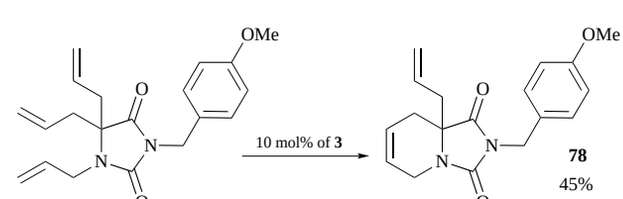




Scheme 32



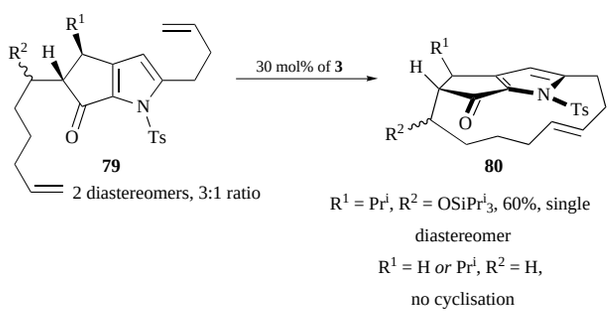




Scheme 33

attempts to close an eight-membered ring using catalyst **3** failed. An eight-membered ring has successfully been made as part of a fused bicyclic system.[79] In the construction of fused bicyclic systems, Barrett *et al.* have shown that ruthenium benzylidene **3** is effective for the construction of [4.2.0] systems (*e.g.* **77**) but gives only low yields of similar [5.2.0] systems.[48] Benzylidene **3** has also been used to make [4.3.0] systems (*e.g.* **78**) in 45–74% yields: in all cases, the RCM step closed the six-membered ring, and the new alkene was in the same position in each.[80] Fused bicycle **78** was produced in preference to the possible spirocycle; the comparatively low yield in this reaction was attributed to competing intermolecular metathesis. Fused bicyclic systems have also been constructed with ruthenium benzylidene **3** using tandem ring-opening–ring-closing metathesis,[71] and using ene–yne metathesis.[67] In the latter case, unlike the closely related catalyst **2** (*cf.* section 3.3.1 above), catalyst **3** gave a good yield even with an electron-withdrawing ester group on the alkyne. As mentioned in section 3.4.2 above, ruthenium alkylidene **3** is also effective at forming [12.3.0] systems such as **73**.[60]

Ruthenium benzylidene **3** has also been used for the construction of several bridged polycyclic systems. In these cases the precise nature of the substrate for catalysis is particularly critical: for example, Fuchs and co-workers found that bulky substituents were necessary to induce a conformation in bicycle **79** which would cyclise to the bridged system **80** (**Scheme 34**).[81] This strained system appears to be on the limits of what can be achieved by RCM. Limitations were also revealed when catalyst **3** was applied to the construction of bridged calixarenes (see section 5).

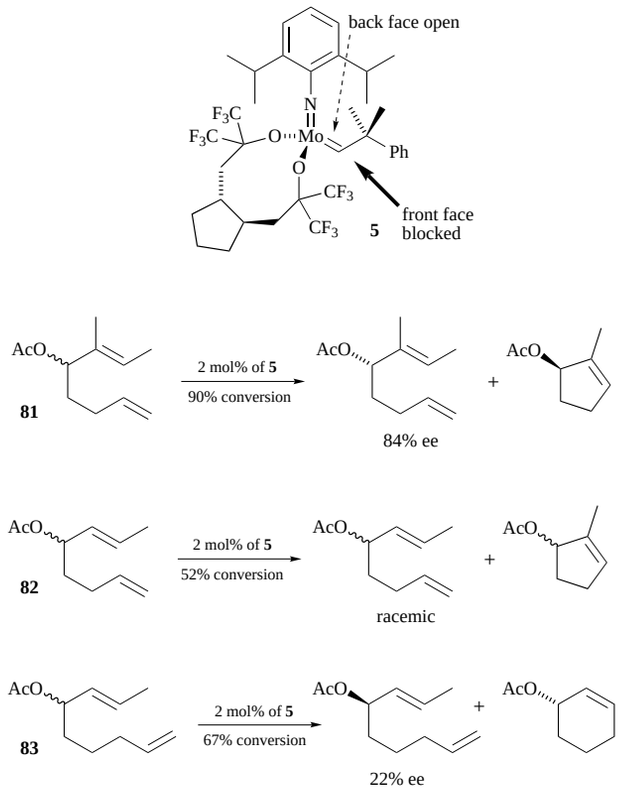


Scheme 34

3.5 A chiral catalyst for RCM

Grubbs' most recent catalyst is a chirally modified version of molybdenum alkylidene **1**. By incorporating a chiral chelating bis-alkoxide in place of the two hexafluoro-*tert*-butoxide units in **1**, chiral catalyst **5** was prepared.[6] In this catalyst, the two faces of the alkylidene are believed on the basis of molecular modelling to have quite different steric properties: one is open to attack while the other is blocked, as illustrated. Catalysts **1** and **5** for RCM are very similar in reactivity; both cyclise the TBDMS ether of hepta-1,6-dien-4-ol rapidly at room temperature, and both can be deactivated by substrates which can chelate to the molybdenum.[6]

Chiral alkylidene **5** was tested for its ability to resolve racemic 1,6- and 1,7-dienes.[82] Resolution was inefficient: at 90% conversion in the best case (**81**), the unreacted substrate had only 84% ee (**Scheme 35**). Varying the solvent and temperature seems to have very little effect. The main influence is clearly the degree of substitution of the substrate alkenes: no resolution of 1,6-diene **82** was achieved, although the homologous diene **83** was partially resolved as shown. Grubbs and Fujimura have proposed models to account for the fact that in the 1,6-diene series the *R* enantiomer is consumed while in the 1,7-diene series the *S* enantiomer is consumed. Improvements to the efficiency of the resolution are reported to be under investigation.



