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Review Commentary

From olefin cyclopropanation to olefin metathesis through catalyst engineering: recent applications of olefin metathesis to fine organic synthesis and to polymer chemistry

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ABSTRACT: An overview of the recent synthetic breakthroughs brought about by the discovery of new, functional group tolerant late transition metal (Rh and Ru)-based catalysts is proposed. Whereas dirhodium(II)-based complexes promote only carbene transfer reactions to olefins (i.e. olefin cyclopropanation), a few ruthenium-based catalysts can be engineered and fine tuned so as to mediate either carbene-transfer reactions or olefin metathesis. The different outcome of the reactions can be rationalized by the capability of the metal center to coordinate or not both the carbene and the olefin. This quite simple-minded approach indicates that several available coordination sites at the metal center favors metathesis reactions to the prejudice of olefin cyclopropanation. Examples of recent applications in ring opening metathesis polymerizations and copolymerizations include the formation of postpolymers of polydienes, of carbohydrate-substituted polymers and of telechelic oligomers. Application of the same ruthenium-based catalysts in ring-closing metathesis is illustrated by the formation of crown ether analogs, of unsaturated peptides and amino acids, of β-lactams, and of different bicyclic systems.

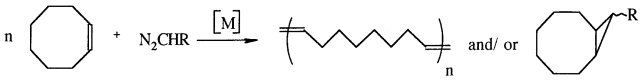
KEYWORDS: olefin metathesis; olefin cyclopropanation; catalyst engineering; fine organic synthesis; polymer chemistry

INTRODUCTION

Attempts to understand how metal complexes mediate the formation of carbon–carbon bonds is a major theme in organometallic chemistry. A much studied example among the carbon–carbon bond-forming reactions is the reaction of metal–carbene bonds with olefins, a reaction leading to different products, depending on the metal, its oxidation state and its ancillary ligands.[1–3]

The aim of this non-comprehensive review is to give a general overview of the breakthroughs brought about in organic synthesis and olefin metathesis by the recent discovery of new metal–carbene complexes based on late transition metals. The search for catalysts based on late transition metals was justified by the extreme sensitivity of the catalysts based on early transition metals (Mo, W, etc.) to oxygen and water, by their poor tolerance towards polar functional groups and, additionally, by their difficult synthesis.

A general overview of carbene chemistry mediated by Group 8, 9 and 10 transition metals (TM) reveals that, among second-row metals, palladium- and rhodium-based complexes provide outstanding cyclopropanation catalysts. These two metals, however, have no applications in olefin metathesis.[2–6] Ruthenium-based complexes, on the other hand, are known to mediate both olefin metathesis and/or cyclopropanation reactions,[7–13] as sketched in Scheme 1 for a cycloolefin.



Scheme 1

Third-row metals usually form relatively stable organometallic complexes that hamper their utilization as catalysts, although there are some notable exceptions.

First-row metals usually form much less active catalysts. Cobalt-catalyzed cyclopropanation remains restricted to activated olefins and has been reported to occur with substantial radical contribution from the cobalt carbenoid. A significant breakthrough in the field comes, however, from a recent report indicating that simple cobalt derivatives efficiently catalyze the ROMP of norbornene when activated by aluminium alkyls.[14]

To date, our level of understanding of these reactions remains primitive and a unified view of the reactions of transition metal–carbene complexes seems out of reach at present. Many fundamental questions remain totally or partially unanswered. Among them are whether there are

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(always) common intermediates in olefin metathesis and in olefin cyclopropanation and, if so, what the factors are that direct the reaction towards carbene transfer or olefin metathesis.

The intermediacy of metallacyclobutanes of early transition metals in olefin metathesis is now well ascertained, but the role of such putative intermediates in reactions catalyzed by late transition metals (cyclopropanation reaction included) is much more speculative and lacks experimental support in a number of cases.

The general trends are that *electrophilic* metal–carbene complexes usually react with olefins to form cyclopropanes (the cycloaddition reaction is classified as a 'carbene transfer reaction') whereas *nucleophilic* metal–carbene complexes (the so-called 'alkylidene complexes') react with electrophiles such as aldehyde or ketone carbonyl groups to give olefins in a Wittig-like fashion. Complexes of this second type (but not all of them) also catalyze olefin metathesis reactions. This view is, however, a gross oversimplification. There are many exceptions to the general rule and there seems to be a continuum of reactivity between the two types of complexes. Variations of the metal oxidation state and/or ancillary ligands in a complex alter the reactivity of the carbene center. The nature of the substrate involved and of the solvent used (coordinating or not) can further influence the outcome of the reaction.

