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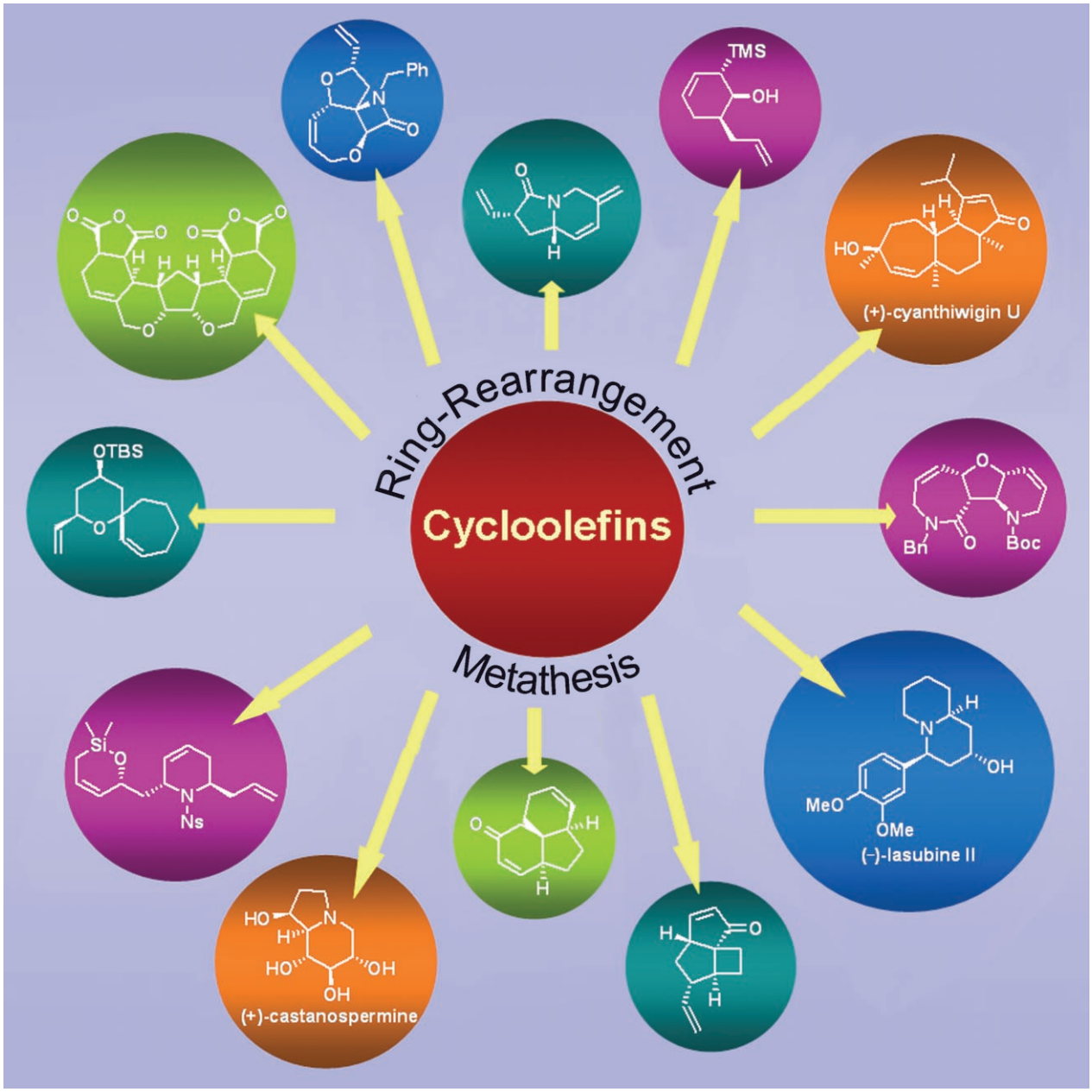
Ring-Rearrangement Metathesis

Nicole Holub and Siegfried Blechert*[a]



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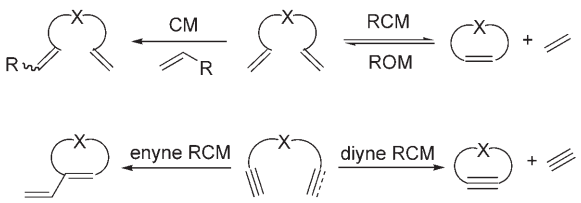
Abstract: Ring-rearrangement metathesis (RRM) refers to the combination of several metathesis transformations into a domino process, in which an endocyclic double bond of a cycloolefin reacts with an exocyclic alkene. RRM has proven to be a powerful method for the rapid construction of complex structures. The extension of the basic ring-opening–ring-closing metathesis process by further metathesis steps as well as an examination of the driving forces, limits, scope, recent advantages, and future perspectives of these domino sequences is presented with various examples, thus reflecting the high efficiency and utility of RRM in organic synthesis.

Keywords: catalysis · domino reactions · metathesis · natural-product synthesis · ring rearrangement

1. Introduction

Alkene metathesis has proven to be a valuable synthetic tool in organic chemistry and is nowadays well-established. A number of reviews on this topic have been published during the last few years, focusing on the application of the reaction in organic synthesis,[1] natural-product synthesis,[2] and polymer chemistry,[3] as well as the development of new well-defined catalysts.[4]

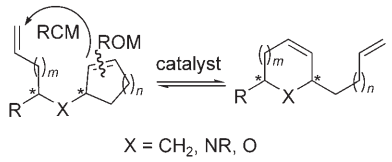
Several synthetically useful intra- and intermolecular variants of this process are known, including the classical ring-opening metathesis (ROM), ring-closing metathesis (RCM), cross metathesis (CM), and polymerization reactions (Scheme 1). Recent investigations also involved the metathesis reaction of an alkyne with either a second alkyne (diyne metathesis)[5] or an alkene (enyne metathesis) (Scheme 1).[6]



Scheme 1. Classification of metathesis reactions.

As all of these transformations (except diyne metathesis) can be promoted by the same carbene catalysts, the combination of several metathesis steps in sequence is apparent. These domino reactions allow the rapid construction of structurally intricate compounds from relatively simple starting materials in one pot, in which the subsequent transformation always occurs at the functionality formed in the previous step. Apart from the ease of the synthesis, these processes are also considered favorable from an ecological point of view, as the amount of energy used, chemical waste produced, and therefore the costs involved can be significantly lowered.

Among the possible combinations of metathesis reactions, ring-rearrangement metathesis (RRM), in particular, has demonstrated its high efficiency for the formation of carbo- and heterocycles. By definition, in these domino reactions a strained carbocyclic alkene is transformed into a new cycle by intramolecular ring opening/ring closing with an exocyclic double bond (Scheme 2). These reversible processes are driven by a combination of thermodynamic factors (loss of ring strain, substitution pattern, or release of a volatile olefin) and kinetic effects such as the formation of a less-reactive carbene complex. A particularly attractive feature of RRM is the complete transfer of stereochemical information from the starting material to the product; RRM has therefore been used intensively in the synthesis of various natural products.



Scheme 2. General principle of the ROM–RCM sequence.

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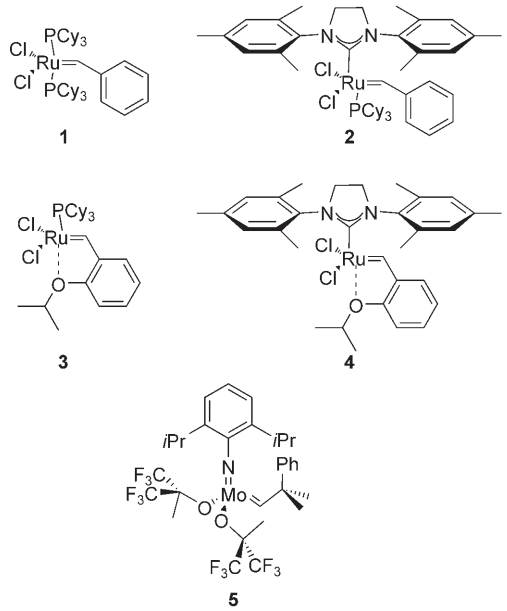
The metathesis catalysts utilized in the reactions described in this Focus Review are shown in Scheme 3. Several other reviews have been published, which address in particular the reactivity, stability, and selectivity of these carbene complexes.[7]



Scheme 3. Selected metathesis catalysts. Cy = cyclohexyl.

Recently, several tandem reactions connecting a metathesis reaction with a reaction of a different type were reported. Useful examples are combinations with Diels–Alder reactions,[8] isomerization,[9] dihydroxylation,[10] hydrogenation,[11] sigmatropic rearrangements,[12] or Pd-catalyzed reactions.[13] Herein, domino reactions that involve exclusively metathesis steps will be described, in particular RRM reactions. Apart from various examples that show the high efficiency of this reaction and their successful application in natural-product synthesis, this article also includes a discussion of the driving forces, limits, and scope as well as the perspectives of this reaction in future organic chemistry.

Abstract in German: Ringumlagerungsmetathesen (RRM) haben sich als effektive und schnelle Methode für die Darstellung von komplexen Strukturen erwiesen. Definitionsgemäß handelt es sich bei diesen Prozessen um die Kombination von mehreren Metatheseschritten, bei denen die Doppelbindung eines Cycloolefins mit einer exocyclischen Doppelbindung in einer Ringöffnungs–Ringschluss-Metathese Sequenz (ROM–RCM) reagiert. Die Erweiterung dieses Konzeptes um zusätzliche Metatheseschritte, als auch die Betrachtung der Triebkräfte und der Grenzen dieser Reaktion werden in diesem Review an aktuellen Beispielen erläutert.

2. Simple ROM–RCM Sequences

2.1. RRM of Alkenyl-Substituted Cycloolefins

The RRM reactions described in this section involve intramolecular metathesis reactions between an endocyclic olefin and an exocyclic C–C double bond. In these transformations, the ring is opened (ROM) and a new one is formed concomitantly (RCM), thus resulting in a rearranged ring system in the product (Scheme 2). This is the shortest general sequence of an RRM reaction.

2.1.1 Monocyclic Substrates

In 1996, Grubbs and co-workers reported pioneering work about the ring rearrangement of dialkenyl-substituted cyclopentenes.[14] These substrates afforded in an RCM–ROM–RCM sequence the corresponding bicyclic products in good yield (Scheme 29). One year later, Hoveyda and co-workers applied the ROM–RCM combination to the synthesis of chromenes and showed effectively the dependency of the process on substrate structure and reaction conditions.[15]

Initial experiments with cycloheptene **6c** indicated that high dilution as well as reaction under ethylene atmosphere was necessary for the suppression of dimerization (Scheme 4). Under these conditions, **6c** rearranged into **7c** in a satisfying 92% yield. The eight-membered analogue **6d** also proved to be a suitable substrate, whereas cyclohexene **6b** afforded the corresponding chromene in only 35% yield, and cyclopentene **6a** did not react at all. This discrepancy in

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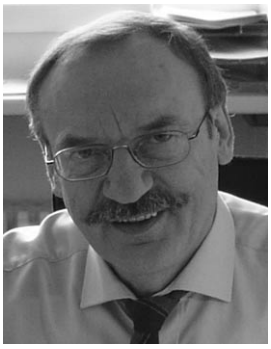

Siegfried Blechert *was born in Aalborg, Denmark, in 1946. He studied chemistry at the Univ. of Hannover and completed his PhD under the supervision of Prof. E. Winterfeldt in 1974. After research with Prof. P. Potier at Gif-sur-Yvette, France, he completed his habilitation at the Univ. of Hannover before taking up a professorship at Bonn Univ. in 1986. In 1990, he accepted the Chair of the Organic Chemistry Department at the Technical Univ. of Berlin, where he is Head of the Chemistry Department since 2004. His research interests focus on metathesis and its application in natural-product synthesis, as well as the development of new catalysts for metathesis and hydroamination.*

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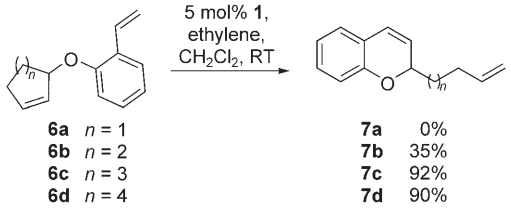
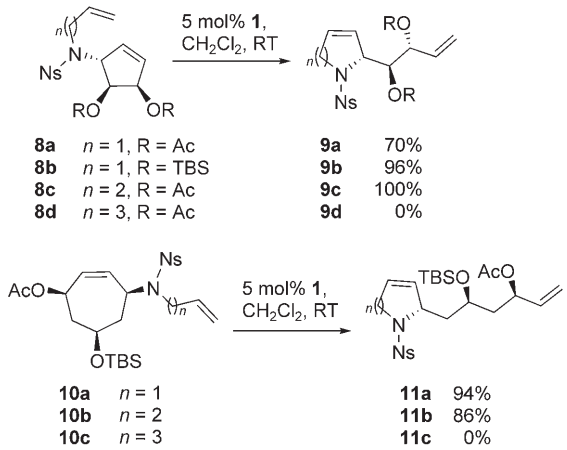


Scheme 4. Synthesis of chromenes by Hoveyda and co-workers.[15]

reactivity was ascribed to a kinetic barrier caused by high angle strain present in the assumed metallacycle intermediates.