Scheme 35

4 Comparisons of catalysts for RCM

4.1 General considerations

In this section the synthesis and handling of the catalysts, as well as suitable conditions for carrying out RCM reactions, will be considered. As before, this review for the most part will consider the well-defined metal alkylidene catalysts, excluding chiral catalyst **5** because it is very similar to achiral molybdenum alkylidene **1**, and has been very little used to date.

In terms of ease of synthesis, stability, and conditions required for long-term storage, molybdenum alkylidene **1** is markedly more difficult than any other catalyst considered. It is extremely sensitive to air and moisture, even in the solid form. When stored overnight as a solid under a small positive pressure of nitrogen gas (in a Schlenk tube connected *via* rubber tubing to a nitrogen/vacuum manifold with N_2 flowing out through a bubbler) catalyst **1** was denatured.[83] This can be judged by a darkening in the colour from orange to brown, and was confirmed by its inability to metathesise diallyl ether. Ideally, molybdenum alkylidene **1** should be stored in a refrigerated glove box, a facility which is unavailable in many laboratories. A glove box is also required for its synthesis and handling, although reactions can be carried out successfully outside the box using Schlenk techniques, provided all liquids are rigorously degassed. Catalyst **1** is commercially available from Strem Chemicals Inc.; the UK distributor is Fluorochem.

By contrast, ruthenium-based catalysts **2** and **3** may be made using Schlenk techniques. Benzylidene catalyst **3** has proved more straightforward to synthesise than alkylidene catalyst **2**. The 'organic' precursor to catalyst **2** is 1,1-diphenylcyclopropene, generally made by eliminating HBr from 1-bromo-2,2-diphenylcyclopropane. In our hands this elimination is unreliable, frequently giving an unidentified but useless by-product. Benzylidene **3** on the other hand is made in straightforward fashion from phenyldiazomethane, and is also commercially available from Strem Chemicals Inc. Both ruthenium-based catalysts **2** and **3** are air stable for reasonable periods in the solid form. This enables the user to weigh the catalysts under air, for example, although it is almost certainly advan-

tageous to store them under nitrogen, argon or vacuum in a sealed vessel such as a Schlenk tube. We have stored ruthenium alkylidene **2** in this fashion for up to a year without apparent deterioration. Once again, deterioration may conveniently be judged by colour change, as well as by reactivity towards dienes. Colour change in solution may also be used to judge catalyst deterioration: ruthenium alkylidene **2** is generally an orange–brown colour, but in the presence of sulfides becomes greenish black, a colour also observed when the catalyst is deliberately denatured by allowing air into contact with the solution.[83]

The other catalysts discussed in sections 2 and 3.1 above have been much less widely used, and the author cannot write from personal experience about their ease of synthesis and use. Among the non-alkylidene catalysts, the DuPont catalyst appears to be particularly easy to use, since it is stored in stable forms and the active catalyst is generated *in situ* when required by mixing stable precursors.[22] The 'classical' catalyst systems are reported to suffer problems of reproducibility, while methyl trioxorhenium appears to work very slowly (see below).

Ring closing metathesis reactions have been carried out under widely varying conditions of solvent, concentration, molar equivalents of catalyst, temperature, and duration. The variability is of course greater for the more widely used catalysts: thus most of the classical or semi-classical catalyst systems (*i.e.* those discussed in section 2) have been used in only one solvent, while the Schrock and Grubbs catalysts have each been used in at least four different solvent systems. The following data are drawn from the papers cited elsewhere in this review unless otherwise indicated.

The classical and semi-classical catalysts fall into two groups: those based on tungsten, which include the Basset and DuPont catalysts; and those based on rhenium. The tungsten-based catalysts are always used in aromatic solvents at elevated temperatures (70–90 °C), and reactions are complete in 12 h or less. Generally less than 10 mol% of catalyst is used, but the substrate concentration has varied from 6 mM to 4 M. The Basset tungsten alkylidene **4** also fits this pattern, although extended reaction times are occasionally necessary. Catalyst **4** has the advantage that it is generally used with comparatively concentrated substrate solutions, or even in the absence of solvent. The rhenium-based catalysts are used in non-aromatic solvents (*n*-hexane or halogenated solvents), at or just above room temperature and for extended durations (1–7 d). More than 10 mol% of catalyst is generally required, and reactions have often been performed under very dilute conditions (0.1–10 mM).

The two most widely used catalysts over the past six years have been the Schrock molybdenum alkylidene **1** and the Grubbs ruthenium alkylidene **2**. Much the most popular solvent in both cases has been benzene, followed by dichloromethane. In addition, the Schrock catalyst has been used in *n*-pentane, *n*-hexane, toluene, xylene, and in the absence of solvent. THF has been used, but is reported to give a rather slower reaction. The chiral version **5** has been used in benzene and toluene. Most RCM reactions catalysed by molybdenum alkylidene **1** have been carried out at 20, 50 or 80 °C; lowering the temperature (to −20 °C with the chiral catalyst) clearly slows the reaction, but heating presumably also accelerates the decomposition of a highly sensitive catalyst. The sensitivity of molybdenum catalyst **1** is also reflected in the reaction durations reported: most are under 12 h, although there are a few reports of reactions continued for up to 3 d in a tightly sealed system. In our hands, this catalyst appears to react extremely rapidly or not at all, and decomposition in solution appears correspondingly rapid. The catalyst is generally used at 2–5 mol%, although it has been successfully used on a large scale down to 0.1 mol%. Substrate solutions are generally comparatively dilute (10–50 mM) although concentrations up to 0.75 M have been used successfully.