The separation between a 'metal–alkylidene' and a 'metal–carbene' complex is thus not clear-cut and some workers now refer to 'metal–carbene' complexes for both situations. This view is supported by the theoretical model proposed by Cundary and Gordon.[15,16] In this model, a clear difference in the bonding of a 'metal–alkylidene' and a 'metal–carbene' is no longer needed, as the properties of the metal–carbene species result from the relative statistical weight of neutral, nucleophilic and electrophilic resonance forms.

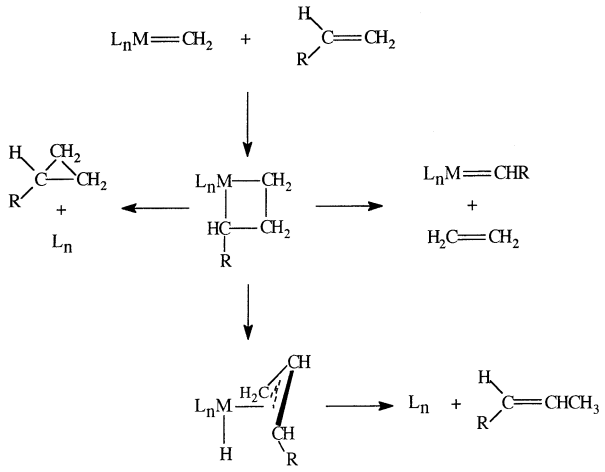
Such a model substantiates the prospect of observing competitive metal–carbene and metal–alkylidene reactions. It also indicates that this behavior should occur mostly with second- and third-row Group 8–10 metals when the loss of exchange energy in forming covalent bonds is not as large as for their first row congeners [about 5 kcal mol^{-1} (1 kcal = 4.184J) smaller on average].[17–19] These expectations are also globally in line with the results of *ab initio* calculations (GAMESS quantum chemistry program) for Group 4–6 metal complexes. According to these studies, the intrinsic nature of the M=C bond can be changed within certain limits by modification of the ancillary ligands and substituents on the carbene (alkylidene) carbon.[15,16] Furthermore, greater polarization of the metal–carbene bond in an $M^{+}=C^{-}$ fashion should correlate with a greater metathesis activity, the heaviest metals being the most nucleophilic at the α-carbon.

Most informative is the observation of amphiphilic metal–carbene complexes. Such complexes are not very common and examples of carbene complexes which react with both acids and bases appear so far to be restricted to ruthenium and rhenium complexes.[20–22]

INTERMEDIACY OF METALLACYCLOBUTANES IN CYCLOPROPANATION REACTIONS

The chemistry of metallacyclobutane compounds has attracted considerable attention in the past two decades. In addition to having been used successfully in organic synthesis, metallacyclobutanes play an important role in a number of catalytic transformations and, *inter alia*, have been proposed as intermediates in olefin metathesis[23] and the cycloaddition of alkenes.[24]

Many metallacyclobutane derivatives of late TM are known. Some of them (e.g. platinacyclobutanes) are thermally stable. Metallacyclobutane decomposition can afford alkanes, olefins, carbene–olefin complexes, allyl complexes and also cyclopropanes (see Scheme 2). The subject has been reviewed recently.[25] The reactions are often poorly selective.



Scheme 2

Metallacyclobutane compounds relevant to catalyzed cyclopropanations are much less well documented,[25] however, possibly because reductive elimination is then a fast process. Actually, the relevance of metallacyclobutanes as intermediates in cyclopropane formation from olefins and diazo compounds may be questioned and remains a matter of debate. The intermediacy of metallacyclobutanes in carbene transfer reactions is in many cases not borne out either by direct observation or by clear mechanistic studies. Formation of an intermediate metallacycle does not appear to be the general rule in olefin cyclopropanation. Formation of a metallacyclobutane requires coordination to the metal center of both the olefin and the carbene. The evidence often points to direct reaction of the metal carbenes with alkenes without prior olefin coordination. For example, olefin coordination does not appear to take place in dirhodium tetracarboxylate-catalyzed cyclopropanation reactions.