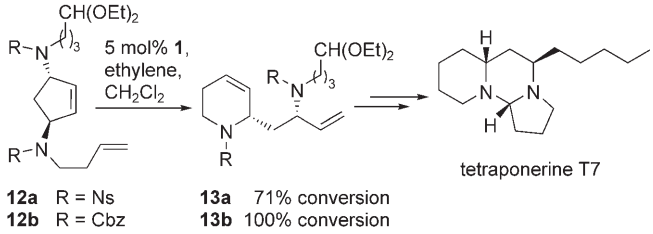
The application of RRM reactions for the synthesis of heterocycles has been investigated extensively in our group.[16] The fact that asymmetry in the carbocyclic substrate is easily introduced and transferred quantitatively to the product offers a simple and rapid entry to chiral heterocyclic systems that are present in an array of natural products. A number of cyclopentene and cycloheptene derivatives with olefinic side chains of varying length were subjected to rearrangement conditions (Scheme 5).[16a] The results



Scheme 5. RRM for the synthesis of heterocycles. Ns = nitrobenzenesulfonyl, TBS = *tert*-butyldimethylsilyl.

impressively indicate the scope of RRM reactions: cyclopentenes **8a–c** and cycloheptenes **10a** and **10b** can be completely converted into the corresponding dihydropyrroles or tetrahydropyridines. Furthermore, the introduction of bulkier substituents at the cyclopentene ring (Ac vs. TBS) shifted the equilibrium to the product (70% vs. 96%). The formation of the seven-membered heterocycles (**9d, 11c**) failed in both cases, thus indicating that the strain in the products is higher than in the appropriate cycloalkenes.

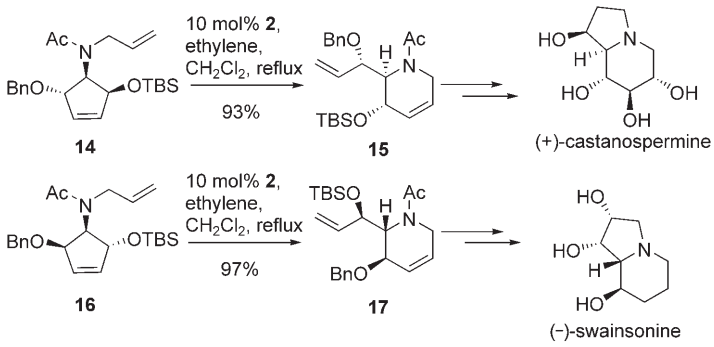
The effectiveness of this concept was illustrated by our group in the synthesis of diverse alkaloids and heterocycles[17] such as the tetraponerines.[17a] Subjection of metathesis precursor **12a** to 5 mol% catalyst **1** resulted in only 71% conversion after two days (Scheme 6). Change of the N-protecting group from Ns to Cbz accelerated the metathesis re-



Scheme 6. Application of RRM to the synthesis of tetraponerine T7. Cbz = benzyloxycarbonyl.

action significantly: after 12 h, starting material **12b** was completely converted into the corresponding tetrahydropyridine **13b**. A possible explanation is that internal complexation of the carbonyl group to ruthenium occurs to yield the more-stable carbene complex, thus shifting the reaction towards the product.

Mariano and co-workers focused on the RRM reaction of unsymmetrically substituted aminocyclopentenediol derivatives to investigate the regiochemical and stereochemical control of the process.[18] Whereas **14** rearranged to the tetrahydropyridine **15**, in which the benzyl group is positioned next to the *N*-acyl group (Scheme 7), reaction of diastereo-



Scheme 7. Examination of regioselectivity in RRM processes by employment of unsymmetrical cyclopentene derivatives. Bn = benzyl.

mer **16** selectively furnished the regioisomer **17** in 97% yield. The high selectivity of this process was ascribed to an energy difference of the ruthenacyclobutane intermediates, thus suggesting the influence of kinetic factors. Tetrahydropyridine **17** was further converted into (−)-swainsonine, whereas **15** served as starting material in a recently published synthesis of (+)-castanospermine,[19] which illustrates the high efficiency of RRM in natural-product synthesis.

Applications of six-membered cycloolefins in RRM processes have seldom been reported. Investigations by Hoveyda and co-workers towards the synthesis of dihydrofurans indicated that the ring rearrangement of cyclohexene derivatives to five-membered heterocycles is thermodynamically disfavored.[20] However, the synthesis of tetrahydropyridine derivatives could be achieved by RRM, thus indicating that the resulting heterocycle is thermodynamically more favored than the corresponding cyclohexene. Dixneuf and co-work-

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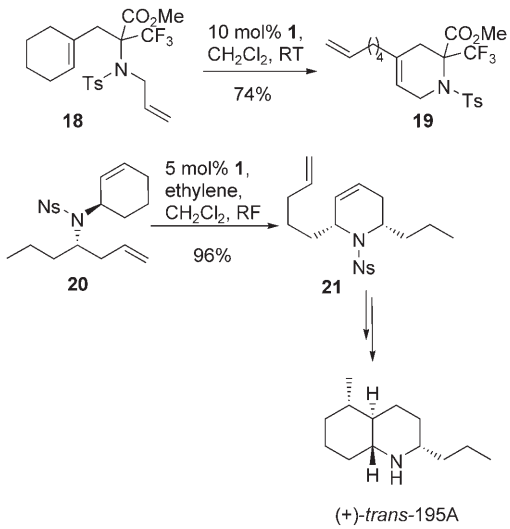
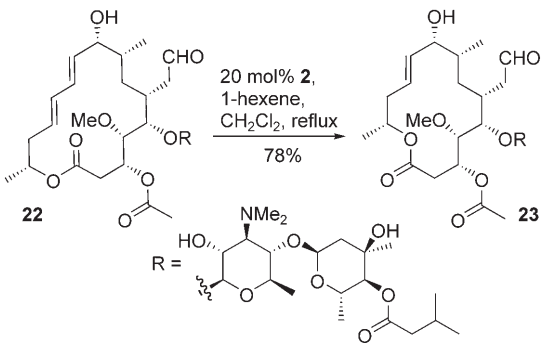
ers, for instance, synthesized cyclic α-amino acid ester **19** by metathesis reaction in good yield (Scheme 8, top).[21] Another example is (+)-*trans*-195A, a frog alkaloid synthesized by our group.[22] In the presence of 5 mol% catalyst **1**, cyclohexene **20** was completely converted into the disubstituted tetrahydropyridine **21** (Scheme 8, bottom).



Scheme 8. Application of cyclohexenes to the domino process by Dixneuf[21] (top) and Blechert[22] (bottom) and their co-workers. Ts = *p*-toluenesulfonyl.

Although the domino reaction published by Lazarova et al. is not ring rearrangement by definition, it demonstrates nicely the synthetic utility of ROM–RCM processes for the contraction of macrocyclic ring systems (Scheme 9).[23] Treatment of macrolide **22** with 20 mol% catalyst **2** and 2 equivalents of 1-hexene resulted in ring-opening followed by RCM with the internal double bond of the butadiene group formed in the intermediate. 1-Hexene served as a substitute for ethylene and was essential for the regeneration of the active ruthenium species.

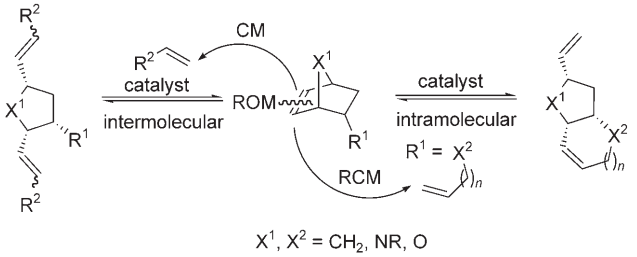


Scheme 9. Ring contraction of macrolides by metathesis.

2.1.2. Bicyclic Substrates

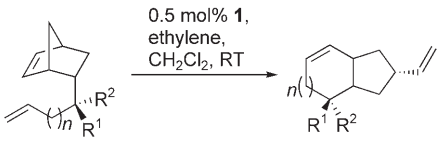
Among the different types of substrates suitable for metathesis reactions, bicyclic systems deserve special attention. Owing to the highly strained ring system, these substrates are highly reactive, and the driving force for the reaction can be clearly attributed to a release of energy. Furthermore, the stereoinformation contained in the positions of the ring junctions is conserved throughout the whole process, which allows for the synthesis of cyclic compounds with well-defined relative stereochemistry.

Norbornenes are well-established in the field of ring-opening metathesis polymerization (ROMP).[3] ROMP can be efficiently suppressed in the presence of a second olefin, which serves as metathesis partner either in an intermolecular (ROM–CM) or an intramolecular reaction (ROM–RCM), thus leading to annulated rearranged bicycles (Scheme 10). Herein the focus will be on RRM reactions; for further details on ROM–CM reactions of norbornene derivatives, see reference [24].



Scheme 10. Inter- (ROM–CM) and intramolecular (ROM–RCM) metathesis reactions of norbornenes.

In 1998, we reported the first synthesis of [*X*.3.0] bicycles by RRM.[25] Under ethylene pressure, **24a–d** were rearranged in good yield to the corresponding annulated bicycles (Scheme 11). Notably, the addition of an acyclic olefin (here ethylene) is necessary to suppress the polymerization process. Even the relatively strained bicyclooctene **25d** was obtained in good yield, although the more-reactive molybdenum-based catalyst **5** was required.



24a	$n = 0$, $R^1 = H$, $R^2 = OTBS$	**25a**	80%
24b	$n = 1$, $R^1 = H$, $R^2 = OTBS$	**25b**	88%
24c	$n = 2$, $R^1 = H$, $R^2 = OTBS$	**25c**	75%
24d[a]	$n = 3$, $R^1 = OTBS$, $R^2 = H$	**25d**	83%

Scheme 11. First application of norbornene derivatives in RRM. [a] 5 mol% **5** used.