Ruthenium alkylidene **2** has been used in THF, *tert*-butyl alcohol (once), toluene, chloroform, and even, for polymerisations, water,[84] as well as benzene and dichloromethane. Reactions are generally performed at 20–50 °C, but there is a report of a reaction in refluxing toluene. Ruthenium alkylidene **2** works noticeably more slowly than the Schrock catalyst **1**, with 15–24 h reactions being typical, and reaction times up to 14 d reported. The latter is exceptional, however, and on a number of occasions reactions have been completed in less than one hour. A typical quantity of catalyst is 4 mol%, with almost all reactions employing 1–10 mol%. In total syntheses however the substrate may represent many months' effort and be available in very small amounts, and in such circumstances stoichiometric amounts of 'catalyst' have been used. The Grubbs catalyst **2** tolerates a very wide range of substrate concentrations, from 2 mM to 2 M, although 30–50 mM is typical.

The newer ruthenium benzylidene **3** shows similar characteristics to alkylidene **2**. Benzene and dichloromethane are the commonest solvents in use, with toluene and (for polymerisations)[84] water also reported. Refluxing dichloromethane is a popular medium, with benzene or toluene employed when a higher temperature is required to drive the reaction. Reactions at room temperature are not uncommon. The benzylidene catalyst **3** appears to be intermediate in speed of action between catalysts **1** and **2**, with reaction times of 2–8 h being typical. Extreme reaction times with this catalyst are 0.5 and 20 h. Once again around 5 mol% of catalyst is typically used, with rather larger amounts (up to 75 mol%) on occasion. Substrate concentrations are generally lower than with ruthenium alkylidene **2**, with 20 mM perhaps typical, and 0.2 M rather high for this catalyst. High dilution and slow addition may sometimes be used with any of the catalysts to effect particularly difficult ring closures when polymerisation competes. The most extreme case employed ruthenium benzylidene **3** with a substrate concentration of 0.5 mM.

4.2 Steric factors and alkene substitution patterns

These have been considered above when describing the various catalysts, so only a brief summary is given here. Once again all data are taken from papers cited above. The catalysts known to carry out RCM have different steric requirements, ranging from Basset's tungsten alkylidene **4** which cannot tolerate an allylic methyl group, to the Schrock molybdenum alkylidene which has been used to make tetrasubstituted double bonds. Molybdenum alkylidene **1** is apparently the only catalyst capable of producing tetrasubstituted alkenes: the tungsten catalyst **4** and a WCl_6–R_4Pb system have been shown to be incapable of doing so, while ruthenium alkylidene **2** consistently fails to form trisubstituted alkenes from dienes (with one exception). The related benzylidene **3** has not been tested for its ability to make trisubstituted cycloalkenes from dienes, but it is known to fail to metathesise trisubstituted alkene substrates. (Both ruthenium catalysts **2** and **3** can form trisubstituted cycloalkenes by ene–yne metathesis.) Metathesising 1,2-disubstituted alkenes generally poses no problem to any of the catalysts covered by this review except the Basset alkylidene **4**, but differential substitution has sometimes been used to control either the position or the stereochemistry of RCM as described above.

When the product of RCM is a large cycloalkene, it may be produced as either *Z* or *E* or a mixture of the two. The outcome of such reactions is clearly governed by the conformation of the substrate and the stability of the possible products, and is extremely difficult to predict in non-rigid systems. Such reactions have most often been applied to the synthesis of saturated rings, using RCM followed by catalytic hydrogenation.

4.3 Comparison of catalysts by substrate functional group

In general, the Schrock catalyst **1** appears to be least tolerant of

functionality in the substrate and the Grubbs catalysts **2** and **3** most tolerant. However there are exceptions to this generalisation, particularly when the functional group contains 'soft' electron pairs (*e.g.* sulfides, amines) which apparently coordinate to ruthenium better than to molybdenum in these catalysts. This surprising observation has been attributed to the greater steric hindrance around the molybdenum atom; its greater ability to metathesise hindered alkenes must then be attributed to the greater overall activity of the molybdenum catalyst, demonstrated by its greater speed of reaction. As mentioned earlier, the Basset tungsten-based catalyst **4** also shows excellent tolerance of a variety of heteroatoms including sulfur. **Table 1** displays the known tolerance and intolerance of the various catalysts for a range of functional groups. The numbers given in the table cells are the reference numbers of papers cited elsewhere in this review.

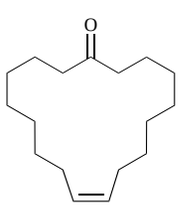
4.4 Comparison of catalysts by developing ring system

All the RCM catalysts known are capable of closing simple five-, six- and seven-membered monocyclic systems. A wide variety of larger monocyclic and more complex bi- and poly-cyclic systems has been made using RCM, and in general only one catalyst has been tested on each particular system. Particularly for the larger and more complex ring systems, success or failure may depend more on the conformation of the substrate than on the properties of the catalyst, given appropriate functional group compatability. This area is imperfectly understood at present, so **Table 2** summarises the known scope and limitations of the various RCM catalysts by developing ring system. As before, the reference numbers are for papers cited elsewhere in this review.

5 Applications of ring closing metathesis

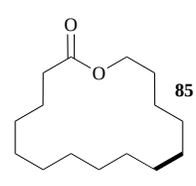
5.1 Total synthesis of natural products and 'non-natural products'

The synthesis of the natural perfumery compound civetone **84** was among the first applications of RCM.[15] This synthesis appeared in 1991, and used the 'classical' mixture of Re_2O_7 and Bu_4Sn. Since the discovery of metal alkylidene catalysts for RCM the method has been applied in a variety of total syntheses, very often of chiral compounds in optically active form. Several of these have been referred to above. The next paragraphs are not comprehensive but indicate the scope of RCM in this area.