Furthermore, partial release of free carbenes from metal carbene complexes may occur, at least in the context of rhodium carbenoid insertions into C—H bonds.[26] An equilibrium between free and complexed carbene was also suspected in some cycloaddition reactions, depending on the carboxylate residues of the dirhodium(II) catalyst.[27] This does not exclude, of course, the possibility that metallacyclobutanes play a pivotal role in some catalyst systems, especially in Cu- and Pd-catalyzed reactions.

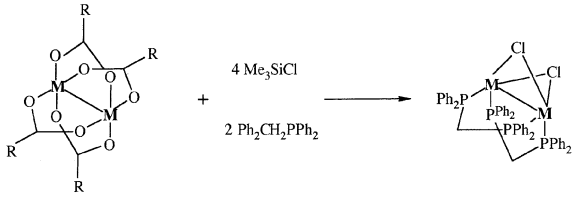
Hence it appears that there is apparently no single general mechanism model for olefin cyclopropanation.[28] The basic mode of ring closure in metal-catalyzed carbene transfer reactions must still be regarded as hypothetical in most cases. The intermediacy of metallacyclobutanes is, however, clearly established in some catalyzed reactions. A further question then is why some metallacyclobutanes yield cyclopropanes whereas others catalyze olefin metathesis. Are the two reactions in competition?

DIRHODIUM(II) AND DIRUTHENIUM(II) CARBOXYLATES

If we look at typical cyclopropanation catalysts, it is noteworthy that to date, all efficient rhodium-based systems possess the rigid dirhodium(II) lantern framework [e.g. as in dirhodium(II) tetracarboxylates and the related dirhodium(II) carboxamidates],[1,3,29] with the exception of some rhodium(III) porphyrins which are stable complexes.

The lantern framework of the complexes confers structural stability on the dirhodium(II) complexes (structure shown in Scheme 3). The anciliary ligands are kinetically stable and there is apparently only one coordination site per metal. Calculations and chemistry indicate moderate back-bonding to the carbene ligand, resulting in very labile electrophilic carbenoid species.[20,21,27] The cyclopropanation reaction proceeds apparently via frontier orbital control, the LUMO corresponding to the carbene p-orbital. The general picture of the reaction mechanism involves interaction of the resulting rhodium–carbene complex with an uncoordinated olefin in a bimolecular reaction. This model has the merit of rationalizing the observation that no metathesis reactions are initiated by dirhodium(II) complexes, *inter alia* because there is no room for olefin coordination, thus hindering metallacyclobutane formation. The reaction mechanism of dirhodium(II)-catalyzed cyclopropanations is similar in many respects to that proposed for rhodium porphyrin-catalyzed cyclopropanation of alkenes by ethyl diazoacetate.[30] In the latter case, the porphyrin ligand acts as a 'wall' that eventually prevents coordination of an olefin in a *cis* position relative to the carbene ligand. It must be stressed, however, that only few direct experimental data bear on the mechanism of the reactions of diazo compounds mediated by rhodium complexes or on metal–carbene intermediates. The putative intermediate carbene complex has never been observed in a catalytic system.

However, addition of one or several equivalents of trimethylsilyl chloride to dirhodium(II) tetraacetate brings about the formation of a new catalyst system, capable of carrying out (up to a certain extent) the ring-opening metathesis polymerization (ROMP) of norbornene. Trimethylsilyl chloride is known to remove bridging acetate ligands[31] and eventually to make room for olefin coordination. This reaction is exemplified in Scheme 3 with dppm (diphenylphosphinomethane) as an added ligand.

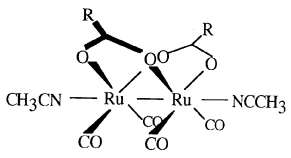


Scheme 3

If the reaction is carried out in neat olefins in the absence of such strongly coordinating ligands, olefins are expected to be ligated to the metal centres instead of the chelating ligand. A typical and very selective olefin cyclopropanation catalyst can thus be engineered so as to also mediate olefin metathesis.

On the other hand, the corresponding diruthenium tetracarboxylates ($s^2p^4d^2d^{*2}p^{*2}$, paramagnetic at room temperature) are much more labile than their dirhodium analogs.[32] Such complexes promote both carbene transfer reactions and olefin cross-metathesis when reacted with a mixture of styrene and norbornene.[33] Whether these different reactions were initiated by a common species remains unknown, however, but the metathetical activity was attributed to the kinetic lability of the carboxylate bridges which allowed the coordination of both the olefin and the carbene ligand. No metathesis was observed in the absence of added diazo compound.

