Sequential Metathesis in Oxa- and Azanorbornene Derivatives

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Ring-opening metathesis (ROM), when applied to the synthesis of bicyclic alkenes, is the basis of ring-opening-metathesis polymerisation (ROMP). This polymerisation reaction can be suppressed in the presence of a second open-chain olefin thus combining the ROM with an intermolecular cross metathesis (CM). In conveniently substituted bicyclic derivatives a third metathetical reaction — ring closing metathesis (RCM) — can be achieved, giving new substituted bicyclic systems. In this account the results of these tandem metathetical reactions performed on oxa- and azabicyclic norbornenic derivatives are highlighted.

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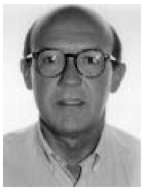

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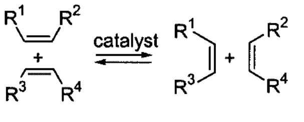
1. Introduction

1.1. Metathesis Reactions from a Bird's-Eye View

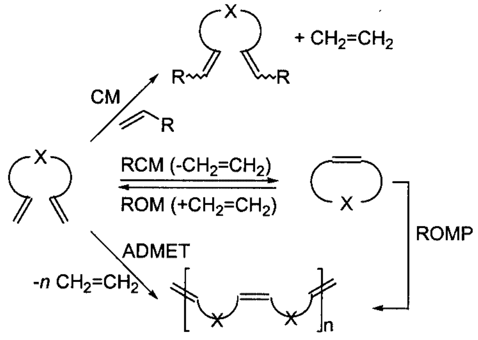
Alkene metathesis, a reaction where the carbon-carbon double bond of an alkene is broken and reformed in the presence of an organometallic catalyst (Scheme 1), is today firmly established as a valuable synthetic tool in organic chemistry.[1]



Scheme 1

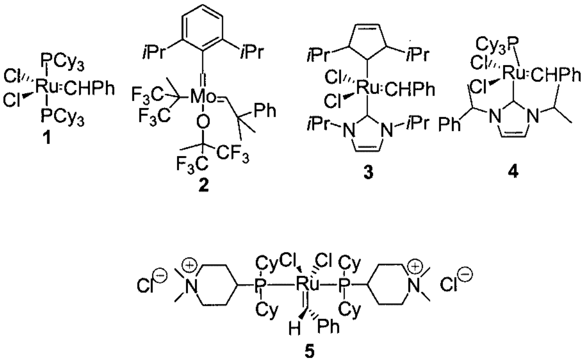
In recent years a number of reviews on this topic have been published focussed on the uses of this reaction in organic synthesis[2] and polymer chemistry.[3]

Metathesis reactions have a variety of applications (Scheme 2), including the classical variants ring-opening-metathesis polymerisation (ROMP), ring-closing metathesis (RCM), acyclic diene metathesis polymerisation (ADMET), ring-opening metathesis (ROM) and cross-metathesis (CM).



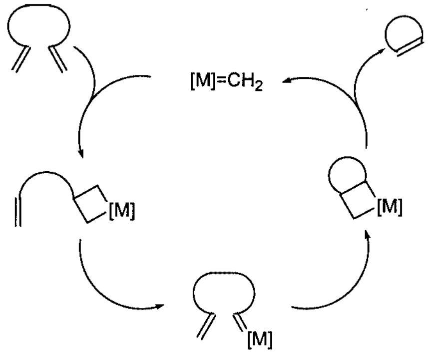
Scheme 2

Many applications of the metathesis process have become possible due to the development of new, well-defined catalysts that are easy to handle and tolerant to most functional groups.[4] Among others, Grubbs'[5] and Schrock's[6] carbene complexes, **1** and **2** respectively (Scheme 3), are the most popular, and are both commercially available. Other catalysts such as imidazolinylidenes **3**[7] and **4**[7b,8] show higher reactivities and, for instance, **4** catalyzes the formation of tetrasubstituted double bonds. Interesting, water-soluble catalysts such as **5**[9] have been also reported.



Scheme 3

From a mechanistic point of view, the commonly accepted sequence of events in a metathesis reaction consists of a formal [2+2]-cycloaddition-cycloreversion involving metallacyclobutane intermediates, with all individual steps of the catalytic cycle being reversible processes (Chauvin mechanism; Scheme 4).[10,11]

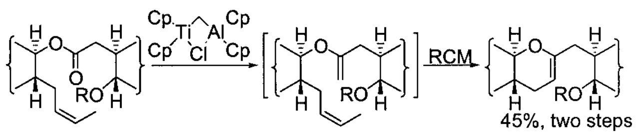


Scheme 4

Because of the reversible character of the reaction it is necessary to shift the equilibrium in order to make the metathesis reaction useful in synthetic terms. In several cases the forward process is entropically driven because one of the molecules produced in the reaction is volatile (ethylene, Scheme 2). Also, when strained cycloalkenes are substrates for metathesis reactions, the release of ring strain constitutes the appropriate driving force for ROM and ROMP.[12] This is the case for the compounds considered in this account.

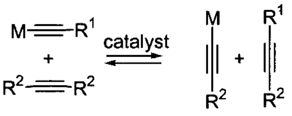
The sequential transformation of the alkenes obtained in metathesis reactions (domino process) is an attractive application of this synthetic method. In this way, domino reactions using different metathetical reactions provide a tool for the synthesis of complex structures in a single catalytic step. Several cases of these domino reactions applied to bicyclic alkenes will be highlighted in the next sections.

Tandem metathesis coupled with other reactions of alkenes such as Diels–Alder[13] or Heck[14] reactions is a fascinating and largely unexplored synthetic field. In this context the fact that Tebbe's reagent is also a catalyst for alkene metathesis allows the transformation of an alkene ester into an acyclic enol ether in a nice example of a tandem reaction in which the RCM is the final step[15] (Scheme 5).