84

Fürstner has applied ruthenium alkylidene **2** to the synthesis of a variety of naturally occurring macrolides including exaltolide **85**[17] and the chiral macrolactone lasiodiplodin **87**, produced in optically active form.[62] Epothilone A **86**, synthesised by both Danishefsky[74] and Nicolaou[76] using ruthenium benzylidene **3**, is a much more complex macrolactone synthesised by RCM, which perhaps represents the present 'state of the art' of natural product synthesis through RCM. Another monocyclic target molecule approached using RCM is the bioactive macrolactam Sch 38516 **88**, synthesised by the group of Hoveyda using the Schrock molybdenum alkylidene **1** among other organometallic species.[38] In all of these cases the double bond produced by RCM was altered later in the synthesis, either by hydrogenation or, in the case of epothilone A, by epoxidation. Hydrogenation is clearly useful when *E*/*Z* mixtures of alkenes are produced by metathesis.



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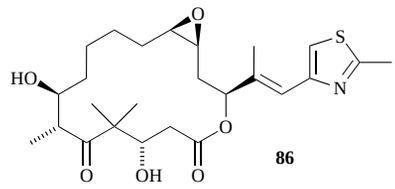

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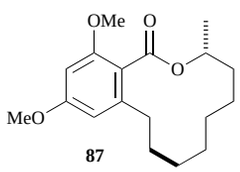

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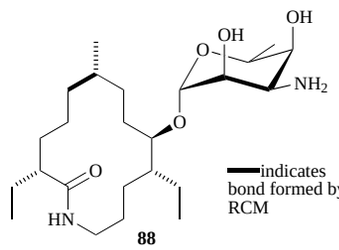
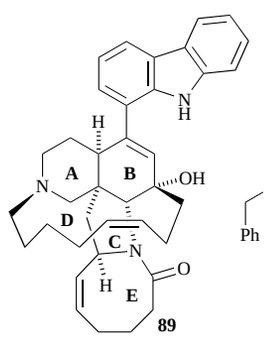


88

Two groups independently have applied RCM in their approaches to manzamine A **89**. Martin has used the Schrock catalyst **1** to form the eight-membered E ring in polycyclic lactam **90**,[85] while Pandit and co-workers have used Grubbs' catalyst **2** to close both the bridging D ring and the E ring in compounds such as **91**.[65] In both of these cases the double bond is required as part of the final target structure. The challenge of closing a bridging ring was also addressed by Fuchs in his synthesis of the roseophilin core unit **92**, although in this case the double bond (formed by ruthenium benzylidene **3**) was once again removed by hydrogenation.[81] Pandit has also published a formal total synthesis of castanospermine **93**, again using ruthenium alkylidene **2**, in which the double bond was stereoselectively dihydroxylated *en route* to the final intermediate.[66]



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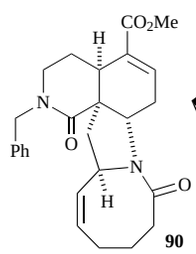

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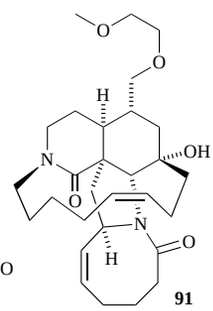

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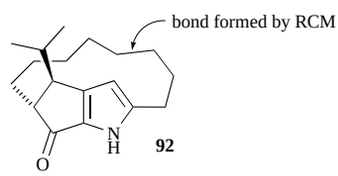

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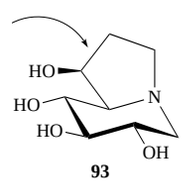


93

Two syntheses make elegant use of RCM by involving a double bond migration after ring closure. These are Crimmins' synthesis of the HIV reverse transcriptase inhibitor 1592U89 **94** from cyclopentene derivative **66**,[70] and Blechert's synthesis of coronafacic acid **95** from bicycle **56** (**Scheme 36**).[49] Crimmins' work is particularly attractive since it leads equally easily to the related carbovir, also an HIV reverse transcriptase inhibitor. Blechert has also published an attractively versatile approach *via* RCM to a range of azasugars including optically active **97**, produced by diastereoselective dihydroxylation of RCM product **96**.[57] Finally, Mori's synthesis of stemoamide **99** is worthy of note, since it involves his ene–yne metathesis reaction at an unusually early stage in the synthesis, followed by a series of transformations until the product **98** of RCM can hardly be recognised.[67] Three of these syntheses used the new catalyst **3**, but for coronafacic acid the Schrock catalyst **1** was required.

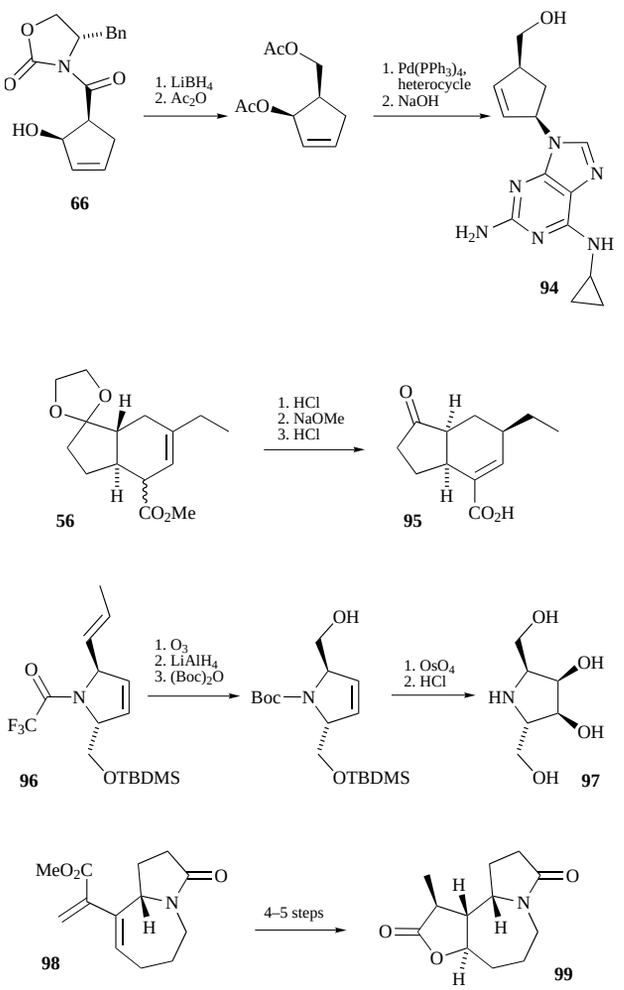
Table 1 References for compatability of catalysts with various functional groups in the substrate