Two possible mechanistic pathways can be taken into account for these domino reactions (Scheme 12). The first involves initial attack at the terminal exocyclic double bond,

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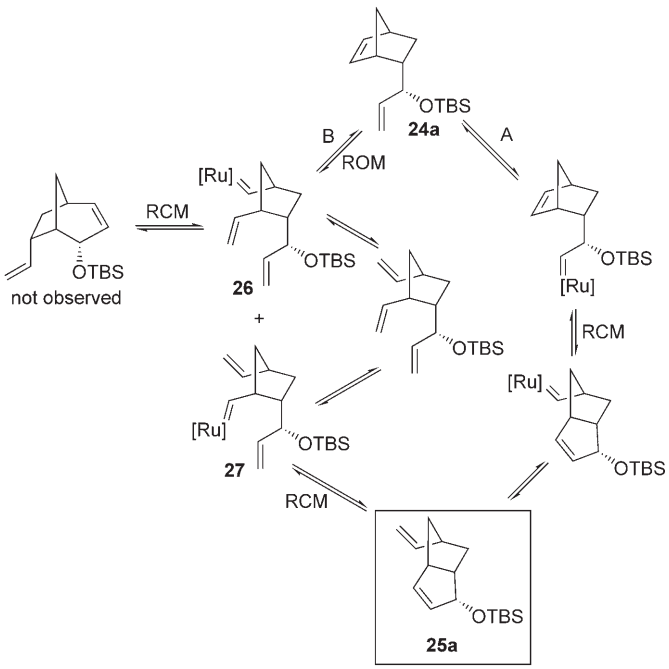
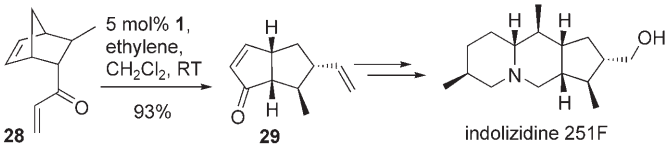


Scheme 12. Mechanistic aspects of ROM–RCM.

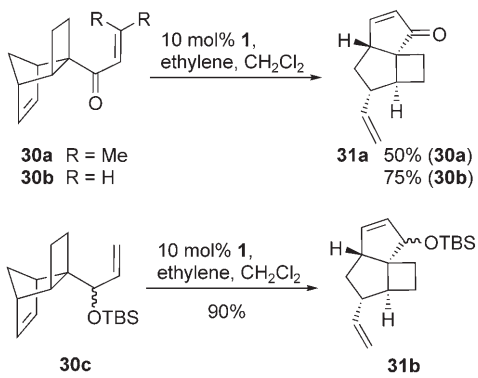
which then reacts with the endocyclic olefin (pathway A). Alternatively, ring opening may occur first (pathway B) to lead to two possible intermediates, **26** and **27**. As ring closing of **26** would result again in a strained bicyclic system, isomerization to **27** is more likely, which results, after RCM, in the formation of the rearranged product. Although the driving force seems to be the loss of ring strain, we cannot exclude the possibility that less-strained substrates are primarily attacked at the exocyclic olefin (pathway A). Furthermore, the by-products observed in our studies indicate that the mechanism is dependent on the ring size formed by RCM. Whereas five-, six-, and seven-membered rings are presumably formed by pathway A, intermediates of type **26** and **27** are more likely formed for the eight-membered analogue **24d**. This is consistent with the use of catalyst **5**, which is much more reactive towards disubstituted olefins than catalyst **1**.

Aubé and co-workers applied this RRM strategy to the synthesis of indolizidine alkaloid 251F.[26] Norbornene **28** was subjected to 5 mol% catalyst **1** under ethylene pressure and furnished the desired [3.3.0] bicyclic compound in 93% yield (Scheme 13).

The synthesis of the carbocyclic core of tricycloclavulone, a marine prostanoid that contains a cyclobutane ring, was achieved by Harmata and Wacharasindhu.[27] In a key step, the tricyclic metathesis precursor **30a**, synthesized by [4+3]-cycloaddition and quasi-Favorskii rearrangement, was subjected to 10 mol% catalyst **1** to give the desired ROM–RCM product **31a** in reasonable 50% yield (Scheme 14). As



Scheme 13. Application of RRM to the synthesis of indolizidine 251F.

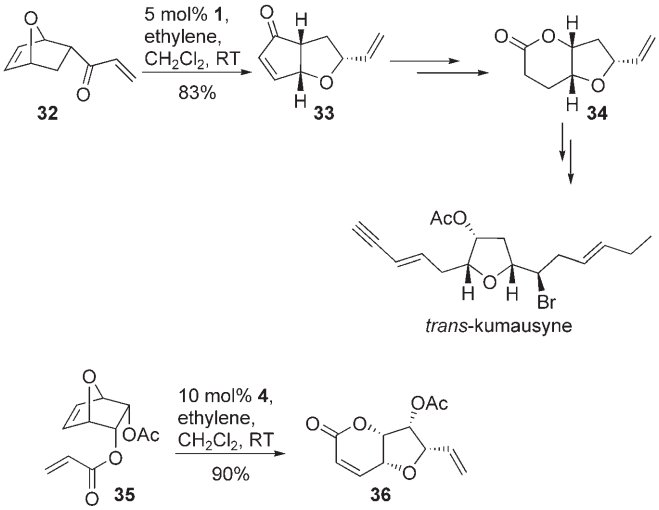


Scheme 14. Synthesis of the carbocyclic core of tricycloclavulone by Harmata and Wacharasindhu.[27]

the problem of this reaction was attributed to the trisubstituted alkene in **30a**, the enone and allylic alcohol derivatives **30b** and **30c** were tested in RRM. Both substrates proved to be more reactive in this domino process and furnished the rearranged products **31a** and **31b** in 75% and 90% yield, respectively.

Another application of this strategy in natural-product synthesis was published by Chandler and Phillips.[28] 7-Oxanorbornene derivative **32** served as precursor for the metathesis reaction and was rearranged to tetrahydrofuran **33**, which was then converted into the [4.3.0] bicyclic lactone **34** by Baeyer–Villiger oxidation (Scheme 15, top). Further steps completed the synthesis of *trans*-kumausyne.

A direct access to a similar [4.3.0] bicyclic lactone by RRM was achieved by Plumet and co-workers.[29] Subjection



Scheme 15. Utilization of oxanorbornenes in the synthesis of bicyclic lactones by Chandler and Phillips[28] (top) and Plumet and co-workers[29] (bottom).

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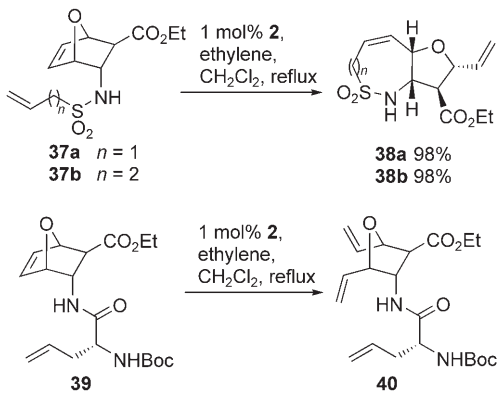
of **35** to 10 mol% catalyst **4** resulted in the clean formation of the rearranged product (Scheme 15, bottom).

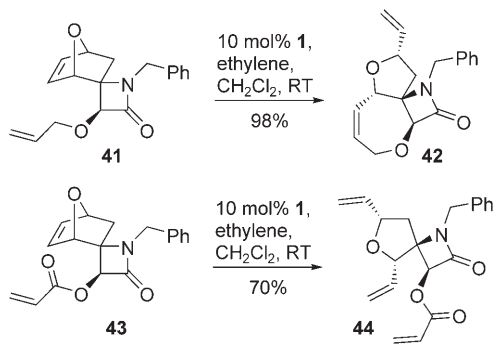
Recently in our group, RRM of 7-oxanorbornenes was examined to synthesize nonnatural amino acids with reverse turn.[30] With a low catalyst loading of only 1 mol%, **37a** and **37b** rearranged quantitatively to the corresponding [5.3.0] and [6.3.0] bicyclic compounds (**38a** and **38b**), whereas the reaction of **39** under the same conditions failed (Scheme 16). Only the ROM product was obtained in this case, thus indicating that the ring-closing step is hindered. Different attempts with **39** under various conditions failed, as well as a separately performed RCM reaction of the isolated product **40**. The lack of reactivity towards RCM may be attributed to the high preference for a *transoid* conformation of the amide bond.



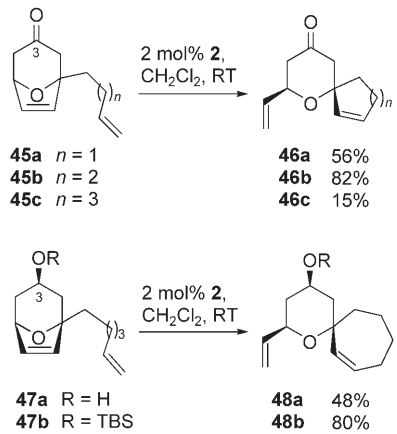
Scheme 16. Nonnatural amino acids from oxanorbornenes by RRM. Boc = *tert*-butoxycarbonyl.

A similar effect was observed by Plumet and co-workers during the synthesis of β-lactam derivatives.[31] Conduction of RRM with spirolactam **41** afforded the tricyclic system **42** in quantitative yield. In contrast, the ester **43** formed selectively the ring-opening product, which could not be cyclized in a separately performed RCM (Scheme 17).

Wright and co-workers investigated the ring rearrangement of bicycles that involves a quaternary carbon at the ring junction.[32] Several 8-oxabicyclo[3.2.1]octane derivatives were rearranged in view of the synthesis of spiro-fused pyrans, which are interesting building blocks in natural-product synthesis (Scheme 18). Initial studies demonstrated that only the five- and six-membered spirocycles **46a** and **46b** were formed in good yield, whereas the seven-membered homologue **46c** was obtained in only 15% yield, with the major by-product arising from dimerization of the terminal vinyl groups.



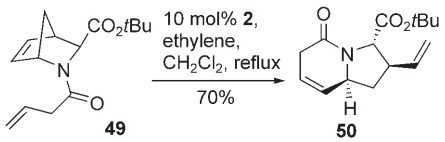
Scheme 17. Synthesis of tricyclic β-lactam derivatives by Plumet and co-workers.[31]



Scheme 18. Synthesis of bicyclic spiropyrans by Wright and co-workers.[32]

In previous studies,[33] a remarkable effect of the group and stereochemistry at C3 was observed, which was ascribed to steric interaction of the axial group with the bridged alkene. Subjection of the reduced forms **47a** and **47b** to RRM conditions led to a dramatic change: the seven-membered spirocycle was formed in 48% (R = H) and 80% (R = TBS) yield, thus impressively illustrating the potential of tuning the reactivity of alkenes in RRM reactions.

2-Azanorbornenes also proved to be suitable RRM substrates, giving rise to indolizidines or quinolizidine structures (Scheme 19). Maison and co-workers investigated the utilization of these substances in several domino processes.[34] RRM of **49** afforded indolizidine **50** in good yield, although side products from dimerization reactions were observed.



Scheme 19. Application of 2-azanorbornenes in RRM processes.

Liu and Rainier investigated the subjection of 7-azanorbornene derivatives to RRM processes in view of the synthesis of perhydroindolidines,[35] a common structural motif of various natural products (Scheme 20). Whereas the metathesis precursor **51a** with an unsubstituted butenyl side chain rearranged by addition of 5 mol% **2** at room temperature in good yield, norbornenes **51b** and **51c** proved to be

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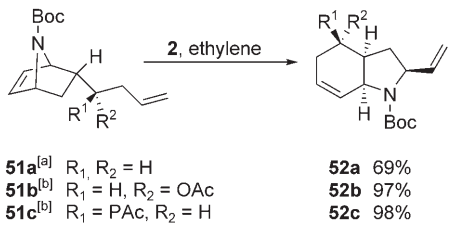


Scheme 20. Application of 7-azanorbornenes in RRM for the synthesis of indolines. [a] 5 mol% catalyst, CH_2Cl_2, room temperature. [b] 15 mol% catalyst, benzene, reflux.

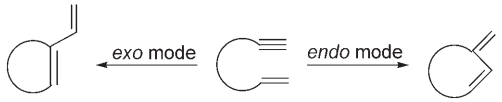
unreactive under these conditions. However, RRM was achieved in refluxing benzene and with a higher catalyst loading of 15 mol%; these conditions resulted in the formation of the corresponding indolines **52b** and **52c** in 97% and 98% yield, respectively.