Scheme 5

Finally, in this brief introduction a comment on the metathesis of alkynes should be made.[16] This reaction (Scheme 6) has been achieved using Schrock's alkylidene complexes of several transition metals[17] or by combination of $Mo(CO)_6$ and phenol additives.[18]

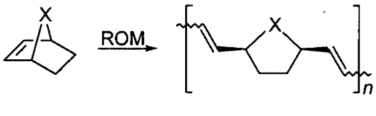


Scheme 6

The application of this reaction to the preparation of polymers,[19] cycloisomerization and CM of acetylene derivatives[20] and synthesis of large rings by RCM[21] have been reported, amongst others.[22]

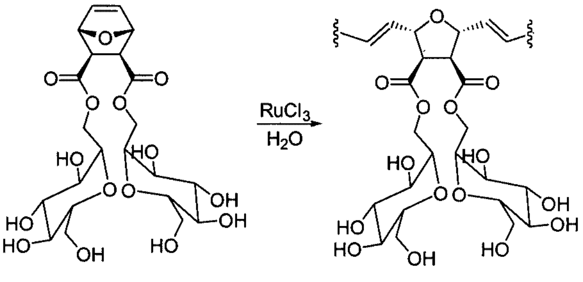
1.2. Metathesis Reactions of [2.2.1]Bicyclic Alkenes. Background

Among the different types of substrates prone to metathesis, the case of bicyclic alkenes deserves special attention for at least two reasons: a) because the strain release experienced in going from reactants to products constitutes an appropriate driving force for ROM and ROMP, and b) because the chiral information contained in the ring junction positions of the starting bicyclic compounds is conserved throughout the process. This allows for the synthesis of cyclic compounds with a well-defined relative stereochemistry of the two resulting alkenyl side chains (Scheme 7).



Scheme 7

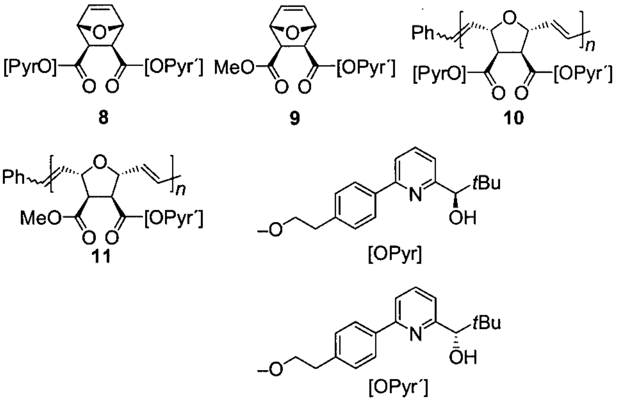
ROM applied to bicyclic alkenes forms the basis of the ROMP of these compounds. This reaction has been applied to norbornene derivatives in order to obtain biomimetic polymers based upon amino acid,[23] peptide,[24] antibiotic,[25] nucleic acid,[26] sulfonamide[27] or carbohydrate[28] subunits. For instance, Kiessling[29] et al. have shown that the ROMP of oxanorbornene derivative **6** can be used to create a polyvalent, carbohydrate-bearing polymer such as **7** that can block protein-initiated cell agglutination (Scheme 8).



6 **7**

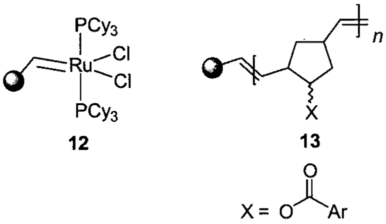
Scheme 8

ROMP has been applied to the synthesis of chiral catalytically active polymers useful in enantioselective reactions such as the addition of diethylzinc to benzaldehyde. For instance, starting from 7-oxanorbornene derivatives **8** and **9** the polymeric catalysts **10** and **11**, respectively, have been synthesised using **1** as catalyst[30] (Scheme 9).

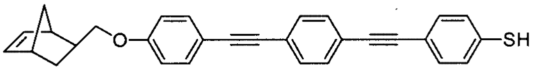


Scheme 9

The immobilized catalyst **12** has also been applied to initiate ROMP of norbornene derivatives[31] (Scheme 10) onto a polymer support giving resins **13** for use in combinatorial chemistry. In the same way, ROMP of norbornenic monomers **14** (Scheme 11) anchored on a gold surface has also been achieved.[32]



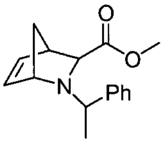
Scheme 10



14

Scheme 11

The ROMP of azabicyclic systems has also been considered in the case of methyl *N*-(1-phenylethyl)-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate (**15**)[33] (Scheme 12).



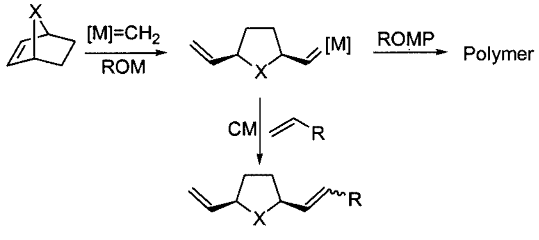
15

Scheme 12

An inorganic carrier based on alumina covered with methylaluminoxane (MAO) which had been crosslinked by various fluorinated diols has been used to immobilize molybdenum carbene complexes of the type [Mo(CH-*t*Bu)(NAr){OC(CH$_3$)$_2$CF$_3$}$_2$] and [Mo(CH-*t*Bu)(NAr)(OTf)$_2$(dme)] (Ar = 2,6-C$_6$H$_3$-*i*Pr$_2$). Polymerisation of **15** dissolved in chlorobenzene gave a yield of *cis*-vinylene of 95%.[34] However, immobilized complexes produced an all-*trans* polymer. This extremely high stereoregularity was not only assumed to be the result of steric hindrance but also of an interaction between the monomer containing nitrogen and the carrier with MAO.

1.3. Tandem Metathesis Reactions of [2.2.1]Bicyclic Alkenes

The ROMP reaction of bicyclic alkenes can be suppressed in the presence of a second open-chain olefin. In this case the final product is formed from the combination of a ROM with an intermolecular CM (Scheme 13). This method is another useful variation of olefin metathesis.