	Catalyst **1**		Catalyst **2**		Catalyst **3**		Other catalysts[a]	
Functional group	Success	Failure	Success	Failure	Success	Failure	Success	Failure
Hydrocarbon	Sita[34] Grubbs[90]	Forbes[30]					W/Pb, Nugent[22] Re, Blechert[19]	W/Pb, Nugent[22]
C–Hal[b]	Grubbs[28] Hoveyda[38] Blechert[41] Martin[45,47]	Grubbs[69]	Grubbs[50]	Grubbs[69]	Blechert[41,57,88] Grubbs[60]		W/Pb, Nugent[22]	W, Grubbs[69]
Alcohol	Grubbs[31]	Blechert[41] Grubbs[50]	Grubbs[50] Pandit[64,65] Blechert[56,57,58]		Crimmins[70] Danishefsky[74] Nicolaou[75,76,77] Grubbs[60] McKervey[87]	Blechert[41]		
Ether	Grubbs[27,31,32] Wagener[29] Armstrong[42] Lee[40] Barrett[44] Martin[45,47]	Maier[35]	Maier[35] Lee[40] Grubbs[50,51,68,69] Mori[53] Hoveyda[52,86] Blechert[58,88] Fürstner[62] Pandit[64,65,66] Armstrong[42]	Mori[53] Hoveyda[86] Lee[40]	Grubbs[60,71] Rutjes[72] Nicolaou[77] Dyatkin[80] McKervey[87] van Maarseveen[89] Blechert[88]	Grubbs[71]	W/Pb, Nugent[22] **4**, Basset[24,25]	W/Pb, Nugent[22] W, Wagener[29]
Silyl ether	Grubbs[6,31,69] Forbes[30] Hoveyda[37] Blechert[41]	Grubbs[69]	Grubbs[50,51,68,69] Mori[53] Blechert[58] Pandit[63,64,65]	Grubbs[51,69] Hoveyda[37]	Blechert[41,57] Barrett[48] Danishefsky[74] Fuchs[81] Nicolaou[75,76,77]		**5**, Grubbs[6,82] W/Pb, Nugent[22] W, Grubbs[69] Re, Blechert[19]	W, Grubbs[69]
Enol ether	Grubbs[32]			Grubbs[32]			Cr, Mori[7]	
Epoxide	Danishefsky[36]		Blechert[20]		Danishefsky[36]			Re, Blechert[20]
Acetal	Grubbs[27,32] Hoveyda[38] Blechert[49]		Grubbs[50]	Blechert[49]	Barrett[44]		W/Pb, Descotes[21]	W/Ti, Tsuji[13] W/Sn, Tsuji[13]
Aldehyde		Grubbs[50]	Grubbs[50]					
Ketone	Forbes[30] Blechert[49]	Forbes[30]	Blechert[20]	Blechert[49]	Danishefsky[74] Fuchs[81] Nicolaou[75,76,77]	Fuchs[81]	Re, Blechert[19,20] Re/Sn, Mol[15]	W/Ti, Tsuji[13] W/Sn, Tsuji[13] Re, Blechert[20]
Ester	Grubbs[31] Danishefsky[36] Martin[47,85] Hoveyda[38] Blechert[49]	Forbes[30] Grubbs[69]	Armstrong[1] Mori[53] Fürstner[17,62] Grubbs[12,51,55,60,69] Pandit[66]	Grubbs[51,60] Blechert[49]	Danishefsky[36,74] Grubbs[60] Mori[67] Rutjes[72] Undheim[78] Nicolaou[75,76,77]	Grubbs[71]	W/Sn, Villemin[16] W/Ti, Tsuji[13,14] W/Pb, Nugent, [22] Descotes[21] Re, Blechert[19] W/Si, Bespalova[18] **5**, Grubbs[82] W, Grubbs[69]	W/Pb, Nugent[22] **5**, Grubbs[82]
Carboxylic acid		Grubbs[50]	Grubbs[50]					
α,β-Unsaturated carbonyl	Grubbs[28] Martin[47,85]	Grubbs[28]	Armstrong[1] Blechert[20,58,88] Grubbs[50] Mori[53] Pandit[66]		Mori[67] Rutjes[72] Nicolaou[75] Fuchs[81]	Fuchs[81]		Re, Blechert[20]
2° Amine	Lee[40]	Wagener[39]		Lee[40]		Rutjes[72]		
3° Amine	Grubbs[28] Wagener[39] Lee[40]			Lee[40] Grubbs[50]	Rutjes[72]			
2° Amide	Hoveyda[37,38]		Ghadiri[54] Grubbs[55,60] Blechert[58,88]	Hoveyda[37] Grubbs[55]	Grubbs[60] Undheim[78] Rutjes[72]	Rutjes[72]	W/Pb, Descotes[21]	
3° Amide	Grubbs[28] Blechert[41] Barrett[44,48] Martin[45,46,47,85]	Grubbs[28]	Grubbs[50,51,55,60] Ghadiri[54] Blechert[58] Guibé[59] Pandit[63,64,65,66] Mori[67]	Grubbs[55]	Blechert[41,57,88] Barrett[48] Grubbs[60,71] Mori[67] Rutjes[72] van Maarseveen[89] Dyatkin[80]		W/Pb, Nugent[22]	W/Pb, Nugent[22]
2° Carbamate			Grubbs[55,60]	Grubbs[55]	Grubbs[60] van Maarseveen[89]			
3° Carbamate	Blechert[41]		Grubbs[50,51,55,60] Pandit[63,64,65] Blechert[56,57,58]	Blechert[56] Grubbs[51,60]	Blechert[41,57] Crimmins[70] Rutjes[72] Winkler[79]			
Sulfonamide	Barrett[48]		Mori[53] Hoveyda[86] Blechert[88]		Barrett[48] Fuchs[81]	Fuchs[81]	Cr, Mori[7]	
Heteroaromatic	Danishefsky[36]	Armstrong[42]			Fuchs[81] Nicolaou[76,77] Dyatkin[80] Danishefsky[36,74]	Fuchs[81]		
Silane	Gibson[8,9]	Grubbs[69]	Mori[53]	Grubbs[69]			**4**, Basset[24] W/Pb, Basset[25] W, Grubbs[69]	W/Pb, Nugent[22]
Sulfide	Lee[40] Armstrong[42] Wagener[43] Barrett[48]		Lee[40]	Lee[40] Armstrong[42]	Barrett[48]	Whitby[73]	**4**, Basset[23,24,25] W/Pb, Basset[25]	W/Pb, Basset[25] **4**, Basset[24,25]
Disulfide	Lee[40]	Lee[40]		Lee[40]		Lee[40]		