2.2. RRM of Alkynyl-Substituted Cycloolefins

Cycloalkenes that bear an exocyclic alkyne moiety have been successfully applied in RRM. In contrast to the sequences discussed so far, these domino reactions are not only driven by the release of ring strain, but predominantly by the formation of a conjugated diene. With the 1,3-butadiene unit formed being relatively unreactive towards the metathesis catalyst, the transformation is strongly shifted toward the product and cannot be seen as an equilibrium.

The regiochemical course of the enyne RCM is not only affected by substrate geometry, but also by the size of the ring formed and the catalyst employed. Two ring closures are possible, leading either to vinylcycloalkenes (*exo* path) or to larger ring systems, in which both alkyne carbon atoms are located in the cycle formed (*endo* path) (Scheme 21).[2b]

Atom-economical domino reactions of alkynyl-substituted

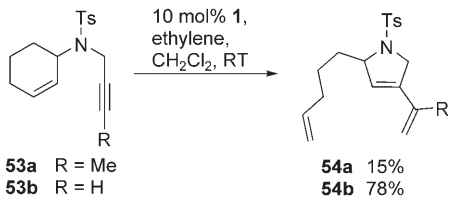


Scheme 21. Possible ring closures of enyne RCM.

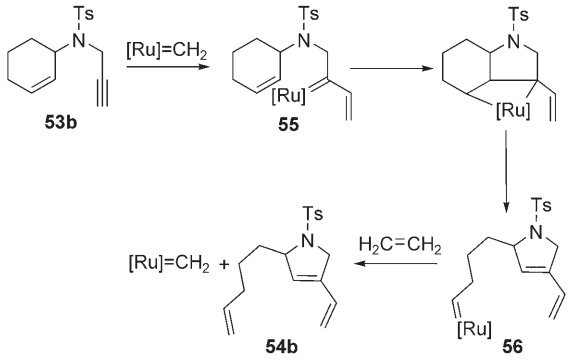
cycloolefins were described by Mori and co-workers.[36] Depending on the position of the alkynyl side chain, different products were observed.

Subjection of monosubstituted substrates **53a** and **53b** to 10 mol% catalyst **1** resulted in formation of the expected rearranged products (Scheme 22), whereupon higher yields were obtained with the terminal alkyne (**53b**) relative to its internal analogue (**53a**).

The assumed mechanism starts with attack of the ruthenium–methylidene complex at the electron-rich triple bond (Scheme 23). Alkylidene complex **55** then reacts with the endocyclic double bond to form the rearranged intermediate **56**, which gives the product after CM with another olefin.



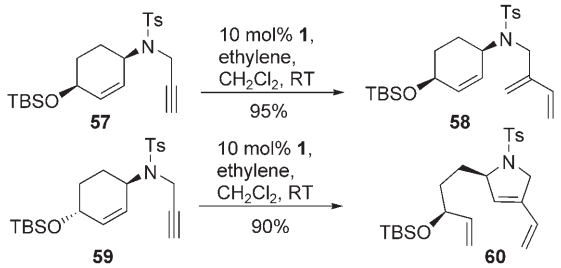
Scheme 22. ROM–enyne RCM of 3-substituted cycloolefins.



Scheme 23. Mechanism of the ROM–enyne-RCM process.

The addition of an external olefin is essential in these processes, as in its absence polymerization of **56** would occur.

Investigation of disubstituted cyclohexene derivatives confirmed the suggested initial attack of the catalyst at the triple bond, as **57** was transformed completely into the CM product **58** (Scheme 24). Due to steric hindrance the RCM process was inhibited, which therefore led to the irreversibly formed butadiene moiety. On the other hand, the *trans*-substituted substrate **59** rearranged to **60** as expected.



Scheme 24. Ring rearrangement of disubstituted cycloalkenes by Mori and co-workers.[36]

Domino reactions of cycloalkenes, in which the alkynyl side chain is connected to one of the sp^2-hybridized carbon atoms, resulted in the formation of bicyclic products (Scheme 25). Whereas substrate **61** rearranged quantitatively to the 5,7-fused-ring system **62**, the cyclohexene analogue **63** led to an unexpected product mixture (**62** and **64**). This could be rationalized by either dimerization of the intermediate **65** or olefin migration (**66**) prior to RCM.

This sequence was also applied to the synthesis of isoquinoline derivatives (Scheme 25, bottom). Recently, Mori

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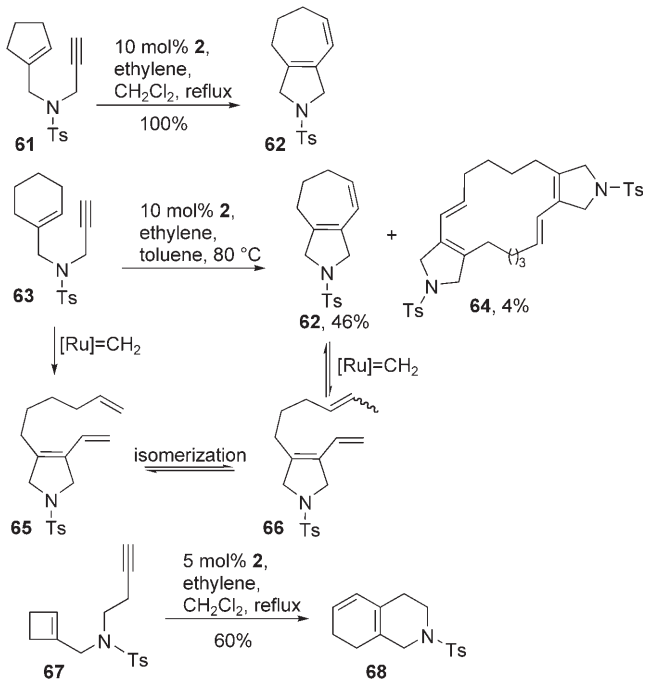
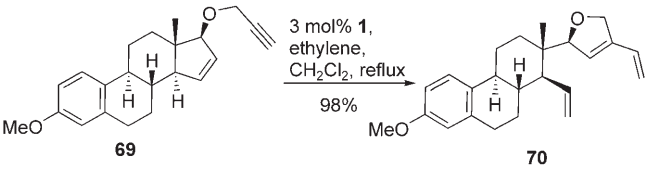


Scheme 25. ROM–enyne RCM of 1-alkynyl cycloolefins.

et al. successfully performed the rearrangement of cyclobutene **67** to the corresponding 6,6-fused-ring system **68**.[37]

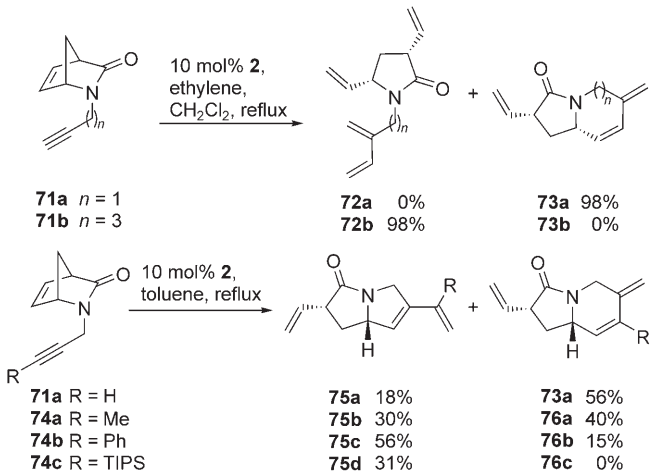
Application of this concept to a steroid skeleton was reported by our group.[38] Compound **69** was subjected to 3 mol% catalyst **1** and yielded exclusively the rearranged substance **70** in outstanding yield (99%) (Scheme 26). Therefore, domino processes that include triple bonds prove to be useful even for complex structures.



Scheme 26. Application of ROM–enyne RCM to a steroid skeleton.

By analogy to the previously described examples, ROM–enyne-RCM sequences were also applied to bicyclic systems. Plumet and co-workers examined the domino process of 2-azanorbornenes.[39] Depending on the length of the alkynyl side chain, different products were observed (Scheme 27, top). Whereas a short propargyllic side chain ($n=1$) led to the clean formation of rearranged product **73a**, a longer side chain ($n=3$) resulted in the formation of product **72b**.

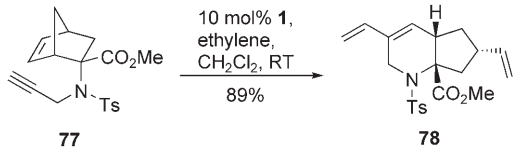
Recently, Mori et al. published further investigations of azanorbornene systems in ROM–enyne-RCM reactions.[40] Interestingly, performing the RRM process with **71a** at higher temperatures led to a mixture of indolizidine **73a** and pyrrolizidine **75a**, a side product which was not observed by Plumet and co-workers at a reaction temperature



Scheme 27. Ring rearrangement of azanorbornenes by Plumet and co-workers[39] (top) and Mori et al.[40] (bottom). TIPS = triisopropylsilyl.

of 40 °C (Scheme 27, bottom). Further examination of this domino process showed that substituted alkynes (**74a–c**) swayed the product mixture towards the pyrrolizidine **75**. Bulkier substituents such as the TIPS group even caused the selective formation of **75d**, albeit in decreased yield.

In the course of our synthetic studies of nonnatural amino acids with reverse turn,[30] a norbornene derivative with an aminopropargylic side chain was subjected to RRM (Scheme 28). Upon treatment of **77** with 10 mol% catalyst **1** under ethylene atmosphere, the rearranged [4.3.0] bicyclic product was obtained in 89% yield.



Scheme 28. ROM–enyne RCM for the synthesis of nonnatural amino acids.

3. Extension of the ROM–RCM Sequence by Another Metathesis Step

The last step in the ROM–RCM sequences discussed so far is the reaction of the formed carbene complex with ethylene under transfer of a methylene group. Further possibilities are therefore offered by intramolecular reaction of the alkylidene complex with other appropriate double bonds in the substrate. This formal extension of the general RRM concept by another metathesis step will be addressed below.

3.1. RCM–ROM–RCM

RRM of dialkenyl cycloalkenes was described in a pioneering work by Grubbs and co-workers.[14] Substrates of this type can undergo an RCM–ROM–RCM sequence to afford

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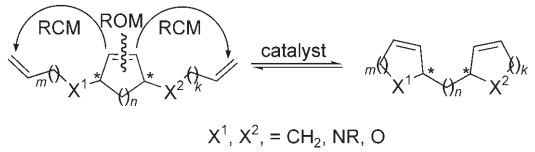
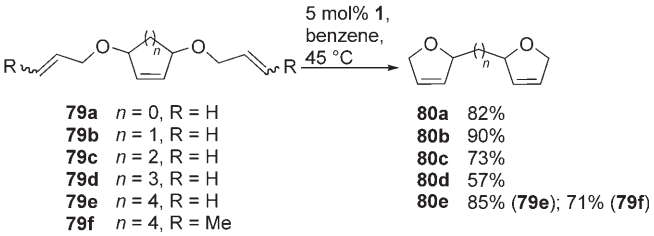
bicyclic products. In contrast to the reactions outlined above, these processes have an additional driving force. Apart from the release of ring strain or unfavorable steric interactions of the substituents present in the starting material, an entropy gain is achieved in these domino reactions due to the formation of a volatile olefin such as ethylene as by-product (Scheme 29).



Scheme 29. General concept of the RCM–ROM–RCM sequence.