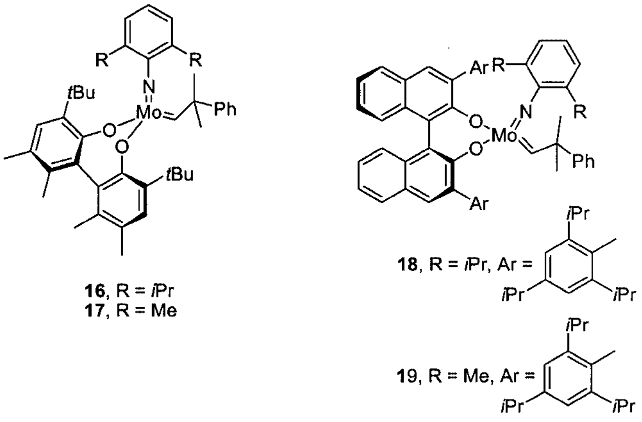
Scheme 13

The major problem of this synthetic protocol is the concurrent self-metathesis of the olefin to give the ROMP product. This is particularly important in the case of highly reactive alkenes such as norbornene derivatives. In these cases the use of a dilute solution using an excess of acyclic counterpart,[35] reduction of the reactivity of the cyclic alkene by steric protection[36] or the application of specific catalysts[37] are useful solutions.

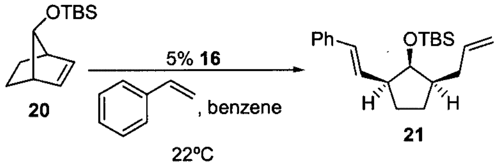
In this context the design and synthesis of optically pure catalysts for olefin metathesis opens the possibility of achieving this sequence in order to obtain chiral, nonracemic products. After the work of Hoveyda et al.[38] with Mo catalysts such as **16−19** (Scheme 14) the sequence-asymmetric ROM-CM (AROM-CM) constitutes an even more important synthetic tool with a wide range of future applications.

For instance, the reaction of *meso*-**20** with 5 mol % of **16** and two equivalents of styrene gives cyclopentane **21** in 57% isolated yield, more than 98% *trans*-olefin selectivity and more than 98% *ee*. (Scheme 15)

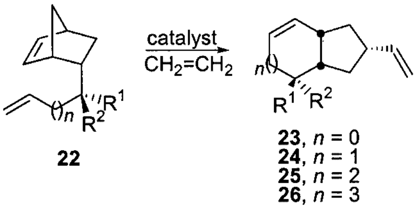
The combination ROM-RCM-CM has been used by Blechert[39] in the case of suitable substituted norbornene derivatives. Thus, compound **22** (Scheme 16) treated with [Ru] **1** or [Mo] **2** catalyst in the presence of ethylene as cross metathesis partner affords the bicyclic systems **23−26**. In these cases different sequences of the metathesis reactions have also been considered.



Scheme 14



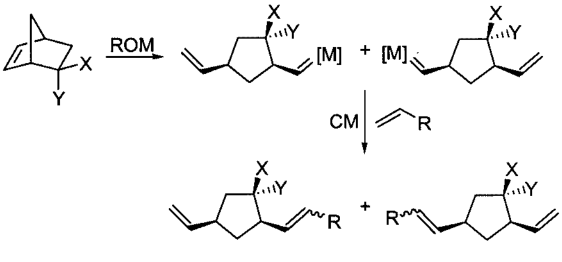
Scheme 15



Scheme 16

1.4. The Question of the Regioselectivity

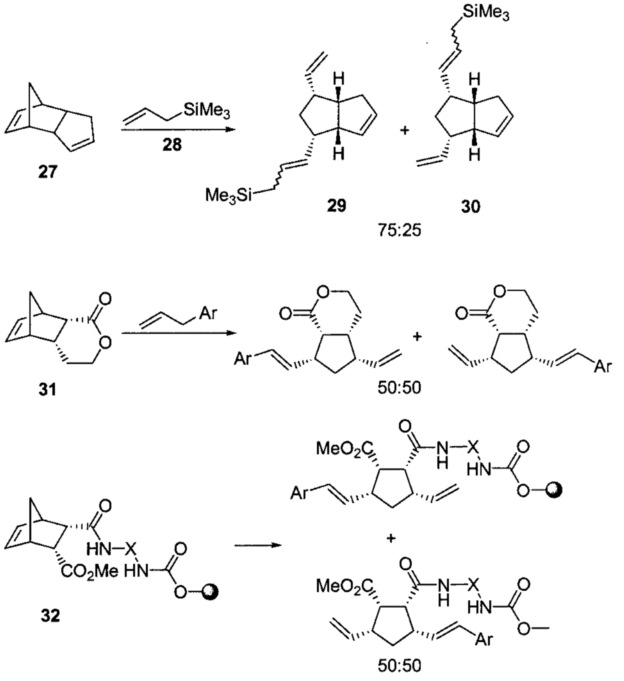
The sequence ROM-CM of a symmetric bicyclic alkene with a terminal olefin produces only one product. However, two regioisomeric cyclic products should be expected from the reaction of an unsymmetrical bicyclic alkene[40] (Scheme 17).



Scheme 17

In the case of substituted norbornenes different results have been obtained depending on the substitution pattern in the bicyclic compound. For instance, in the case of the ROM-CM of compound **27** with allyltrimethylsilane (**28**) in the presence of Grubbs' ruthenium catalyst **1**, a 75:25 mixture of compounds **29** and **30** was obtained[35b]

(Scheme 18). In contrast, the ROM-CM of compounds **31** or the resin-bound norbornene **32** in the presence of styrene produced the corresponding regioisomers as a 50:50 mixture[41] (Scheme 18).18



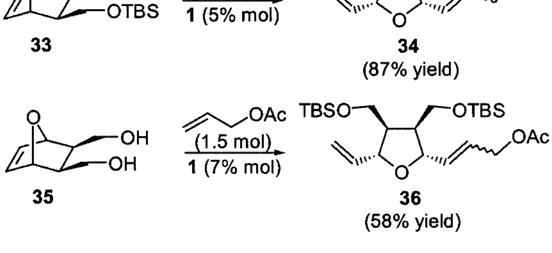
Scheme 18

Therefore, control of the regioselectivity is crucial in the development of synthetically useful intermolecular metatheses and some aspects of this problem will be discussed in the case of the sequence ROM-CM achieved on 2-substituted 7-oxabicyclo[2.2.1]heptene derivatives.