Although the activation of the diruthenium(II) complexes with diazo compounds gave relatively poor ROMP catalysts, it was concluded that metathesis activity could probably be increased by utilizing metal complexes bound to more labile ligands. This led first to the study of some diruthenium(I) dicarboxylates of general formula $[Ru_2(RCO_2)_2(CO)_4(MeCN)_2]$ (Scheme 4), where the metal is axially ligated to labile acetonitrile ligands in the hope of favoring the simultaneous ligation of the carbene ligand and of the olefin after disengagement of one or several CO ligands.

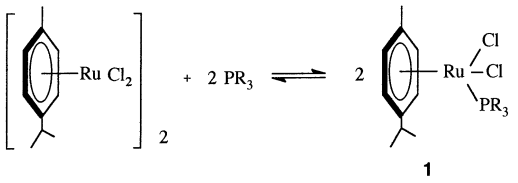


Scheme 4

It turned out that these complexes were again kinetically too stable. The release of CO ligands is not straightforward at moderate temperatures. Accordingly, these complexes did not promote olefin metathesis below 100 °C but they were good cyclopropanation catalysts.[34] Some ROMP was, however, initiated at 100 °C (about 5% conversion with cyclooctene and more than 70% conversion with the more strained norbornene). Hence, although cyclopropanation is easily the most preferred reaction pathway, such ruthenium complexes nevertheless also have the ability to initiate olefin metathesis. This contrasts with what is commonly observed with dirhodium carboxylates where the ligands are kinetically inert under the reaction conditions.

RUTHENIUM(II)–ARENE COMPLEXES

The search for metal complexes containing more labile ligands led to the discovery of another class of versatile and very efficient catalyst precursors based on the air-stable and readily available $[(arene)RuCl_2]_2$ complexes. According to the ligand with which they react, these dimeric species give new, monomeric complexes that can promote either olefin metathesis or olefin cyclopropanation. For instance, on reaction with an equimolar amount of phosphine they form the monoadduct complexes **1** (Scheme 5). When the phosphine is tricyclohexylphosphine (PCy_3), a bulky and basic phosphine, the resulting complex is an outstanding olefin metathesis catalyst precursor.

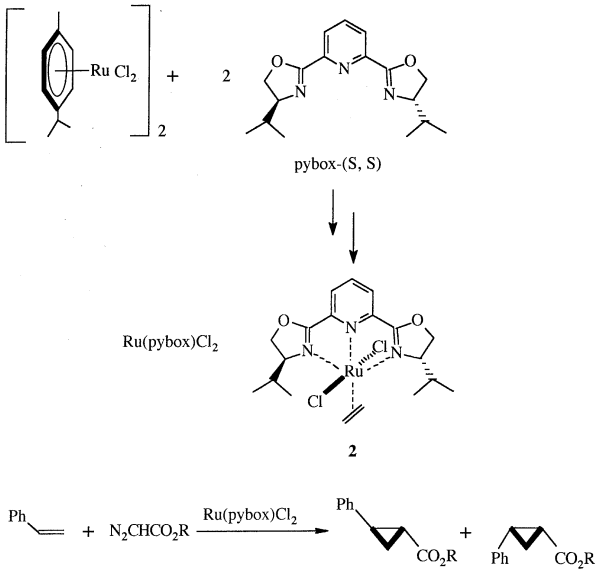


1

Scheme 5

Complexes such as (*p*-cymene)$RuCl_2PCy_3$ spontaneously not only promote the ROMP of norbornene derivatives (i.e. of strained cycloolefins) to high molecular weight polynorbornenes, but also they are effective at polymerizing cyclooctene, functionalized cyclooctenes and other low-strain cycloolefins to polyalkenamers when activated *in situ* by the addition of a diazo compound.[35] Cyclooctene, for instance, undergoes immediate ROMP when a catalytic amount of trimethylsilyldiazomethane (TMSD) is added to the reaction mixture. The diazo compound reacts with the Ru complex to form highly active [Ru]=$CHSiMe_3$ alkylidene species which show good tolerance to organic functions and initiate the ROMP. The catalytic activity for olefin metathesis is attributed to an easy release of the arene ligand upon addition of the diazo compound, permitting olefin coordination and subsequent formation of ruthenacyclobutanes.[35] The formation of the ruthenacyclobutane has not been demonstrated however.