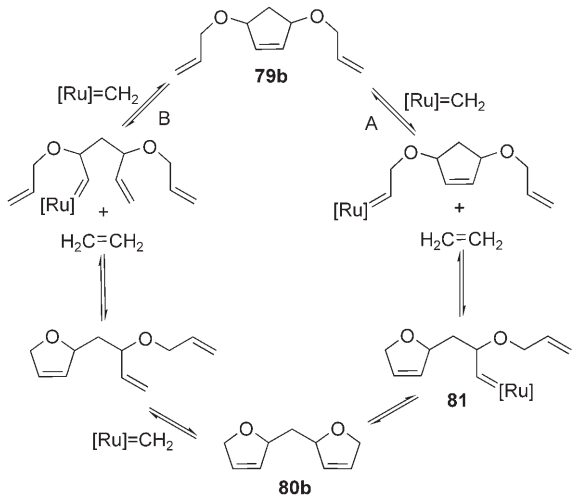
The observed effects, which concern the dependence of reactivity on substrate structure, are in accordance with the results for ROM–RCM processes. Whereas cyclobutene and cyclopentene derivatives **79a** and **79b** underwent fast ring opening and yielded at high concentrations the rearranged bicyclic cyclopentenes, the six-, seven-, and eight-membered analogous **79c–e** gave only somewhat low yields, presumably due to intermolecular reaction and formation of oligomeric products (Scheme 30).



Scheme 30. Pioneering work of Grubbs and co-workers[14] in the synthesis of bisdihydrofurans by RCM–ROM–RCM.

Performance of the reaction at higher dilution succeeded in suppressing the intermolecular reaction, and the desired rearranged products (**80c–e**) were obtained in good yield, with cyclohexene **79c** requiring the lowest reaction concentration. Another way to limit the oligomerization was the addition of steric demand to the terminal olefins by increasing their substitution. Subjection of the corresponding crotyl ether **79f** to the metathesis conditions used for cyclobutene **79a** resulted in the formation of bisdihydrofuran **80e** in good yield (71%), although with a significantly slower conversion and, therefore, a longer reaction time.

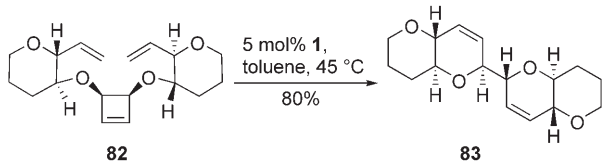
Two possible mechanistic pathways were discussed with regard to the observed effects (Scheme 31). Mechanism A involves initial metathesis at one of the terminal double bonds and subsequent attack of the endocyclic olefin. Final ring closure of **81** gives the rearranged product **80b**. Alternatively, the sequence may begin with ring opening of the endocyclic olefin, followed by double ring closure (mechanism B). Although the increase in product formation by



Scheme 31. Assumed mechanism for the RCM–ROM–RCM process.

using lower concentrations and more-substituted olefins is more consistent with pathway A, the second mechanism cannot be completely ruled out, especially for substrates with notable ring strain.

Nicolaou et al. employed a symmetric cyclobutene as metathesis precursor in the synthesis of different polycyclic ethers.[41] Compound **82** was rearranged successfully in the presence of 5 mol% catalyst **1** and proved the adaptability of this concept to complex structures (Scheme 32).



Scheme 32. Application of concept to complex structures by Nicolaou et al.[41]

RRM reactions of this type have often been applied in natural-product synthesis.[42] Ring rearrangement of the seven-membered rings **84a** and **84b** led to the core of the alkaloids (−)-anaferine,[43] (+)-dihydrocuscohygrine, and cuscohygrine,[44] which were synthesized by our group (Scheme 33). Variation of the length of the attached alkyl chain enabled access to either dipyrrolidine **85a** or dipiperidine **85b** in 72% and 87% yield, respectively.

The first enantioselective synthesis of (+)-dumetorine by using an RCM–ROM–RCM strategy as the key step was recently published by our group.[45] Although the migration of the double bond into conjugation with the ester group is required for the complement of the natural product, cyclopentene **86** was chosen as the most-promising candidate for the metathesis reaction (Scheme 34). As most known ruthenium catalysts are derived from **1**, we wished to probe its effectiveness as a cheap, commercially available catalyst for RRM. Unfortunately, initial metathesis experiments gave

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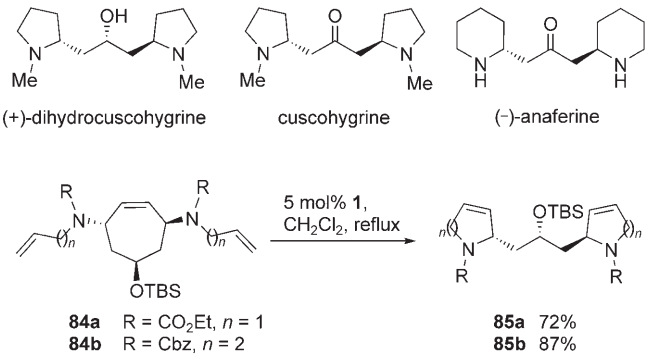
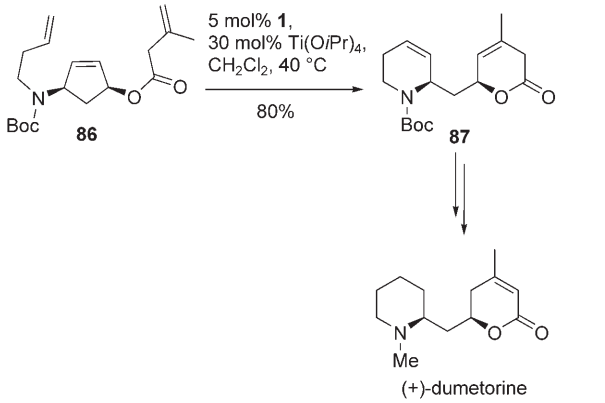
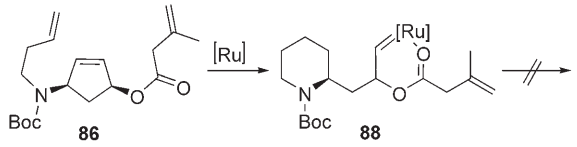


Scheme 33. Synthesis of piperidine- and pyrrolidine-containing natural products.



Scheme 34. Application of RCM–ROM–RCM to the synthesis of (+)-dumetorine.

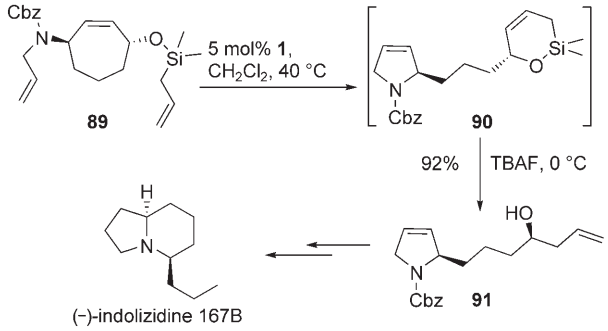
only 7% product, and most of the starting material was recovered. The low yield was attributed to the formation of a stable and unreactive chelate complex (**88**), in which the initially formed ruthenium–alkylidene is chelated by the oxygen atom of the ester moiety, thus inhibiting further reaction (Scheme 35).



Scheme 35. Proposed intermediate in RRM without the addition of Lewis acid.

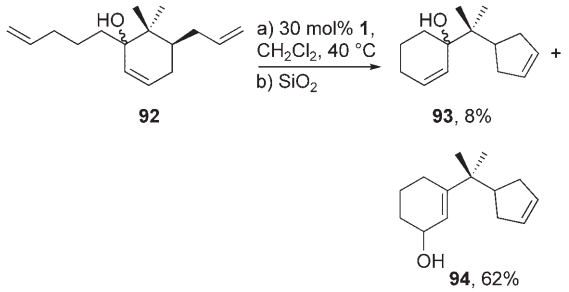
Titanium isopropoxide was reported to be an effective coadditive[46] that suppresses the formation of cyclic chelated intermediates. Indeed, when 30 mol% coadditive was added to the reaction mixture, the rearranged product **87** was obtained in 80% yield, thus enabling the completion of the synthesis.

This concept is not restricted to the formation of bicyclic systems that contain rings of the same size. RRM of disubstituted cycloheptene **89** cleanly gave the rearranged product **90**, which contains a dihydropyrrole ring and a six-membered cyclic silyl ether. Compound **90** was then directly deprotected by addition of TBAF (Scheme 36), and further steps gave rise to the indolizidine alkaloid 167B.[47]



Scheme 36. Application of RCM–ROM–RCM to the synthesis of bicyclic systems with different ring sizes. TBAF = tetrabutylammonium fluoride.

The ring rearrangement of cyclohexenes has only rarely been reported in the literature. A successful application of these substrates in a domino process was described in a work by Mehta and Nandakumar.[48] In the presence of 30 mol% catalyst **1**, compound **92** was converted through an RCM–ROM–RCM process into a mixture of two products: the expected and major product **93**, together with a small amount of **94** (Scheme 37). However, after purification by



Scheme 37. Ring rearrangement of cyclohexenes by Mehta and Nandakumar.[48]

column chromatography, **93** converted almost exclusively into the more-stable **94** through an allylic rearrangement. The success of this domino process can presumably be ascribed to the high substitution pattern present in the starting material.

Strained bicyclic molecules have proven their utility in simple RRM sequences. Depending on the position of the attached side chains, the RCM–ROM–RCM process of disubstituted norbornene derivatives enables access to complex tricyclic structures.

Holtsclaw and Koreeda examined the domino process of norbornenes that involves both tethers at the bridge carbon atom (Scheme 38).[49] Treatment of **95b** with catalyst **1** led to the exclusive formation of expected tricycle **96b**, whereas

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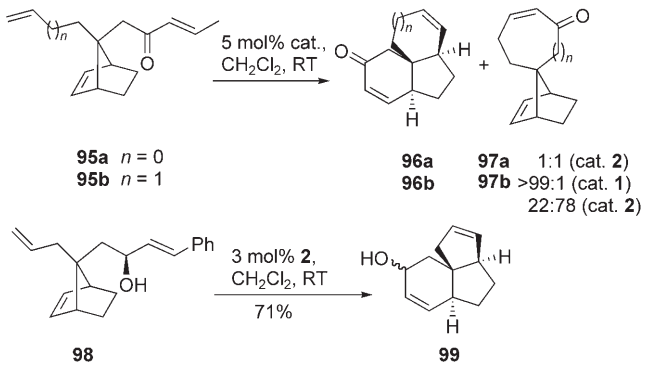
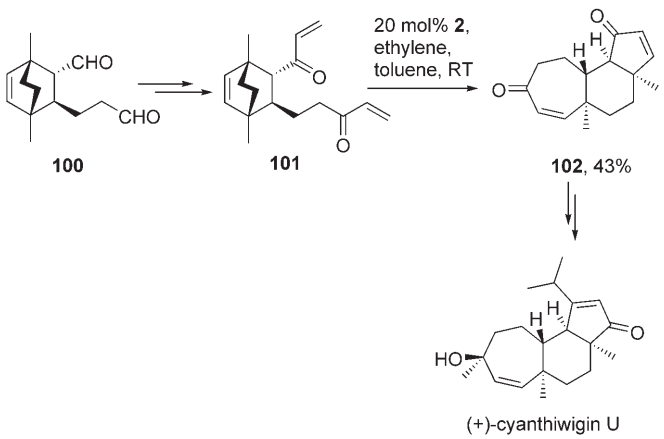
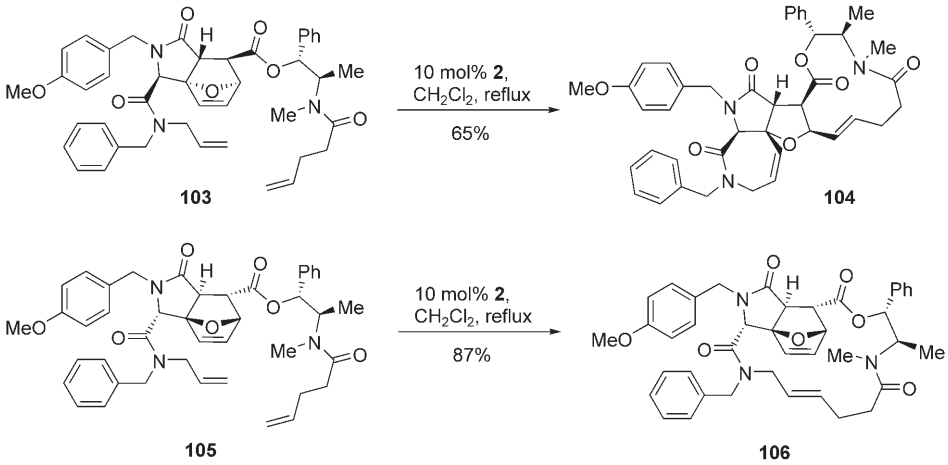


Scheme 38. Formation of tricyclic systems by Holtsclaw and Koreeda.[49]



Scheme 39. Application of the domino process to the synthesis of (+)-cyanthiwigin U.

catalyst **2** yielded a mixture of **96b** and the ring-closing product **97b**. Interestingly, after isolation, **97b** was rearranged again to the angularly fused tricycle **96b** under the same reaction conditions, thus indicating the thermodynamically unfavorable nature of the spirocyclic cycloheptenone. On the other hand, RRM under various conditions with norbornene **95a**, which has a shorter alkyl chain, resulted in different mixtures of starting material and the rearrangement and ring-closing products. To overcome this problem, alcohol **98** was used as an alternative metathesis precursor, and a significant change in reactivity was observed: tricycle **99** was obtained selectively and in good yield with an even-lower catalyst loading of 3 mol%. This example illustrates again the broad possibilities of fine-tuning the metathesis processes.