2. Tandem Metathesis Reactions in 7-Oxabicyclo[2.2.1]heptene Derivatives

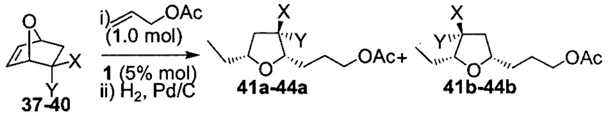
2.1. Sequence ROM-CM. Regiochemical Considerations

The truncation of the ring-opening-metathesis polymerisation of 7-oxanorborn-5-enes by a cross metathesis with a second open-chain alkene was pioneered by Blechert et al.[35b] (Scheme 19). These authors carried out the ring-opening metathesis of 7-oxanorbornene derivatives **33** and **35** with Grubbs' ruthenium catalyst **1** in the presence of allyl acetate or 3-butenenitrile to afford the tetrasubstituted tetrahydrofuran derivatives **34** and **36**.



Scheme 19

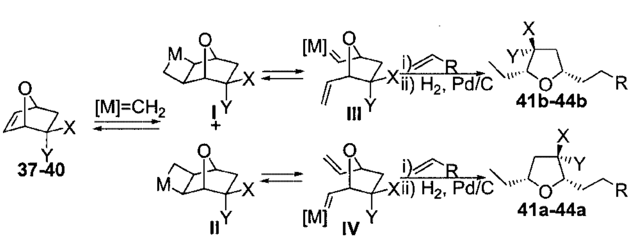
As we have previously pointed out, regiochemical issues arise when the starting 7-oxanorbornenes are not symmetrically substituted with respect to the alkene moiety. The ROM-RCM of differently 2-substituted 7-oxanorbornenes afforded different results depending on the substituent at C-2 (Scheme 20).[42] In this way, the reaction of ketone **37** with allyl acetate took place with no regioselectivity at all (**41a**:**41b** = 50:50). This was also the case with the alcohol **38** (**42a**:**42b** = 50:50). On the other hand, the reaction of the acyloxy derivatives **39** and **40** gave rise to the majority formation of the corresponding tetrahydrofurans **43b** (**43a**:**43b** = 19:81) and **44b** (**44a**:**44b** = 23:77). In the RCM-CM of **40**, the combination of cross-, ring-opening- and ring-closing metathesis was not observed (domino metathesis, vide infra). It is worth mentioning that, in the case of compounds **43** and **44**, the larger alkenyl group of the main products is located on the less-hindered side of the tetrahydrofuran ring.



37, 41, X, Y = C=O, (75%, **41a:41b** = 50:50)
38, 42, X = H, Y = OH, (80%, **42a:42b** = 50:50)
39, 43, X = H, Y = OAc, (75%, **43a:43b** = 19:81)
40, 44, X = H, Y = OCOCH=CH$_2$, (75%, **44a:44b** = 23:77)

Scheme 20

Thus, according to the mechanism proposed by Chauvin et al.,[10] cycloaddition of the propagating carbene species CH$_2$=[M] {[M] = RuCl$_2$(PCy$_3$)$_2$} to the C=C bond of the bicyclic alkene, which is favoured due to strain release, gives rise to a fused metallacyclobutane (intermediates **I** and **II**, Scheme 21). The cycloreversion of the metallacyclobutane leads to ring opening, with formation of a new carbene species (intermediates **III** and **IV**). Cycloaddition of the latter to the acyclic alkene affords the cross-metathesis products, regenerating the active catalyst.



Scheme 21

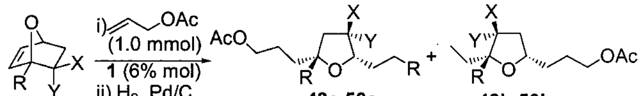
Two different considerations may be applicable to justify the observed regioselectivity of a given ROM-CM process: First, the preferred orientation in the reaction could stem from steric effects in the cycloaddition of the CH$_2$=[M] carbene to the bicyclic alkene (ROM step). Due to the steric requirements of the bicyclic moiety, cycloaddition should take place from the *exo* face.[43] Now, steric hindrance by substituents X and Y and the ligands of the metal moiety may lead to the preferential formation of carbene **I** over **II**. However, although the electronic bias of the C=C bond in the starting bicycles seems not to play a decisive role, complexation effects may also influence the regiochemistry of the cycloaddition.

Second, the cross-metathesis step may be dependent on steric hindrance or complexation effects which affect the reactivity of carbenes **III** and **IV**. Taking into account the steric effect of the side chain, intermediate **IV**, with the carbene centre in the more encumbered position, should be less reactive than **III**.

Both these arguments account for the obtention of a product with the larger alkenyl group (RCH=CH) located on the less-hindered α-carbon of the final tetrahydrofuran ring, thus favouring the formation of compounds **43b−44b**, over their regioisomers **43a−44a**.

Similar effects in the outcome of ROM-CM reactions have also been observed in the cyclobutane series, where subtle differences in the stereochemistry of the starting materials give a quite different distribution of reaction products.[44]

In agreement with the previous considerations on the different steric interactions which arise throughout the ROM-CM process, it was expected that 7-oxanorbornenes substituted both at C-1 and C-2 should show a better regioselectivity than their C-1 unsubstituted counterparts (Scheme 22).



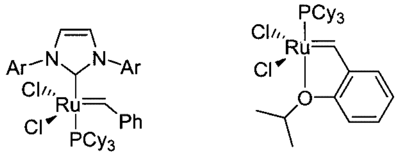
45-47 **48a-50a** **48b-50b**

45, X, Y = C=O, R = CH_3 (60%, **48a**:**48b** = 20:80)
46, X, Y = OCH_2CH_2O, R = H (70%, **49a**:**49b** = 21:79)
47, X, Y = OCH_2CH_2O, R = CH_3 (15%, **50a**:**50b** = 0:100)

Scheme 22

This proved to be the case, as treatment of compound **45**[45] with allyl acetate in the presence of **1** (6mol %) gave rise to compounds **48** with good regioselectivity in favour of **48b** (60%, **48a**:**48b** = 20:80). This result should be compared to that of compound **37** (Scheme 20), which gave rise to the corresponding tetrahydrofurans **41** with no regioselectivity at all. Similarly, the ROM-CM reaction of the dioxolane **47** (Scheme 22) took place in a fully regioselective fashion (15%, **50a**:**50b** = 0:100), although with poor yield. This result can be compared with the ROM-CM of **46** (70%, **49a**:**49b** = 21:79).