Upon reaction with chelating bi- or tridentate ligands, $[(p\text{-cymene})RuCl_2]_2$ forms 18-electron complexes **2** that do not promote olefin metathesis (Scheme 6; the only labile ligand is ethene). This can again be rationalized by the fact that only one site is then available for coordination. Therefore, these complexes no longer mediate olefin metathesis but only carbene transfer reactions (olefin cyclopropanation), sometimes with high enantioselectivities.[36–38]



Scheme 6

This naive approach, although it ignores a number of important factors such as a colinear or perpendicular binding of the incoming olefin to the M=C bond, or the puckering of the metallacycles[39,40] which might influence the outcome of the reaction, fits well the observations made so far and seems to have a good predictive value, at least for the family of ruthenium(II)-based catalysts discussed here.

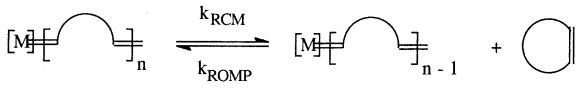
Grubbs and co-workers[41,42] have recently reported on analog catalytic systems and isolated the first well defined and air-stable ruthenium(II)–carbene complexes of general structure [*trans*-$(PCy_3)RuCl_2$=CHR]. Such complexes are very efficient metathesis catalysts. They also promote the ROMP of low-strain olefins as well as the catalytic ring-closing metathesis (RCM) of functionalized dienes.[41,42] These catalysts are currently finding an ever increasing role in organic synthesis.

SYNTHETIC APPLICATIONS OF RUTHENIUM-BASED CATALYSTS

Organic and natural products synthesis

As new catalysts have become more available and more

tolerant of functionality, the olefin metathesis reaction has started to play an increasingly more significant role in organic synthesis, a trend that is expected to develop further in the coming years. In particular, the discovery of efficient catalysts for the cyclic metathesis of non-conjugated dienes stands as one of the major developments in the field of organic annulations during the past decade. In this context, ruthenium-based carbene complexes have recently emerged as a new class of particularly versatile catalysts.[42,43] The same catalysts that promote the ROMP of cycloolefins also promote the ring-closing metathesis (RCM) of terminal diolefins. Whereas in ROMP ring strain is a requisite driving force because the reaction is entropically disfavored, RCM is entropically driven (Scheme 7).

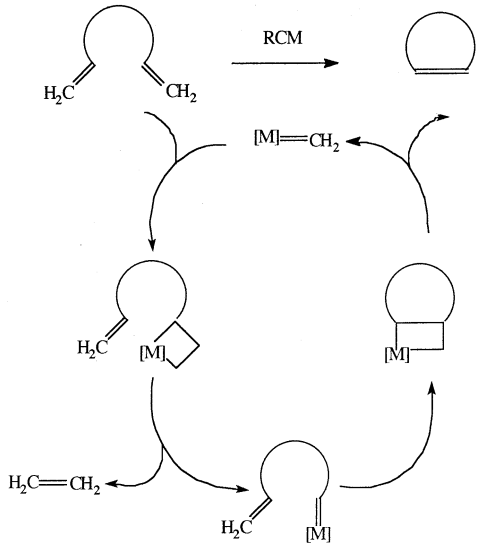


Scheme 7

As with all ring-forming reactions, the RCM of medium-sized rings is controlled by several factors that include ring strain, the kinetics of ring closing and competing metathesis-based polymerization (ROMP and acyclic diene metathesis, ADMET).

The real synthetic breaktrough brought about in cyclization reactions is illustrated below by some recent applications, permitting easy access to a variety of (new) carbocycles and heterocycles, including *inter alia* crown ethers, unsaturated pseudopeptides, non-natural and conformationally restricted amino acids and peptides and β-lactams.

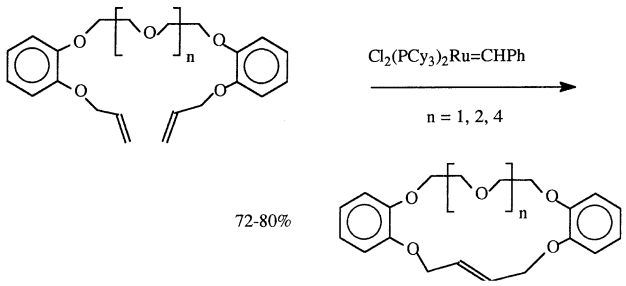
Scheme 8 depicts the general mechanistic pathway of a ring-closing metathesis reaction.