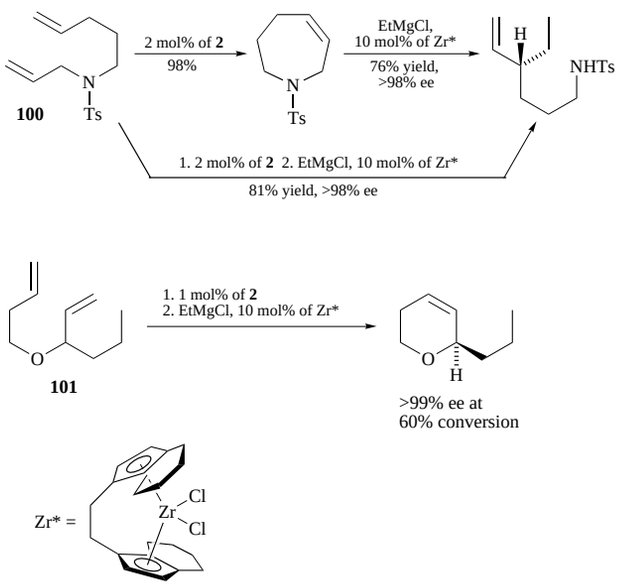
Table 1 (*Continued*)

Functional group	Catalyst **1**		Catalyst **2**		Catalyst **3**		Other catalysts[a]	
	Success	Failure	Success	Failure	Success	Failure	Success	Failure
Ferrocenyl			Guibé[59]		Rutjes[72]			
Stannane		Grubbs[69]		Grubbs[69]			**4**, Basset[25]	W, Grubbs[69]
Other FGs	Silyl acetal, Grubbs[27]		Ammonium salt, Grubbs[50] Mori[53]		1° amide, Barrett[44] carbonate, Grubbs[60] *C*-methoxy imine, Undheim[78]	*C*-methoxy imine, Undheim[78]	Phosphine, **4**, Basset[24,25,26]	

[a] Cr = $(OC)_5Cr{=}C(Me)OEt$; Re = $MeReO_3$; Re/Sn = Re_2O_7 + Bu^n_4Sn; W/Pb = $(ArO)_2Cl_2W{=}O$ + Et_4Pb *or* $(ArO)_2WCl_4$ + Bu^n_4Pb and related systems; W/Si = WCl_6 + Ph_2SiH_2 *or* WCl_6 + $(Me_2SiCH_2)_2$; W/Sn = WCl_6 + Me_4Sn; W/Ti = WCl_6 + Cp_2TiMe_2 *or* $WOCl_4$ + Cp_2TiMe_2; W = tungsten analogue of **1**. [b] Hal = F, Cl, Br or I.



Scheme 36



Scheme 37

5.2 Tandem use with other reagents

So far there is only one example of the use of RCM in a tandem process with other reagents. This is the work of Hoveyda and co-workers, who have demonstrated how their asymmetric zirconium-catalysed alkylmagnesation of cyclic alkenes can be coupled with ruthenium-catalysed RCM, either in separate steps or in a one-pot procedure. The tandem process may be used with achiral starting materials such as sulfonamide **100**,[86] or for kinetic resolution of chiral substrates such as ether **101** (**Scheme 37**).[52]

5.3 Amino acids, peptides and macromolecules

Several groups have applied RCM strategies to the synthesis of rigidified amino acids and small peptides. Thus Hammer and Undheim have used RCM with ruthenium benzylidene **3** on their spirocyclic systems to control both absolute stereochemistry and conformation in amino esters **76**.[78] Rutjes and co-workers have shown how cyclic (protected) amino acids such as **102** and **103** can be produced in optically active form by RCM with the same catalyst;[72] this work is reinforced by similar studies of Grubbs' group on racemic compounds, using their ruthenium alkylidene catalyst **2**.[55] Garro-Hélion and Guibé have used RCM, again with Grubbs' catalyst **2**, to construct the rigid pseudodipeptide (δ-amino acid) **104** in optically active form.[59] Grubbs' group has produced a series of cyclic di-, tri- and tetra-peptides including **105** and **72** (dipeptides), **106** (tripeptide) and **54** and **73** (tetrapeptides); these studies used both ruthenium catalysts **2** and **3**.[55,60] RCM has also been used with cyclic polypeptide substrates, most notably that of Clark and Ghadiri.[54] In their study, two molecules of a cyclic octapeptide self-assembled, held together by hydrogen bonds in such a conformation that the metathesis catalyst **2** was able to join the rings covalently to give polycyclic peptide **107**. Sadly the ring closing reaction was not stereoselective, producing all possible *E*/*Z* isomeric combinations; the product was characterised following alkene hydrogenation.