As we have previously indicated, the use of modified Grubbs' ruthenium catalysts in metathesis-based processes is gaining popularity.[46] The replacement of one PR_3 of the original catalyst **1** by an *N*-heterocyclic carbene (NHC) renders new catalytically active species which show an enhanced reactivity with respect to the previous ones, thus allowing for transformations which were not possible with the original catalyst. However, in the case of 2-substituted 7-oxanorbornenenes, the use of **51** (Imes Ru catalyst; Scheme 23) promoted an increase in polymerisation products, therefore diminishing the yield in ROM-CM products.[45] Furthermore, from a regiochemical point of view, the same regiochemistry was observed when **51** was used as the catalyst as when Grubbs' catalyst **1** was used. This was also the case when Hoveyda's second generation alkoxy-substituted carbene **52** was tested,[47] although in this case no polymerisation occured, and the starting materials were recovered in high yields even after prolonged reaction times.



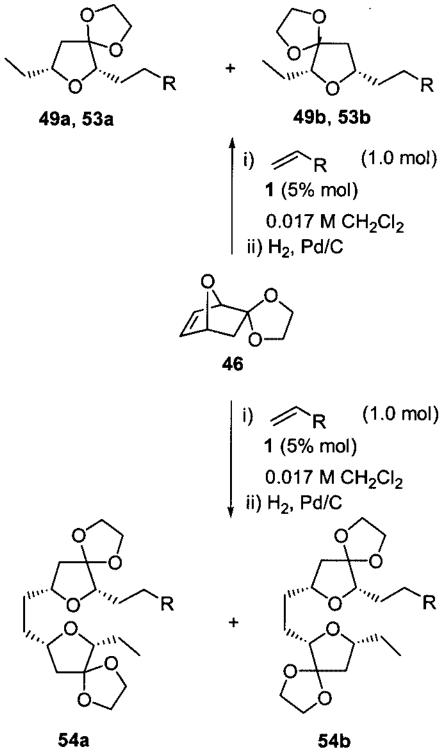
51 **52**

Ar = 2,4,6-trimethylphenyl

Scheme 23

2.2. Sequence Ring Opening Dimerization (ROD)-CM

The reaction of dioxolane **46** (Scheme 24) deserves special consideration. The ROM-CM process with allyl acetate as the acyclic alkene and Grubbs' catalyst **1** took place with a good regioselectivity in favour of the corresponding tetrahydrofuran **49b** (**49a**:**49b** = 21:79).[42] This was also the case when 3-phenyl-1-propene was used as the cross-coupling counterpart (**53a**:**53b** = 20:80).



49, R = CH_2OAc (80%, **49a**:**49b** = 21:79)
53, R = CH_2OBn (70%, **53a**:**53b** = 20:80)
54, R = CH_2OAc (60%, **54a**:**54b** = 94:6)

Scheme 24

As expected, when the molar concentration of reactants was progressively increased, the yield of ROM-CM products dropped in favour of polymerisation products. However, optimisation of the reaction conditions allowed for an effective truncation of the polymerisation process, with formation of dimers **54** (Scheme 24).[48] Therefore, this procedure allows for the linking of two tetrahydrofuran moieties by an ethylene bridge, in a completely stereoselective fashion. It is worth mentioning that only two out of the four possible dimers were observed, and that the selectivity in favour of **54a** was fairly high.

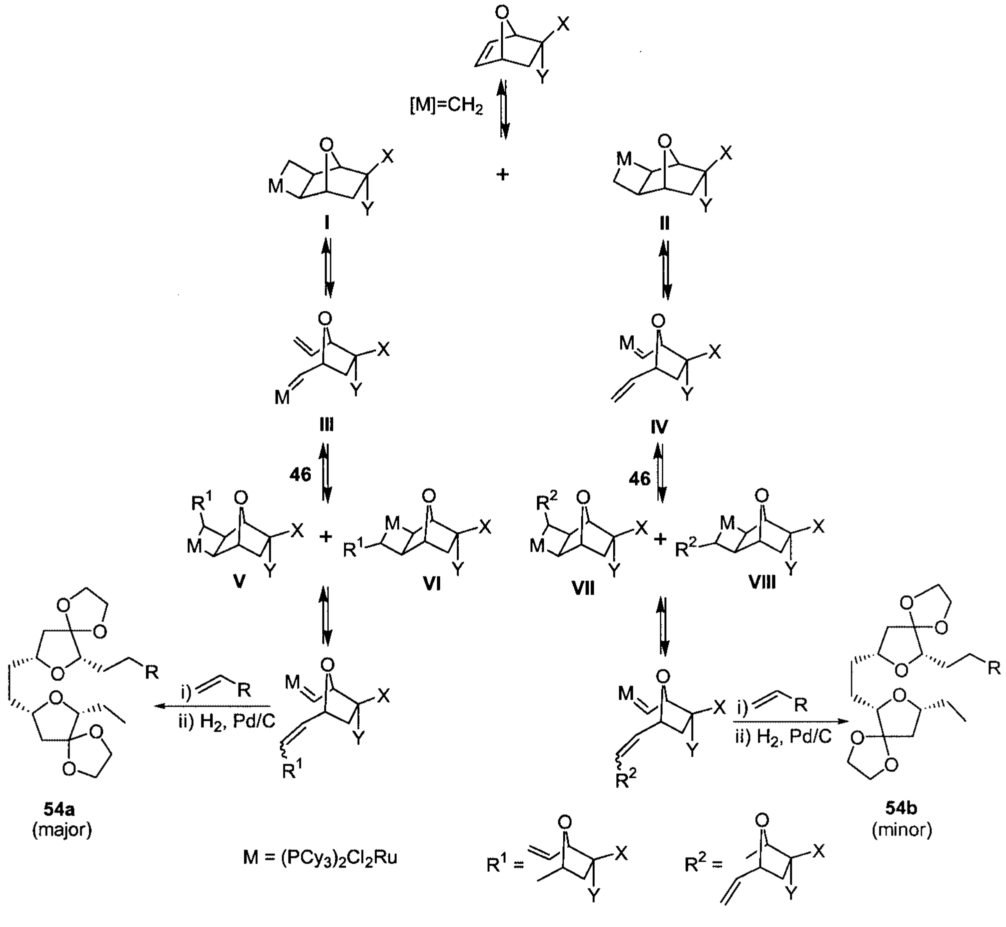
To understand the regiochemistry of the ROD-CM in 2-substituted 7-oxanorbornenes such as **46**, the postulated reaction course for the alkene metathesis reaction must once again be considered (Scheme 25).