Scheme 40. Stereochemical control in domino processes by Schreiber and co-workers.[51]

Recently, Pfeiffer and Phillips reported the synthesis of (+)-cyanthiwigin U, a diterpenoid isolated from both fungal and marine sources.[50] The key step, utilized for the construction of the tricyclic core, represented a two-directional domino ROM–RCM sequence of bicyclo[2.2.2]octane **101** (Scheme 39). In the presence of 20 mol% catalyst **2** and ethylene atmosphere, **101** rearranged smoothly to the tricyclic skeleton of the natural product.

An interesting example of stereochemical control in domino processes was published by Schreiber and co-workers.[51] Subjection of diastereomers **103** and **105** to 10 mol% catalyst **2** furnished two different metathesis products (Scheme 40). Whereas reaction of **103** resulted in formation of the rearranged ring system **104**, its stereoisomer **105** underwent ring closure to the 17-membered amide **106** in 87% yield, thus demonstrating the influence of a single stereocenter on the resulting reaction pathway.

Although the extension of the basic ROM–RCM sequence by more ring-closing steps is possible in principle, the limitation of this concept became visibly clear in the synthesis of polyheterocyclic systems by Winkler et al.[52] Treatment of oxanorbornene **107** with 30 mol% catalyst **2** under ethylene atmosphere resulted in the tris heterocycle in nearly quantitative yield (Scheme 41). Encouraged by this result, the sequence was applied to the dimeric norbornene structure **109**, with an envisaged ROM–triple-RCM sequence in which new six-, seven-, and eight-membered rings of a polyheterocyclic system should be formed. However, only by addition of an equimolar amount of catalyst was the process accomplished by formation of product **110** in 10% yield. On the other hand, the fact that such a metathesis cascade is in principle realizable is an impressive result.

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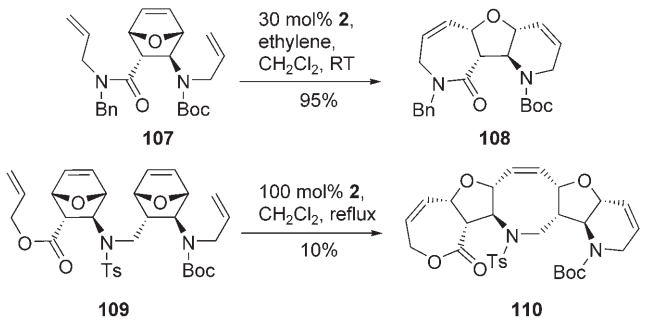
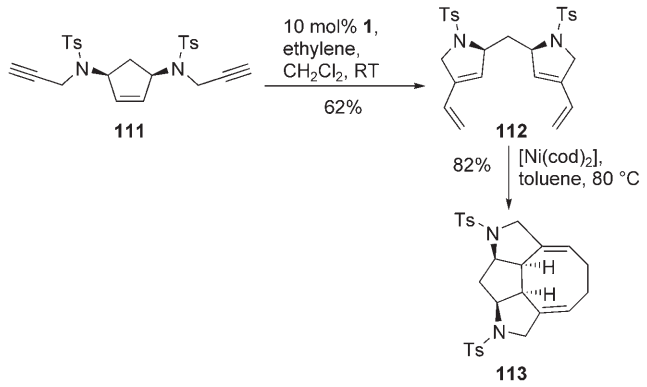


Scheme 41. Examination of the scope of domino processes by Winkler et al.[52]

3.2. Enyne RCM–ROM–Enyne RCM

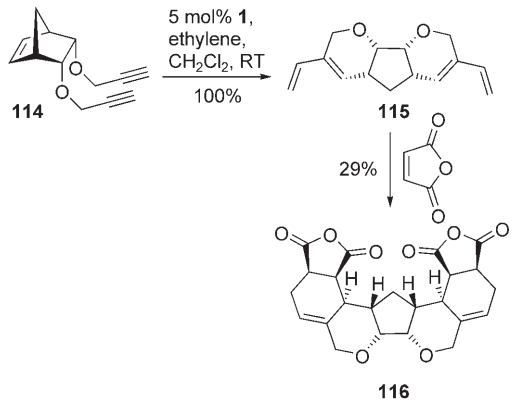
In contrast to the RCM–ROM–RCM process involving double bonds, a similar sequence with substrates that bear triple bonds is not as widely exploited. During the course of our studies of ROM–enyne RCM, dialkyne-substituted cyclopentenes were employed in a domino reaction.[38] Treatment of **111** with 10 mol% catalyst **1** gave the bicyclic dihydropyrrole in good yield (Scheme 42). As one molecule of



Scheme 42. Enyne RCM–ROM–enyne RCM of alkynyl-substituted cyclopentenes. cod = 1,5-cyclooctadiene.

ethylene is incorporated into bisdiene **112**, the addition of an external olefin is essential for this enyne-RCM–ROM–enyne-RCM process; this demonstrates the difference with the corresponding process with double bonds, in which one equivalent of ethylene is released. These bicycles are obvious precursors for further functionalization by Diels–Alder reaction or other cycloadditions, such as nickel-catalyzed cycloaddition leading to [4+4] tetracyclic adduct **113**.

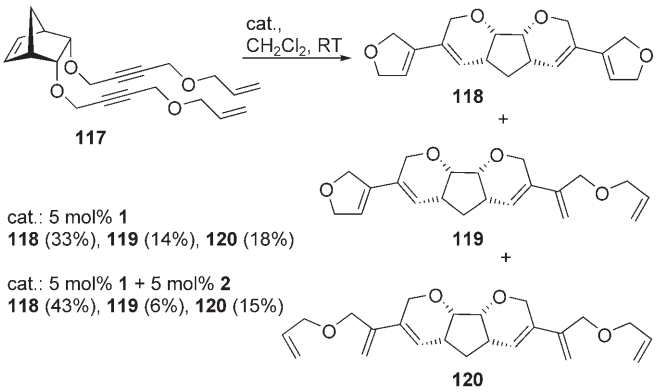
Banti and North examined the RRM of bisalkyne-substituted norbornenes.[53] Subjection of **114** to 5 mol% catalyst **1** yielded quantitatively the tricyclic product **115** (Scheme 43). Further cycloaddition was performed with different dienophiles, thus leading to polycyclic structures. These two steps were also successful in a one-pot sequence, although lower yields were attained. For instance, by addition of maleic anhydride to the reaction mixture, the hepta-



Scheme 43. Synthesis of polycyclic ring structures by RRM and Diels–Alder reaction.

cycle **116** was obtained as a single stereoisomer that encompasses ten consecutive stereocenters.

This concept was extended by another RCM process, when norbornene derivative **117**, which bears two alkenynyl side chains, was employed in RRM.[54] The resulting mixture showed that, in each case, the starting material underwent opening of the norbornene ring and subsequent enyne RCM, but the products differed in the extent to which they underwent the following ring closure with the double bonds (Scheme 44). The process was optimized by using an additional 5 mol% catalyst **2**, although by-products were still present.



Scheme 44. RCM–enyne RCM–ROM–enyne RCM–RCM of norbornenes.

3.3. ROM–RCM–CM and ROM–Enyne RCM–CM

The domino processes discussed so far concern intramolecular reactions. Extension of the intramolecular domino metathesis processes described in previous sections to an intermolecular reaction, namely, cross metathesis (CM), was also successfully applied in organic synthesis (Scheme 45). Although CM is afflicted with difficulties in *E*/*Z* selectivity and chemoselectivity in the choice of reaction partner (three isomers are possible in a reaction of two different olefins),

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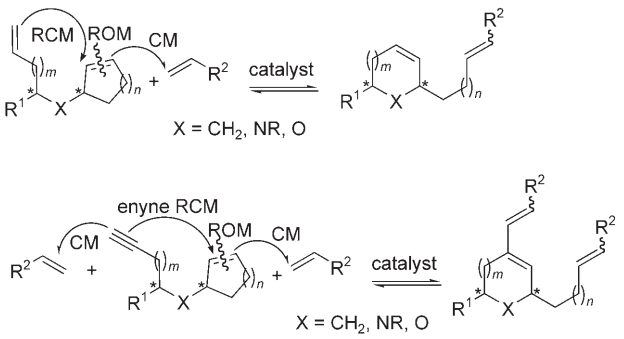
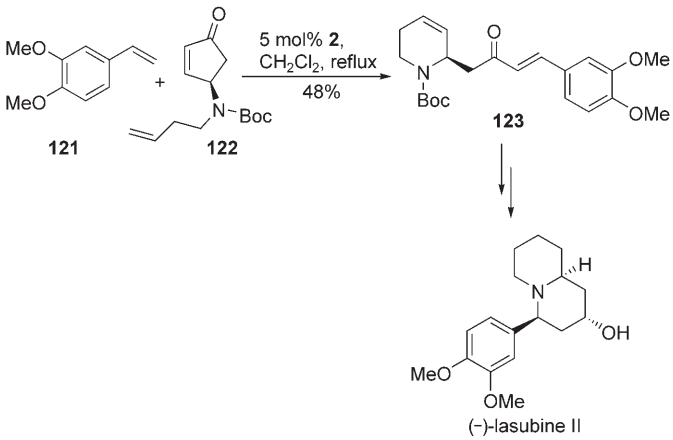


Scheme 45. General concept of RRM extended by a CM step.

the choice of suitable substrates and catalysts alleviates the limitation of these problems.

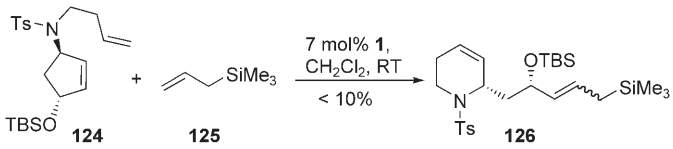
In our synthesis of quinolizidine alkaloid (−)-lasubine II, an ROM–RCM–CM sequence was utilized as the key step (Scheme 46).[55] Earlier experiments in our group[56] with cy-



Scheme 46. Application of the ROM–RCM–CM sequence to the synthesis of (−)-lasubine II.

clopentene **124** resulted in clean formation of the rearranged product; however, only small amounts of the desired CM product **126** were observed (Scheme 47).