RCM has also been applied to large non-peptide molecules. McKervey and Pitarch have explored the scope and limitations of ruthenium catalyst **3** as applied to substituted calixarenes.[87] They found that a rather long spacer was needed between calixarene and alkene for RCM to take place: thus for example diene **108** ($n = 2$) cyclised readily, whereas diene **108** ($n = 1$) formed only cyclic dimers (**Scheme 38**). Two groups have considered metathesis of polymer-bound substrates. Blechert and co-workers have shown that both ruthenium-based catalysts **2** and **3** can metathesise polymer-bound substrates such as **109** efficiently.[88] In this case the substrates were bound to the polymer through an ether link. An imaginative approach used by van Maarseveen *et al.* was to bind the substrate to the polymer by an olefin link, and use ruthenium benzylidene **3** to cyclise the substrate and cleave it from the resin in one reaction.[89] Thus

Table 2 References for compatability of catalysts with various developing ring systems

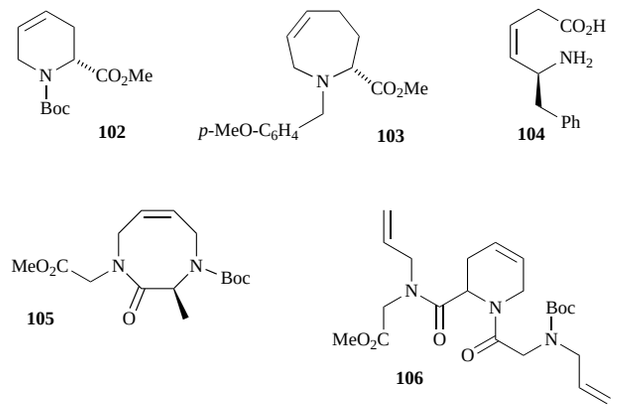
	Catalyst **1**		Catalyst **2**		Catalyst **3**		Other catalysts[a]	
Ring system	Success	Failure	Success	Failure	Success	Failure	Success	Failure
Monocycles: 5-Ring	Grubbs[6,27,28,31,32,90] Forbes[30] Wagener[29,39,43] Sita[34] Lee[40] Blechert[41] Gibson[8,9] Armstrong[1,42]	Grubbs[28] Forbes[30] Wagener[39]	Armstrong[1,42] Lee[40] Mori[53] Grubbs[12,50,68,69] Blechert[56,57,58,88]	Lee[40] Armstrong[42] Grubbs[55,60]	Blechert[41,57] Crimmins[70] Grubbs[71] Undheim[78]	Whitby[73]	**5**, Grubbs[6,82] Cr, Mori[7] W/Si, Bespalova[18] W/Pb, Nugent[22] Basset[25] **4**, Basset[23,24,25,26]	**5**, Grubbs[82] W/Pb, Nugent[22] Basset[25] W, Wagener[29] **4**, Basset[24]
6-Ring	Lee[40] Blechert[41] Grubbs[27,28,31,32]	Grubbs[28] Lee[40] Blechert[41]	Lee[40] Mori[53] Grubbs[50,55,60] Hoveyda[52] Guibé[59] Blechert[58,88]	Lee[40] Mori[53]	Blechert[41,88] Grubbs[71] Rutjes[72]	Grubbs[71] Blechert[41]	**5**, Grubbs[82] Re, Blechert[19] W/Pb, Nugent[22]	W/Pb, Nugent[22]
7-Ring	Grubbs[27,28] Forbes[30]	Forbes[30] Maier[35] Wagener[43]	Maier[35] Grubbs[50,55,60] Mori[53] Hoveyda[86]	Grubbs[60]	Barrett[44] Rutjes[72] van Maarseveen[89]		Re, Blechert[19] W, Grubbs[69]	
8-Ring		Forbes[30] Wagener[43]	Grubbs[51,55,60] Hoveyda[86]	Grubbs[51,60] Hoveyda[86]		Rutjes[72]		W/Pb, Nugent[22]
9-Ring		Wagener[43]		Grubbs[60]				
11-Ring		Forbes[30] Wagener[43]		Grubbs[60]				
12-Ring					Grubbs[60]			W/Pb, Nugent[22]
14-Ring	Hoveyda[37,38]		Fürstner[17]	Hoveyda[37]	Grubbs[60]			
16-Ring	Danishefsky[36]		Fürstner[17]		Danishefsky[36,74] Nicolaou[75,76,77]		Re, Blechert[19] W/Sn, Villemin[16]	
17-Ring							Re/Sn, Mol[15]	W/Ti, Tsuji[13] W/Sn, Tsuji[13]
21-Ring			Fürstner[17]				W/Ti, Tsuji[13,14]	
Other large monocycles							W/Sn, 15-ring, Villemin[16] W/Ti, 19-ring, Tsuji[13,14]	
Fused bicycles:[b]								
[5.2.0]	Barrett[44,48]				Barrett[48]			
[3.3.0]	Martin[46,47]			Blechert[56]				
[4.3.0]	Grubbs[32,69] Blechert[41] Martin[46,47] (t) Blechert[49]	Armstrong[42] Grubbs[69]	Blechert[58] Pandit[66] Grubbs[68,69]	Grubbs[69] (t) Blechert[49]	Blechert[41] Dyatkin[80]		W, Grubbs[69]	W, Grubbs[69]
[5.3.0]	Martin[46,47]		Blechert[20] Mori[67] Grubbs[68,69] (c) Blechert[20]		Mori[67]		Re, (c) Blechert[20] (t) Blechert[19,20]	Re, Blechert[20] (c) Blechert[20]
[6.3.0]	Martin[46,47]				Winkler[79]			
[12.3.0]			Grubbs[55,60]	Grubbs[55]	Grubbs[60]			
[4.4.0]	Martin[46,47]		Grubbs[68,69]					
[5.4.0]	Martin[46,47]		Grubbs[68,69]					
[6.4.0]	Martin[45,46,47]		Grubbs[51] (c) Grubbs[51] (t) Grubbs[51]					
[10.4.0]			Fürstner[62]				W/Pb, Descotes[21]	
Other fused bicycles	[6.2.0], Barrett[44] [7.2.0], Barrett[44]	[10.3.0], Martin[46,47]		[9.4.0], Grubbs[60]	[4.2.0], Barrett[48]			
Spirocycles					6+5, 6+6, 6+7, Undheim[78]	6+8, Undheim[78]		
Bridged bicycles	[9.4.1], Forbes[30]	[9.8.1], Forbes[30]					W/Pb, [11.3.1], Descotes[21]	
Fused polycycles	Martin[47,85] Grubbs[32]				Grubbs[71]			
Bridged polycycles			Ghadiri[54] Pandit[63,64,65]		Grubbs[60] Fuchs[81] McKervey[87]	Fuchs[81] McKervey[87]		