Scheme 8

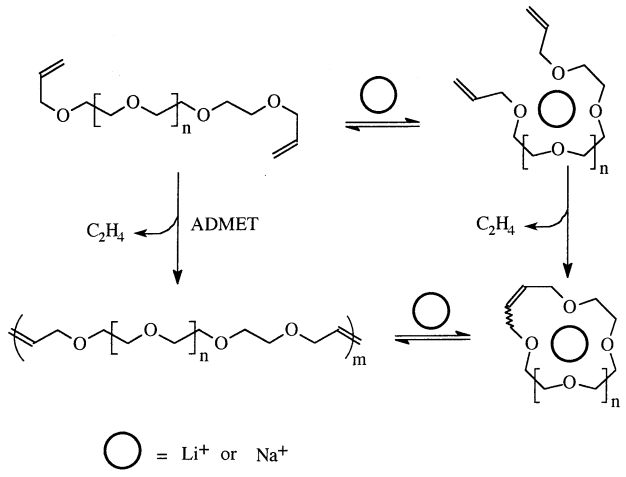
From an industrial perspective, ring-closing metathesis has many potentially attractive features for the large-scale manufacture of cycloalkenes. The new generation of catalysts being fairly active, the metal species is often present in less than 1% equiv. relative to the unsaturated substrate. This technology utilizes no additional co-catalyst. Cyclization takes place under mild conditions in little or no solvent, and produces only a volatile side product, usually ethene.

Synthesis of crown ethers. Ruthenium alkylidene catalysts provide straightforward access to a new family of unsaturated crown ether analogs, as illustrated in Scheme 9.[44]



Scheme 9

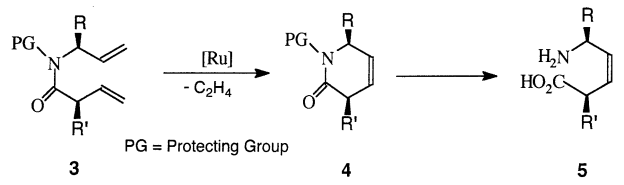
Yields of crown ethers derived from linear polyethers can be significantly increased when an appropriate metal ion template is utilized to preorganize the cyclization. Marsella *et al.*[45] have shown that preorganization of linear polyethers possessing terminal olefins around a suitable complementary metal ion indeed provides the conformational restrictions required to favor RCM. Identically, the template-directed depolymerization of dilute solutions of terminally unsaturated polyethers results in the formation of cyclic ethers in the presence of the appropriate metal ion (Scheme 10)



Scheme 10

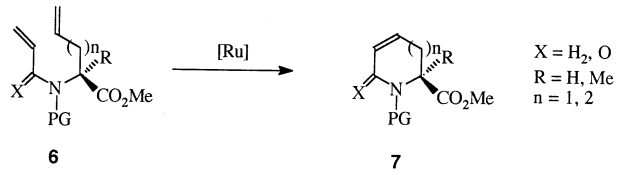
Synthesis of peptides and amino acids. Backbone modification of biologically active peptides constitutes a strategy which may be aimed at various goals. Metathetical ring closure of dienic amides **3** (Scheme 11) constitutes the key step in the synthesis of the unsaturated

lactams **4**, which are direct precursors of the dipeptide (*Z*)-ethylenic isosteres **5**.[46]



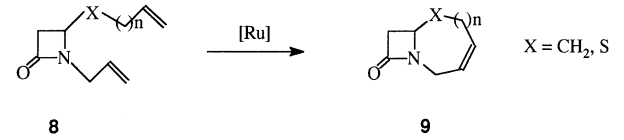
Scheme 11

In the same vein, the cyclization of enantiopure amino acid-derived precursor **6** gives the corresponding unsaturated cyclic amino acid **7** as shown in Scheme 12. The resulting six- and seven-membered rings are versatile functionalized heterocyclic ring systems that either can be used as building blocks in drug or natural product synthesis or serve, for example, as conformationally restricted amino acids analogs.[47]



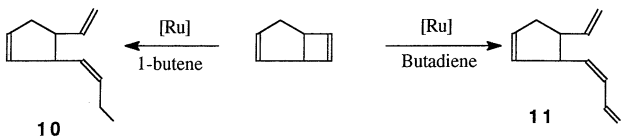
Scheme 12

Synthesis of *β*-lactams. A number of previously unexplored systems are now amenable to alkene metathesis. For instance, *β*-lactams are well tolerated under metathesis conditions, furnishing both mono- and bicyclic systems in good to excellent yields. The carbacephem **9** was readily prepared from **8** in excellent yield (81%) with 5 mol% of $RuCl_2(PCy_3)_2$=CHPh as catalyst when X = CH_2 but in a much lower yield (22%) when X = S[48] (Scheme 13).