In these cases the cycloaddition of carbenes **III** and **IV** to the acyclic alkene could compete with their cross-coupling with another molecule of the starting 7-oxanorbornene. In this case, the steric interaction between the substituents at C-2 of the bicyclic ring and the bulky tetrahydrofuran unit (R^1 or R^2) introduced in the first step becomes the dominant steric effect, and may overwhelm the steric interaction between the substituents X, Y at C-2 with the metal moiety. In such a situation, formation of **54a** from intermediate **VI**, and formation of **54b** from intermediate **VIII**, would be expected. This result highlights the delicate balance of steric interactions of the different carbene species in the outcome of the ring-opening and cross-coupling metathesis

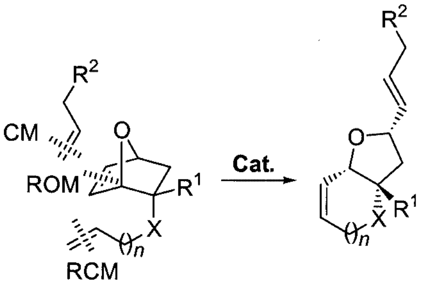
2.3. Sequence ROM-CM-RCM (Domino)

As previously stated in the general introduction section, ring-closing metathesis has been extensively used for the preparation of cyclic compounds from acyclic precursors. The combination of ring-opening (ROM), ring closing (RCM) and cross (CM) metathesis into an overall process known as *domino metathesis*, has allowed the construction of new cyclic compounds starting from bicycles in a stereocontrolled way.[39] The application of this methodology to 2-*endo-substituted* 7-oxanorbornenes constitutes a useful process for the assembly of fused tetrahydrofuran rings with defined stereochemistry (Scheme 26). This procedure is suitable for the introduction of a quaternary stereogenic centre at the bridgehead position C-5 of the resulting new bicycles.

It was observed that, for the obtention of high levels of regioselectivity in the domino metathesis process, the nature of the lateral unsaturated chain is of crucial significance. Thus, reaction of the allyl ethers **55** with **1** and allyl acetate gave rise, after hydrogenation, to a mixture of 2,6-dioxabicyclo[4.3.0]nonanes **58** and **59** as 80:20 mixtures (Scheme 27).[49] These results are in parallel with the regio-

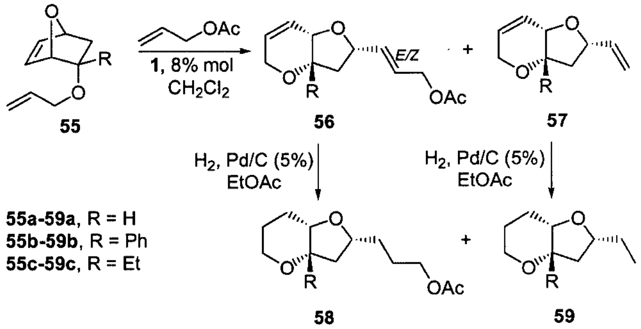


Scheme 25



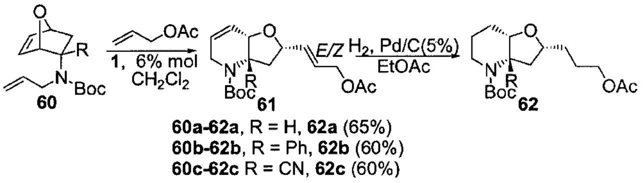
Scheme 26

chemistry observed in the intermolecular ROM-CM reactions of 2-substituted 7-oxanorbornenes (vide supra).



Scheme 27

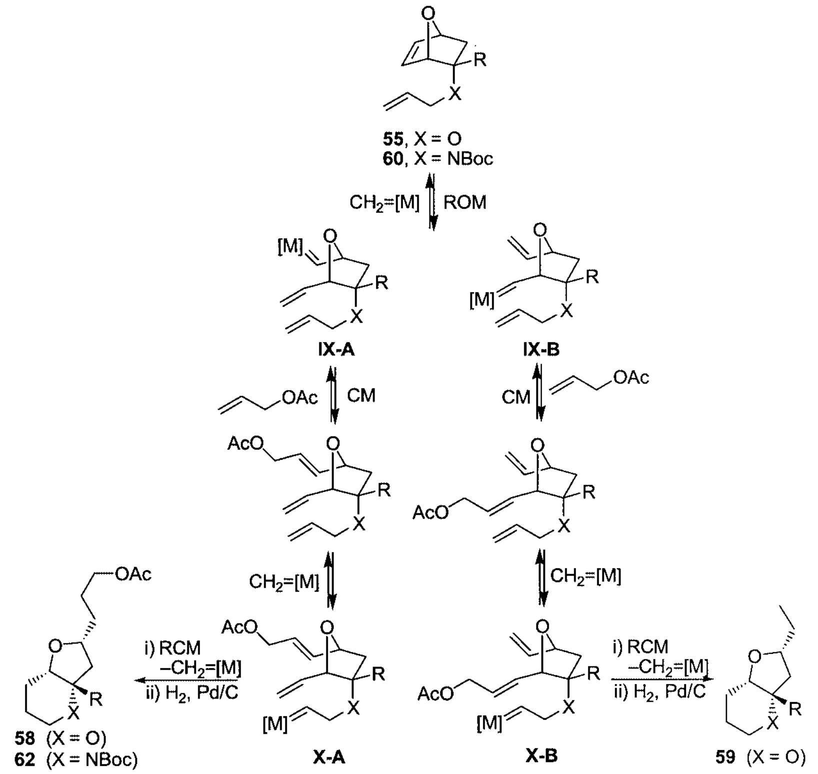
In contrast, when the same reaction was carried out starting from the Boc-protected allylamines **60**, the corresponding oxazabicycles **61** (and **62** after hydrogenation) were exclusively formed as single regioisomers (Scheme 28).[50]



Scheme 28

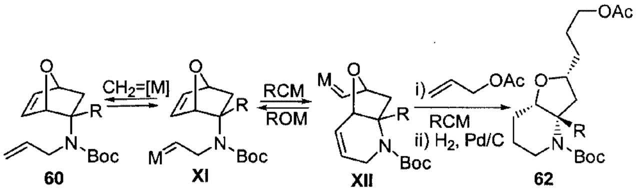
In keeping with the interpretation of the regiochemical results given for the intermolecular ROM-CM reaction of 2-substituted 7-oxanorbornenes, the results of the intramolecular ROM-CM-RCM process can be understood by an initial reaction of the carbene-propagating species with the endocyclic C=C bond of the starting bicycle in a ROM-CM reaction (Scheme 29). Then, RCM of the intermediate tetrahydrofurans should render the final domino metathesis products in a ratio related to that of the ROM-CM regioisomers.