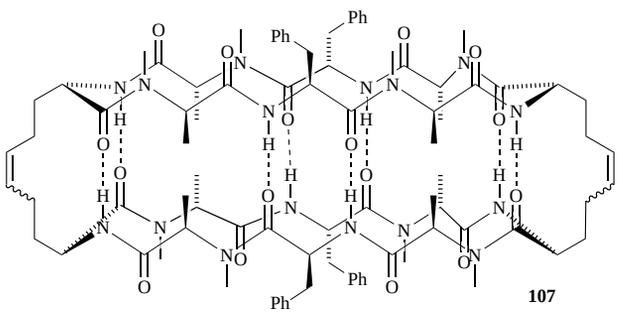
[a] See Table 1. [b] Ring junction stereochemistry is indicated: (c) means *cis*, (t) means *trans*, no indication means amide or double bond at ring junction.

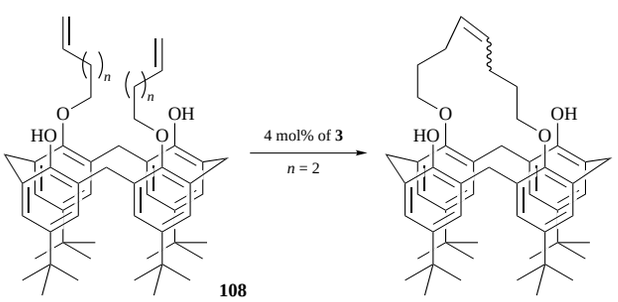
resin-bound amide **110** was released from the resin as cyclic amide **111**. As the authors point out, this reaction leaves the catalyst covalently bound to the resin, and an equivalent of ethylene or *n*-octene must be added to release the catalyst by cross-metathesis as shown. One-step cleavage from a solid support and cyclisation was used by Nicolaou in a synthesis of epothilone A, but there is no mention of a simple alkene being added to the reaction mixture, and the isolated yield of cyclic alkenes (53%) was lower than the amount of catalyst added (75 mol%), so this reaction was probably not truly catalytic.[77]

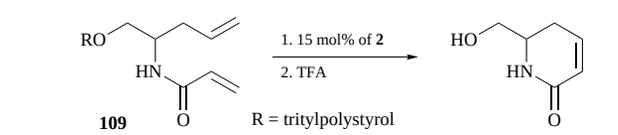
Perhaps the closest combination of small-molecule RCM and polymer chemistry has been achieved, fittingly, by Grubbs. The catalyst used was $(Cy_3P)_2Cl_2Ru{=}CH_2$ (*cf.* section 1.2). When 1,2-polybutadiene **112** was treated with this catalyst, adjacent side-chains were coupled to give the new polymer **113** (**Scheme 39**).[90] Monitoring the experiment by ^{1}H NMR spectroscopy showed that initial reaction, as might be expected, is regio-random, but this is followed by a second step in which the catalyst apparently moves down the partially cyclised polymer converting the random arrangement of rings to a regular pattern in which no terminal alkene side-chains remain: all have been cyclised.

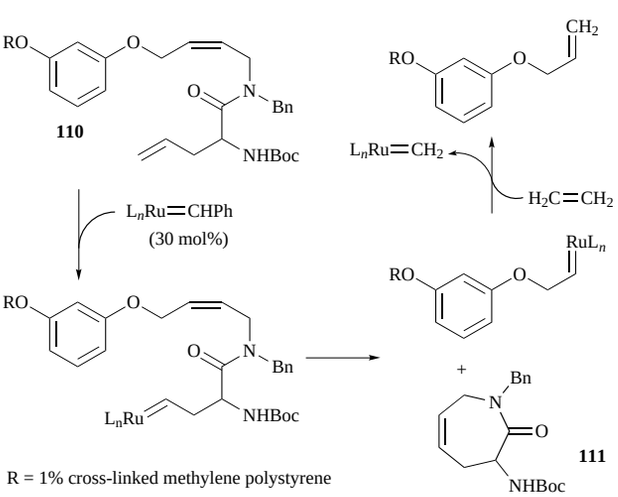
The applications described in section 5 demonstrate that ring closing metathesis has come of age as a synthetic technique. It is no longer a novelty, to be included in the title of every





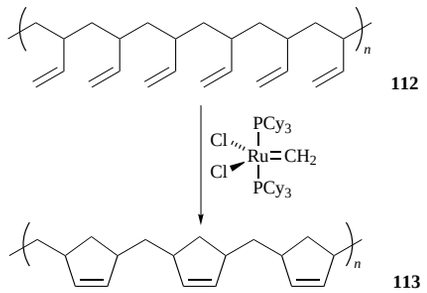






Scheme 38

paper: it is a synthetic tool available to every practising organic synthetic chemist.



Scheme 39

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