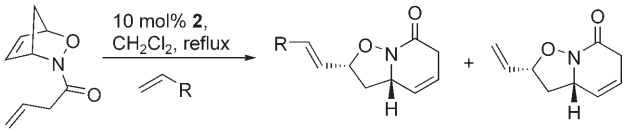
The failure of the final CM step was attributed to the bulky TBS group, which has a favorable effect on the equilibrium of ring rearrangement,[16a] but an adverse steric effect on CM. Transformation of the TBS-protected alcohol into the corresponding enone **122** was performed, as these substrates were proven to be efficient in CM. Indeed, treatment of **122** with 5 mol% catalyst **2** and 3 equivalents of



Scheme 47. ROM–RCM–CM sequence described by Stragies and Blechert.[56]

olefin **121** resulted in the formation of *E*-configured product **123** in 48% yield. The main by-product observed was the one resulting from CM between **121** and **122**, which demonstrates clearly the concurrent reaction and, therefore, the main problem of these sequences.

Recently, Kouklovsky and co-workers applied for the first time dihydrooxazines in an ROM–RCM–CM process to give direct access to isoxazolo[2,3-a]pyridine-7-ones (Scheme 48).[57] These versatile scaffolds are structural



127a	R = CH_2TMS	**128a**	**129a**	85:15	93%
127b	R = $(CH_2)_5Me$	**128b**	**129b**	60:40	85%
127c	R = $(CH_2)_3OH$	**128c**	**129c**	96:4	91%

Scheme 48. Application of dihydrooxazines in ROM–RCM–CM. TMS = trimethylsilyl.

motifs shared by tyrosine kinase inhibitors and can be synthetically viewed as latent 1,3-*cis*-aminoalcohols. Initial experiments with bicyclic substrate **127a** under ethylene atmosphere failed. However, addition of allyltrimethylsilane as external olefin furnished a 60:40 mixture of **128a** and **129a** in 91% yield. Optimization of the **128**/**129** ratio up to 85:15 was achieved by increasing the amount of catalyst **2** to 10 mol% (in two portions of 5 mol%). Different external alkenes were tested under the optimized reaction conditions, with 1-pentene-5-ol being the best CM partner (91%, **128c**/**129c** = 96:4).

Phillips et al. employed a norbornene derivative in an ROM–RCM–CM process during the synthesis of the bicyclic fragment of geodin A[58] and (+)-cylindramide A,[59] two tetramic acid containing macrolactams (Scheme 49). In both cases, bicycle **130** served as the metathesis precursor, which should undergo CM with different olefins after rearrangement. Application of **131** as CM partner led to the formation of 54% of product **133** ($E/Z = 1.5:1$) along with 30% of **132**, thus indicating the partial failure of the final CM step. Interestingly, when olefin **134** was employed, none of the CM unreacted rearranged product was found, and the desired bicycle **135** was formed in 59% yield, with a selectivity of $E/Z = 2:1$.

Recently, Funel and Prunet examined the synthesis of fused tricyclic frameworks by an ROM–RCM–CM sequence (Scheme 50).[60] By addition of different alkenes, the formation of tricycles **137a–c** was achieved. Amazingly, cleaner and better results were obtained when substituted olefins were employed, in comparison to the reaction under ethylene atmosphere. This effect was ascribed to the fact that nongaseous alkenes favor the domino process by competing with polymerization. CM proceeded stereoselectively in both cases (only *E*) and without the detection of bicyclic CM adducts.

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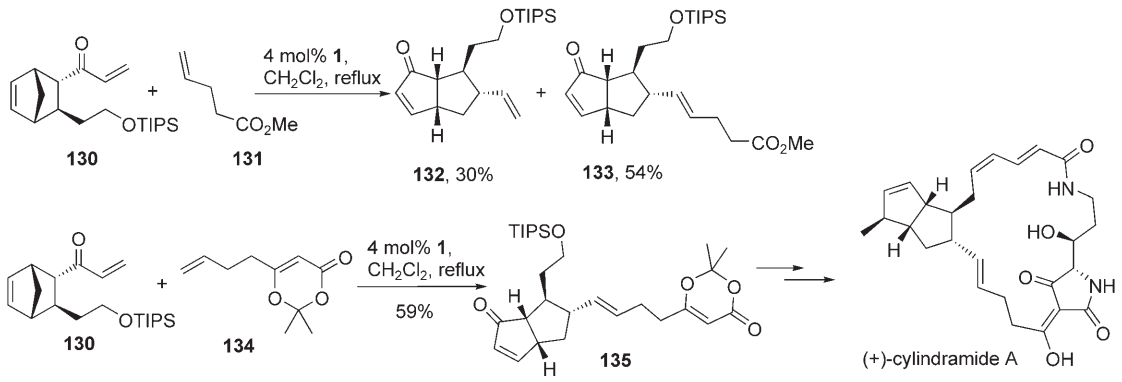
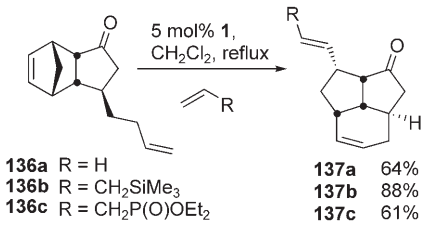


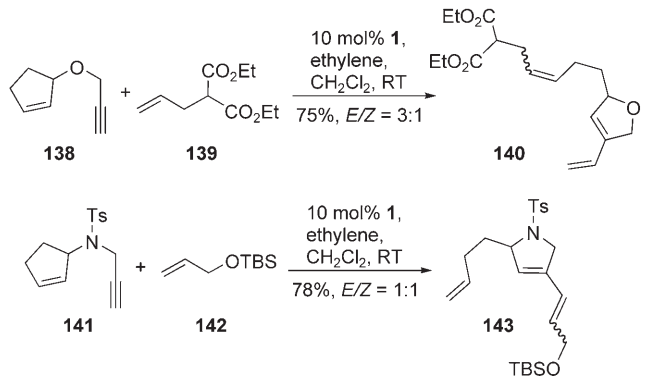
Scheme 49. Synthesis of naturally occurring macrolactam (+)-cylindramide A by Phillips et al.[58,59]



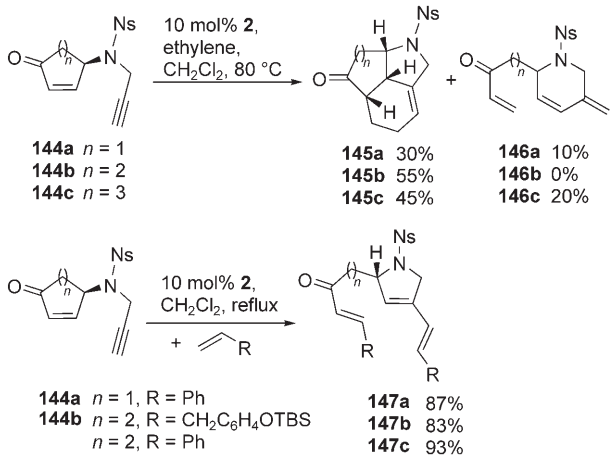
Scheme 50. Norbornene derivatives as substrates in ROM–RCM–CM processes by Funel and Prunet.[60]

As the addition of an external olefin was proven to be essential for ring rearrangements that involve triple bonds, the observation of ROM–enyne-RCM–CM processes should be straightforward. In accordance with the expected mechanism (Scheme 23), we observed the incorporation of olefin **139** at the terminal alkene in the synthesis of dihydrofuran **140** (Scheme 51).[61] Interestingly, the transformation of N-substituted cycloalkene **141** led to CM between olefin **142** and the butadiene moiety.[38] Whether this change in mechanism is dependent on an electronic or chelating effect of the heteroatom is still unclear.

Products of ROM–enyne-RCM processes were shown to be suitable substrates for cycloadditions. Therefore, we examined the ring rearrangement of cyclic enones **144a–c** with regard to further functionalization of the adduct by CM (Scheme 52).[62]



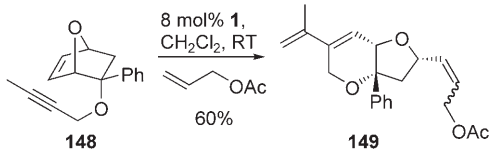
Scheme 51. Selective CM of cyclopentenes in the ROM–enyne-RCM–CM process.



Scheme 52. RCM–enyne RCM of cycloenones.

Although treatment of enones **144a–c** with 10 mol% catalyst **2** proceeded efficiently, an unexpected product mixture was obtained. Besides the cycloaddition products, cyclohexenes **146a–c** were also isolated, which indicates that apart from the *exo* product, enyne RCM also proceeded by *endo* ring closure (Scheme 21). By addition of olefins other than ethylene as CM partners, the formation of the *endo* product was completely suppressed and gave the rearranged systems **147a–c** in good yields. Notably, both the olefin and the butadiene moiety of the heterocycles underwent CM and gave the products with *E* selectivity.

Plumet and co-workers used this sequence for norbornene **148**.[63] Conduction of the domino metathesis with 8 mol% catalyst **1** and allyl acetate as CM partner led to formation of bicycle **149** in good yield (Scheme 53). Only the CM be-



Scheme 53. Oxanorbornenes as substrates in the ROM–enyne-RCM process.

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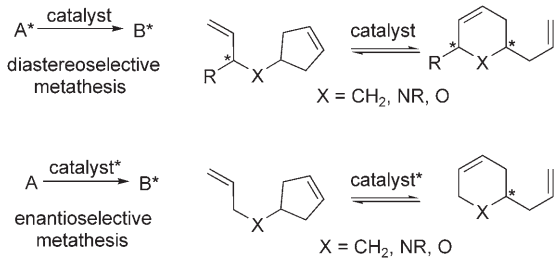
tween allyl acetate and the terminal olefin was observed; the butadiene unit proved to be unreactive, which might be explained by the disubstituted alkyne in **148**.

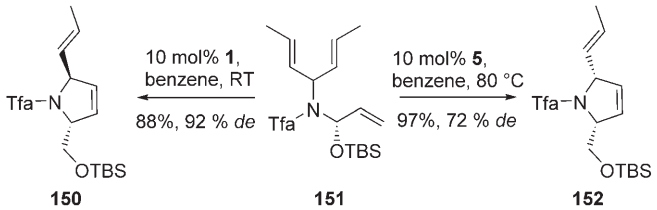
4. Chirality-Inducing RRM

There are two possible pathways for the generation of a new chiral center by means of metathesis: induction by chiral information in the catalyst itself (enantioselective metathesis) or the application of chiral substrates, in which the existing stereocenters influence product formation in a diastereoselective manner (Scheme 54).



Scheme 54. Chiral induction in metathesis reactions.

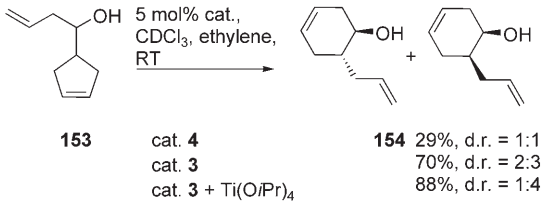
The advantages of diastereoselective metathesis sequences are that no expensive and difficult-to-access metal complexes are required and a wide spectrum of substrates can be employed. The first diastereoselective RCM (dRCM) was reported in 1996.[64] Depending on the catalyst utilized, chiral triene **151** gave, upon ring closure, the disubstituted cyclopentene with different diastereoselectivities (Scheme 55). Whereas catalyst **5** led to the *cis*-substituted product **152** (72% *de*), cyclopentene **150** with *trans*-configured side chains was obtained with excellent diastereoselectivity (92% *de*) when **1** was employed.



Scheme 55. The first example of diastereoselective RCM. Tfa = trifluoroacetamide.

Recently, a diastereoselective RRM (dRRM) process was reported by our group.[65] By analogy to dRCM, a stereocenter positioned in the side chain of cycloalkenes should influence the generation of a new chirality center in the rearranged product. The challenge of these processes consists in adjusting the reaction towards the desired product, preferably with high selectivity.