This argument accounts for the formation of compounds **58** and **59** as 80:20 mixtures. The formation of compounds **62** as single isomers can be understood, at first glance, as a consequence of the enhanced steric bulk of the Boc moiety. However, a second argument may apply, which is based on the well-known chelation effect of Ru by adjacent carbonyl



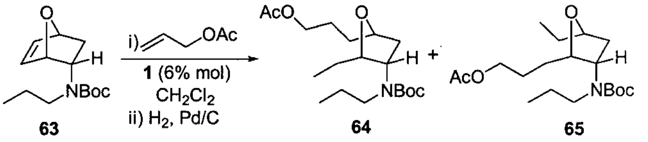
Scheme 29

groups[51] (Scheme 30). Coordination of Ru by the carbamate moiety of compounds **60** may trigger the initial carbometallation step at the terminal C=C bond of the lateral chain instead of the endocyclic C=C bond. Then, RCM followed by CM should afford exclusively compounds **62**.



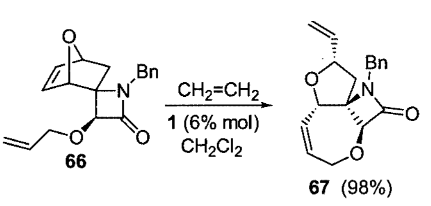
Scheme 30

As a matter of fact, when the propylamine **63** was reacedt with allyl acetate using **1** as catalyst, compounds **64** and **65** were obtained with 80:20 regioselectivity (Scheme 31). A comparison of this result with that obtained in the domino metathesis reaction of compounds **60** confirmed that steric arguments are not the only parameters that control the regioselectivity of a ROM-CM or a domino metathesis reaction.



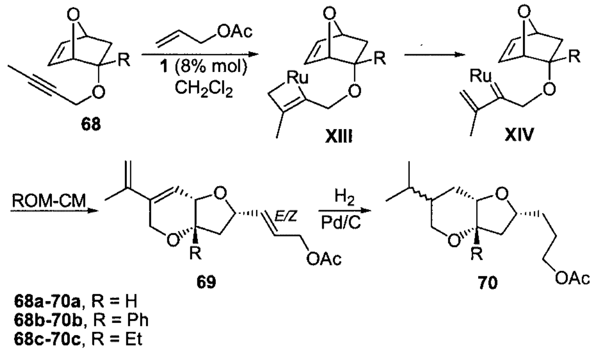
Scheme 31

The directing effect exhibited by the N-C=O moiety has been extended to the synthesis of tricyclic β-lactams.[45] The domino metathesis of compound **66** with ethylene using **1** (6 mol %) as catalyst afforded only compound **67** (Scheme 32).



Scheme 32

The directing effect of the lateral chain has also been exploited in the domino metathesis of the propargyl ethers **68** (Scheme 33).[45] In this case, the formation of a vinyl carbene from the cyclometallation of the triple bond in **68** followed by ring opening to intermediate **XIV** was the dominant process. The reaction afforded the bicycles **69** exclusively, which was then hydrogenated to **70**.



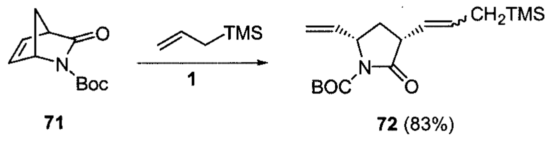
Scheme 33

Thus, these examples apparently show that the regioselectivity is maximal when the domino metathesis reaction is directed first to the double bond of the lateral chain, whereas the ROM-CM-RCM sequence starting from the C=C endocyclic bond affords the domino metathesis products with diminished regioselectivity.

3. Tandem Metathetical Reactions in 2-Azabicyclo[2.2.1]heptene Derivatives

3.1. Sequence ROM-CM

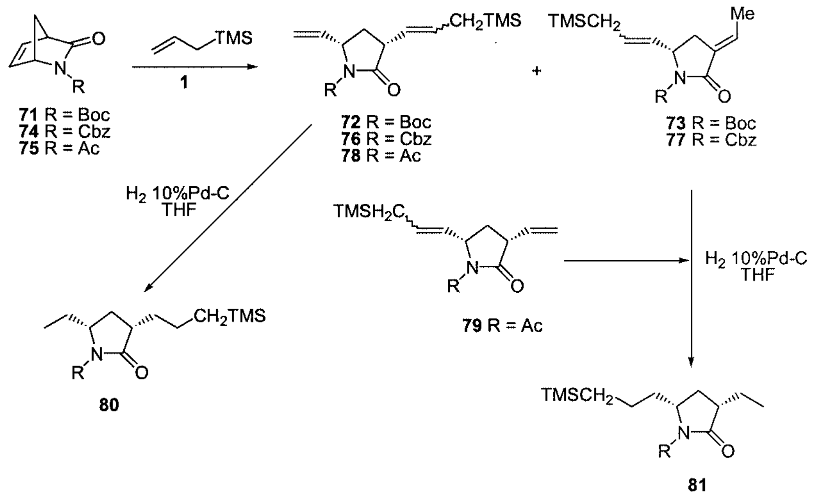
Surprisingly the metathesis of azabicyclic systems has received little attention despite its synthetic potential. The first example of a ruthenium-catalysed metathesis reaction of azabicyclic system came from the group of Blechert.[35b] This report disclosed that the ring-opening cross-metathesis reaction of *N*-Boc-2-azabicyclo[2.2.1]hept-5-en-3-one (**71**) with allyltrimethylsilane catalysed by Grubbs' catalyst **1** proceeds in a completely regioselective manner to give only one regioisomer **72** as an *E*/*Z* mixture (Scheme 34).