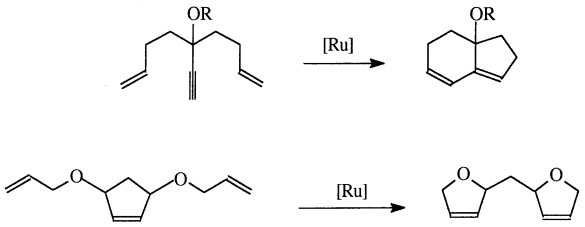
Scheme 13

Synthesis of polyunsaturated molecules. The synthesis of the brown algae pheromones multifidene (**10**) and viridiene (**11**) is possible by using slow addition techniques. Although different isomers are produced, the newly formed olefins are predominantly *cis*[49] (Scheme 14).



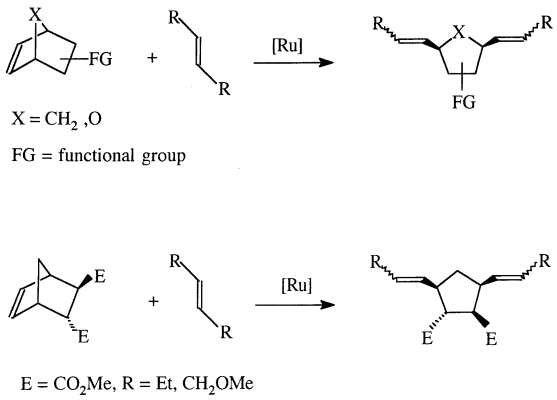
Scheme 14

Synthesis of bicyclic systems. The combination of enthalpically driven ROMP and entropically driven RCM constitutes a new strategy for the synthesis of organic ring systems. The method utilizes the unsaturation of an acetylene or of a cycloolefin as a relay between the two olefins of the diene, allowing the metathesis catalyst to proceed from one ring to the other to form bicyclic systems. Two examples of this methodology are sketched in Scheme 15.[50,51]



Scheme 15

Cross-metathesis. An attractive route to highly substituted five-membered rings results from the ring opening of a strained olefin in an excess of a less reactive olefin. For example, the mixed metathesis of substituted norbornenes or oxanorbornenes in *trans*-2-hexene gives high yields of substituted cyclopentanes or tetrahydrofurans, respectively.[52] The role of the linear olefin is to trap the reactive intermediate from the ring-opening reaction. Applications of this synthetic strategy are illustrated in Scheme 16.



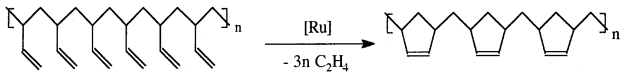
Scheme 16

Polymerization reactions

Strained and less strained monomers such as cyclobutene, norbornene, cyclopentene and cyclooctene are successfully polymerized with ruthenium-based catalysts whereas cyclohexene derivatives do not react in this fashion. There are only a limited number of cycloheptene derivatives that have been polymerized. The RCM of dienes to eight-membered rings is usually accompanied by competitive ring-opening polymerizations. The main reason for this can be traced to the strain inherent in eight-membered rings. However, the introduction of a conformational constraint greatly enhances the ability of the dienes to undergo RCM to afford the eight-membered cycle.[53,54]

Owing to the good tolerance of the ruthenium-based catalysts to a variety of polar functional groups, a large number of polymers and copolymers of substituted strained and low-strain cycles have been prepared.[35,41,55] Under appropriate conditions, the polymerizations are living and, moreover, they can be carried out in water.[56,57] Some recent and potentially far-reaching achievements in the field are described below.