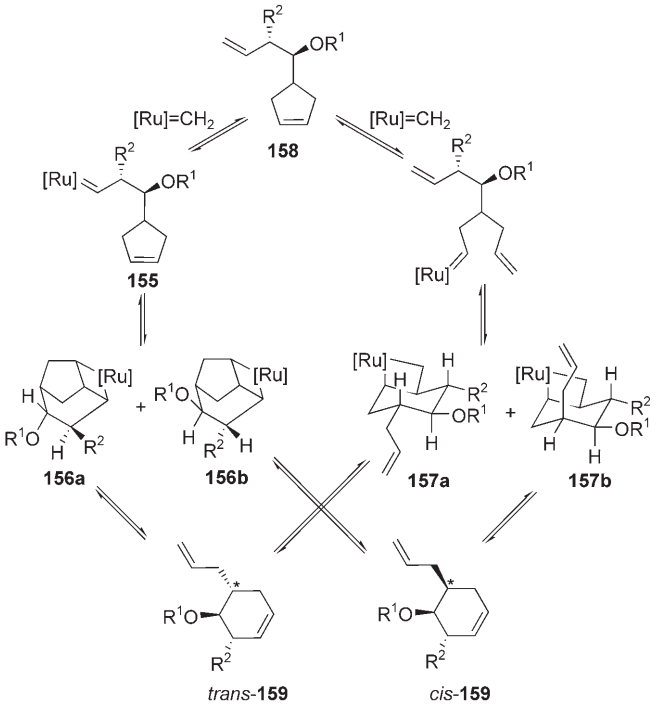
As expected, initial experiments with cyclopentene **153** demonstrated that diastereoselectivity and conversion strongly depend on the catalyst (Scheme 56). Subjection of **153** to 5 mol% catalyst **4** resulted in only 29% conversion



Scheme 56. Catalyst dependency of dRRM processes.

without selectivity, whereas catalyst **3** gave the *cis* product with 2:3 (d.r.) selectivity after 70% conversion. The selectivity was improved by the addition of 1.5 equivalents of titanium isopropoxide, which shifted the diastereomer ratio to 1:4. Equilibration experiments performed with isolated **154** resulted in no change in the diastereomer ratio, thus confirming the kinetic control of the process.

Mechanistically, dRRM can be either thermodynamically or kinetically controlled (Scheme 57). Intermediate **155** is the result of an initial interaction of the catalyst with the exocyclic double bond; it then undergoes ring closure via the tricyclic intermediates **156a** and **156b** to the rearranged products. Alternatively, initial endocyclic-double-bond attack can occur, followed by RCM via the diastereomers **157a** and **157b**. In both cases, chiral induction can be caused by either the energy difference of the diastereomeric inter-



Scheme 57. Proposed mechanism for dRRM.

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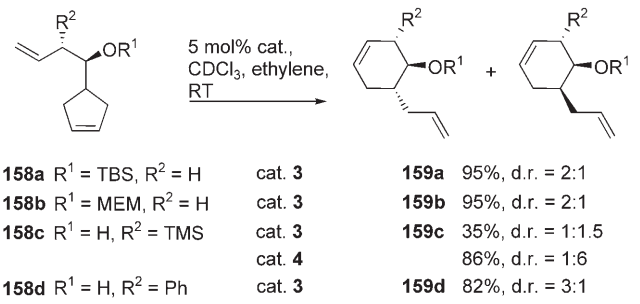
mediates (kinetic control) or that of the products formed (thermodynamic control).

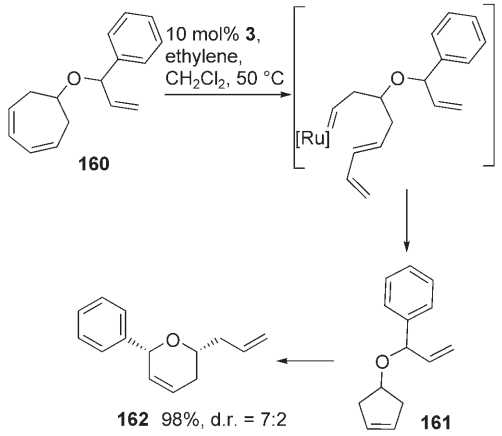
To investigate the influence of precoordination of the metal center in contrast to steric influence, different O-protecting groups were tested in dRRM (Scheme 58). In all



Scheme 58. Examination of the electronic and steric influences of dRRM. MEM = 2-methoxyethoxymethyl.

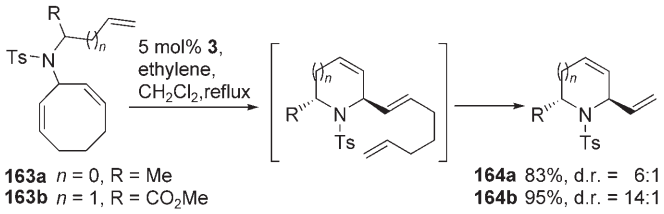
cases, no effect of the structure, together with a moderate selectivity towards the *trans* product, was observed. However, the introduction of a second stereocenter into the side chain was found to have a strong influence on the selectivity. Rearrangement of the TMS-substituted cyclopentene **158c** in the presence of catalyst **3** resulted in low diastereoselectivity (d.r. = 1:1.5). On the other hand, with catalyst **4**, **158c** was converted into cyclohexene **159c** with high selectivity (d.r. = 1:6) in favor of the *cis* isomer, thus demonstrating the strong influence exerted by the catalyst in this process. Interestingly, the slim phenyl substituent gave preferentially the *trans* product with inverse selectivity relative to the unsubstituted substrate **153** (Scheme 56).

The synthesis of heterocycles by employing dRRM has also been achieved.[65] Upon treatment of cycloheptadiene **160** with 10 mol% catalyst **3**, the unexpected rearranged product **162** was obtained in 98% yield and with high diastereoselectivity (d.r. = 7:2) towards the *cis* isomer (Scheme 59). As the formation of cyclopentene **161** was detected by GC–MS and NMR spectroscopy during the course of reaction, a reasonable explanation for the product is initial ring opening followed by subsequent RCM to the five-membered ring through cleavage of butadiene, which then rearranges to **162**. This formal ring contraction is similar to the one reported by Lazarova et al.[23] (Scheme 9).



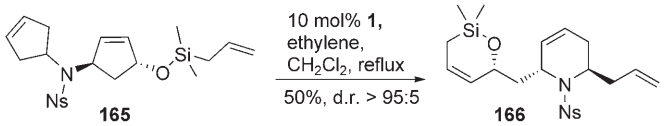
Scheme 59. dRRM of cycloheptadiene **160** with unexpected ring contraction.

For the synthesis of N-heterocycles, cyclooctadienes **163a** and **163b** were chosen as suitable precursors, as they cannot undergo ring contraction due to the domino process. Treatment of **163a** with 5 mol% **3** yielded tetrahydropyridine **164a** in 83% yield, in which the side chain was cleaved by either CM or RCM to cyclopentene (Scheme 60). Even higher selectivity was observed for the allylglycine derivative **163b**, which rearranged in favor of the *trans* piperidine with a diastereomer ratio of 14:1.



Scheme 60. dRRM of cyclooctadienes in the synthesis of N-heterocycles.

Diastereoselective RCM–ROM–RCM processes have also been proven to be possible.[66] Upon treatment with 10 mol% catalyst **1**, **165** rearranged cleanly with a gratifying selectivity of d.r. > 95:5 in favor of the *trans* piperidine **166** (Scheme 61).



Scheme 61. The first example of diastereoselective RCM–ROM–RCM by Neidhöfer and Blechert.[66]

Recently, we reported the first natural-product synthesis that includes dRRM as the key step (Scheme 62).[67] Compound **160** was shown to rearrange via cyclopentene **161** to the *cis*-configured dihydropyran with high selectivity (Scheme 59). Therefore, we chose cyclopentene **167** as a suitable metathesis precursor. However, the envisaged incorporation of styrene **169** by CM required the migration of the terminal double bond. This was achieved in a one-pot sequence by treatment of **167** with 10 mol% **3** followed by addition of sodium borohydride after complete dRRM to form the ruthenium hydride catalyst for isomerization in situ. Final CM and hydrogenation gave rise to (−)-centrolobine.

Enantioselective RRM (entRRM) processes have been realized by Schrock, Hoveyda, and co-workers.[68] Chiral molybdenum complex **170a** showed very good reactivity and enantiomeric excess in different RRM processes

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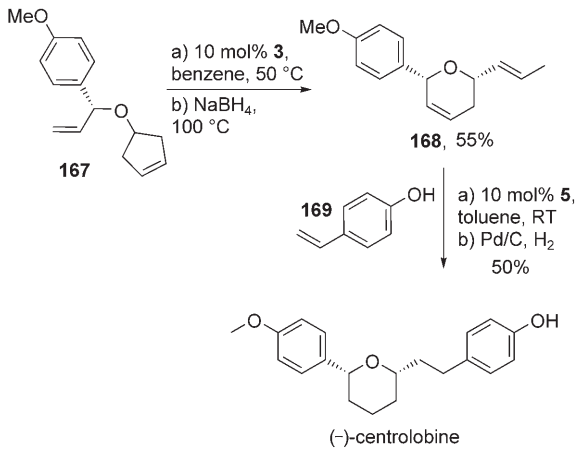
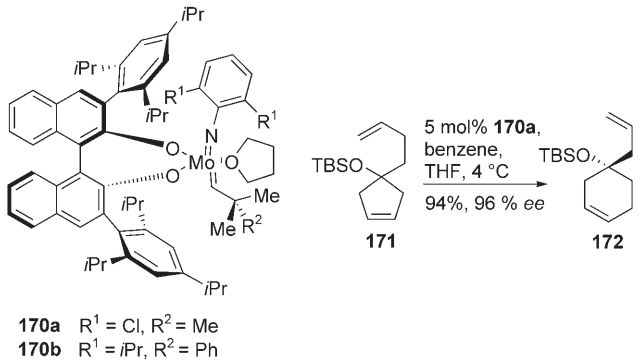


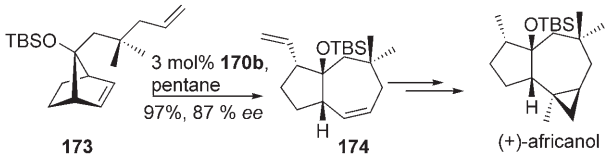
Scheme 62. Application of dRRM in the synthesis of (−)-centrolobine.

(Scheme 63). Cyclopentene **171**, for instance, was rearranged in 94% yield and with 96% *ee*.



Scheme 63. An example of enantioselective RRM published by Schrock, Hoveyda, and co-workers.[68]

The utility of this concept was demonstrated through an enantioselective approach to (+)-africanol.[69] Upon treatment of **173** with 3 mol% **170b**, the [5.3.0] bicycle **174** was obtained in 97% yield and with 87% *ee* (Scheme 64). Although this process proved to be efficient for a number of substrates, it is still limited by the required utilization of an air- and moisture-sensitive chiral catalyst.



Scheme 64. Application of entRRM in the synthesis of (+)-africanol.

5. Conclusions and Outlook

Ring-rearrangement metathesis has proven to be a very efficient and versatile method for the construction of carbocycles, heterocycles, and polycyclic structures. Owing to the enormous possibilities presented by varying the applied cycloolefin (monocycle vs. bicycle), the side chains (length, position, substitution pattern), and the RCM partner (alkene vs. alkyne), an array of cyclic substrates is accessible. The extension of the ROM–RCM sequence by further metathesis steps has been also established in organic synthesis and leads to even more complex structures, although the need of catalysts with higher activities is still required, as seen in examples that involve four or five metathesis reactions in sequence.

Domino metathesis has often been applied in natural-product synthesis. The transfer of stereoinformation is an attractive feature, but chiral starting materials are still needed. Further development of asymmetric processes is therefore essential. Either by easily accessible, cheap, and efficient chiral catalysts or by highly diastereoselective processes, the consistency of ring-rearrangement metathesis in future organic synthesis can be confirmed.

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