Scheme 34

This regioselectivity, according to the authors, is presumably due to steric effects in the formation of a metallacyclobutane, although complexation cannot be ruled out. Recently, Ishikura et al.,[52] have revisited the same reaction and found that, along with the 3,5-pyrrolidinones **72**, compound **73** (as an *E*/*Z* mixture) was also produced in a ratio of approximately 2.5:1, determined after hydrogenation of the reaction mixture to compounds **80** and **81** (Scheme 35).

Similarly, the treatment of derivatives **74** and **75**, possessing less-bulky protecting groups at the nitrogen, allowed the isolation of compounds **76** and **77** from **74**, and **78** and **79** from **75**. Catalytic hydrogenation of the reaction mixture afforded the two regioisomers **80** and **81** in ratios of approx-



Scheme 35

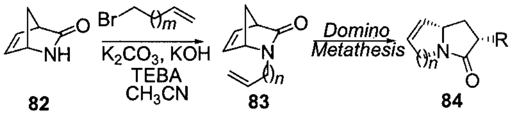
imately 1.2−1.5:1, respectively. This regioselectivity seems to be ascribable to a steric interaction between the N-substituents and the trimethylsilyl group of allyltrimethylsilane in the metallacyclobutane intermediate.

3.2. Sequence ROM-CM-RCM

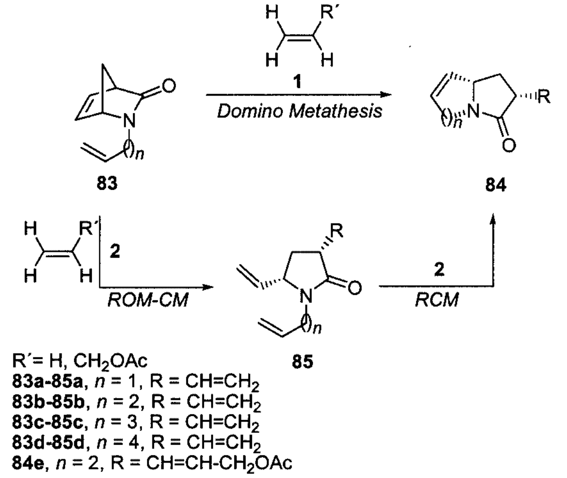
A new method[53] has been described for the enantioselective synthesis of the azabicyclic γ-lactams **84**, of different ring sizes, starting from (1*S*)-2-azanorborn-5-en-3-one (**82**) as a common precursor in a two step procedure: i) PTC N-alkylation of **82** in the presence of triethylbenzylammonium chloride (TEBA), and ii) domino metathesis (Scheme 36).

In the presence of Grubbs' ruthenium catalyst **1**, the reaction of compounds **83b,c** (Scheme 37) with ethylene afforded the expected azabicyclic γ-lactams **84b,c** (60% isolated yield) arising from a domino metathesis process.

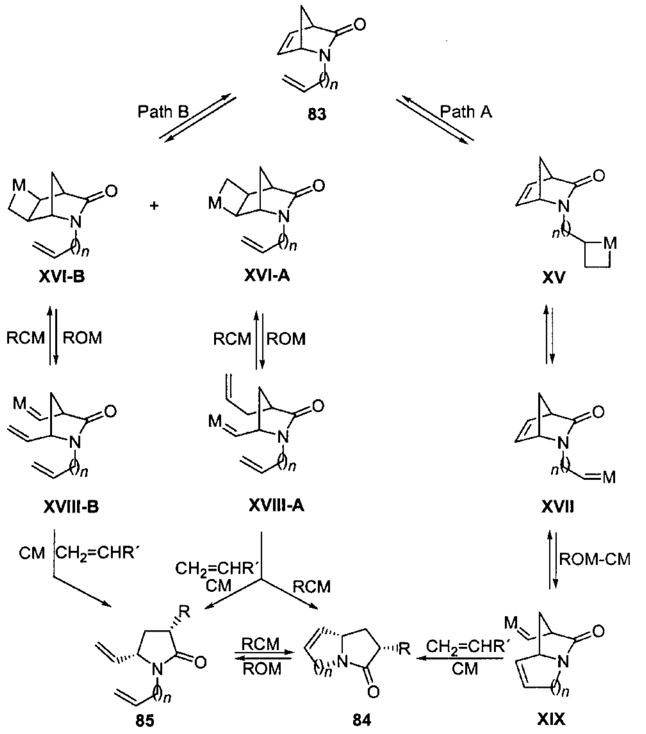
On the other hand, compounds **83a** and **83d** did not cyclize and the products of ring-opening cross-metathesis **85a** and **85d** were instead isolated. No significant improvements were noticed upon increasing the amount of, or changing, the catalyst. In a similar fashion, compound **83b** reacted with allyl acetate in the presence of **1** to afford compounds **84b** and **84e** in an approximate 1:1 ratio; with [Imes-Ru] as catalyst, the ratio changed to 1:2. However, the isolated



Scheme 36



Scheme 37



Scheme 38

products **85a,d** cyclize under ring-closing metathesis conditions with **1** giving rise to the expected domino metathesis products **84a,d** in 60% and 50% isolated yields, respectively. Taking into account these results the operation of two alternative equilibrating reaction pathways is proposed (Scheme 38).

First, initial metallacyclobutanation of the terminal alkene moiety of **83** may lead to intermediate **XV** (path A). Intramolecular ROM-CM of **XV** would lead to carbenes **XVII** and **XIX**, which would go on to form the domino metathesis products **84** upon reaction with an external alkene by CM. On the other hand, initial cyclobutanametallation of the endocyclic double bond of **83** may afford the regioisomeric intermediates **XVI-A** or **XVI-B** (path B), which lead to carbenes **XVIII-A** and **XVIII-B**, respectively. Intramolecular RCM of **XVIII-A** would afford the domino metathesis products **84**, whereas intermolecular CM with an external alkene would give rise to the ROM-CM products **85**. The latter may be interconverted into **84** by RCM. Also, intermediate **XVIII-B** could afford the ROM-CM products **85** by CM with an external alkene.

4. Conclusions

The results presented herein show that sequential metathesis in oxa- and azanorbornenic derivatives has proven to be a reliable technique for the preparation of a diverse range of structures. The high regio- and stereoselectivity obtained in the metathesis reaction mean that it is clearly of great value in many synthesis. Fundamentals have been established for the mechanistic understanding of these reactions. However, much work remains to be done to define further mechanistic aspects and to exploit their potential in organic synthesis.

Acknowledgments

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