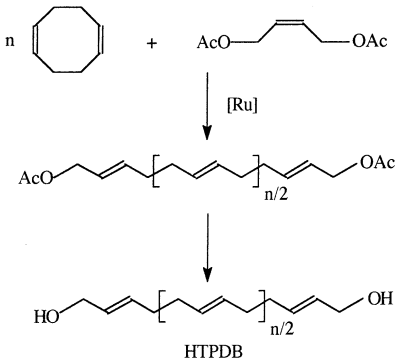
Post-polymerization of polydienes. Post-polymerization modifications of polydienes containing suitably spaced olefins is now possible and is catalyzed by ruthenium alkylidenes. The selective cyclization of neighboring vinyl substituents in 1,2-polydienes is almost quantitative (Scheme 17). The process is sensitive to the microstructure of the polymers. Cyclization of tactic polymers provides a novel route to stereoregular copolymers. The mechanism of the reaction is reported to have two manifolds, an initial random pairing of olefins, followed by migration along the polymer chain to scavenge isolated olefins.[58]



Scheme 17

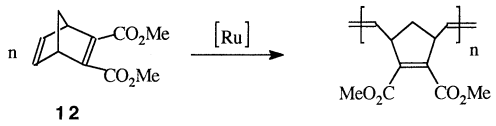
Carbohydrate-substituted polymers. Carbohydrates on the surface of cells play important roles in mediating a range of recognition events and polymeric materials bearing pendant carbohydrates could serve as cell surface mimics. Carbohydrate-substituted polymers have been synthesized by ROMP of 7-oxanorbornene derivatives[59] and of sugar-substituted norbornenes[60] to produce polymers suitable for protein-binding applications (see Scheme 18 for an example). These materials display a significant increase in functional affinity and selectivity when compared with the corresponding monosaccharides. The resulting polymers also function as high-avidity ligands in cell agglutination assays.

Synthesis of telechelic oligomers. The polymerization of cycloolefins in the presence of a difunctionalized chain transfer agent constitutes an attractive route for the synthesis of end-functionalized oligomers and polymers (telechelic polymers). Thanks to the robust nature of the catalyst, the limitations encountered with early transition metal-based catalysts are much less severe with ruthenium alkylidenes. The reactions can usually be carried out at low catalyst loadings and in the absence of solvent. The polymerization of 1,5-cyclooctadiene in the presence of a suitable amount of *cis*-1,4-diacetoxy-2-butene leads to telechelic oligomers with number-average functionalities close to 2.0 (Scheme 19). The oligomers can be easily deprotected to give the commercially important dihydroxytelechelic polybutadienes (HTPBD).[61]



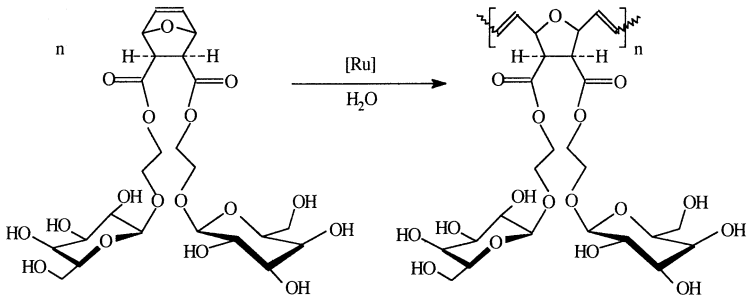
Scheme 19

Ready synthesis of substituted, tactic polynorbornadienes. Full control of the microstructure of poly(2,3-dicarbomethoxynorbornadiene) was recently achieved with the extremely simple catalyst obtained from $[RuCl_2(p\text{-cymene})_2]$ and trimethylsilyldiazomethane. This catalyst system polymerizes the diester of norbornadiene (**12** in Scheme 20) to a fully tactic ROM polymer, apparently the all-*trans*-syndiotactic polymer.[34]



Scheme 20

To the best of our knowledge, this is a rare example of a stereocontrolled polymerization with a (pre)catalyst devoid of any chirality. Similar tactic polymers have been synthesized by Schrock and co-workers[62,63] with a chiral molybdenum alkylidene catalyst.



Scheme 18

CONCLUSIONS

The stable and commercially available ruthenium(II) arene dimer complexes constitute readily available catalyst precursors which can be easily engineered to yield either excellent cyclopropanation or metathesis catalysts for the ROMP of strained and less-strained olefins. The active species which are formed *in situ* seem closely related to the well defined alkylidene complexes described by Grubbs and co-workers. The same catalysts that promote the ROMP of cycloolefins can also promote the ring-closing metathesis of diolefins and, thanks to their high functional group tolerance, these catalysts are now finding a wide range of applications in fine organic synthesis.

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