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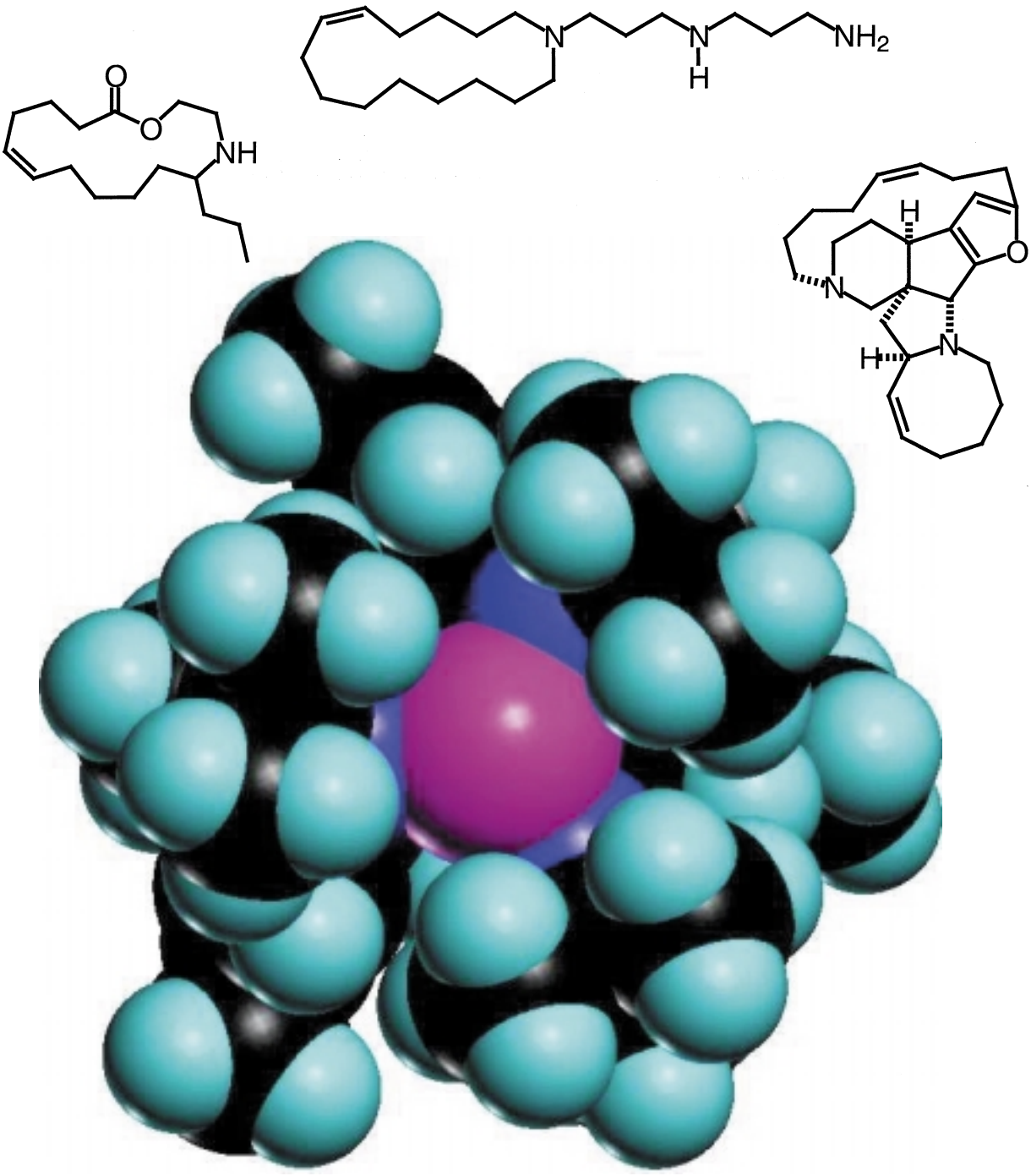
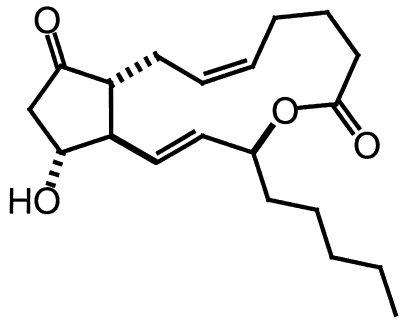




Space-filling model of [{(Ar)(*t*Bu)N}$_3$MoCl], a novel catalyst for ring-closing alkyne metathesis, and structures of some natural products formed with this emerging new methodology.

Olefin Metathesis and Beyond**

Alois Fürstner*

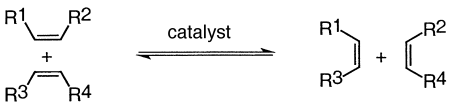
The advent of well-defined catalysts for olefin metathesis which combine high activity, durability, and excellent tolerance towards polar functional groups has revolutionized the field. The past decade has seen the rapid embrace of these reagents as tools for advanced organic and polymer chemistry and the success of this development is witnessed by a plethora of elegant applications to the synthesis of natural and nonnatural products. This review article provides an overview of these developments and intends to familiarize the reader with some very recent advances which hold the promise to expand the scope of the reaction even further. Moreover, the positive impact of metathesis on the fundamental logic of retrosynthetic planning is demonstrated by means of typical examples. Finally, it will be shown that metathesis is by no means restricted to alkenes as substrates, and some comments on metathesis reactions following unconventional mechanistic pathways will also be presented.

Keywords: alkenes · alkynes · carbenes · carbynes · metathesis

1. Introduction

The fundamental discovery by Karl Ziegler that catalysts formed in situ from certain transition metal salts and main group alkylating agents promote the polymerization of olefins under unprecedentedly mild conditions has had a tremendous impact on chemical research as well as on industrial production.[1] Early on it was discovered that some "Ziegler-type" catalysts do not only lead to the addition polymerization of olefins, but can also effect a mechanistically entirely different process, that is, the mutual alkylidene exchange reaction of alkenes.[2] This transformation, comprising the cleavage and the formation of double bonds, is nowadays generally referred to as "alkene metathesis" (Scheme 1);[3] it was soon emancipated from its polyolefin roots and it has evolved into an independent and highly prosperous field of research.

The first generation of metathesis catalysts exhibits the characteristics of "mixed" Ziegler catalysts:[2] Specifically, they show high activity at the expense of a poor compatibility with polar functional groups, due to a strongly Lewis-acidic and alkylating character. It is obvious that this property makes them hardly attractive for applications in advanced organic synthesis and it essentially restricted the scope of olefin metathesis to the production of unfunctionalized polymers.



Scheme 1. The principle of olefin metathesis.

Basic research in organometallic chemistry, however, has completely changed this situation. The discovery of metal alkylidene complexes,[4] followed by the insight that some species of this type constitute well-behaved single-component catalysts for olefin metathesis, gave the essential clue for settling the long lasting debate on the actual mechanism of this transformation ("Chauvin mechanism")[5] and has triggered the development of a new generation of high-performance, reasonably stable, and—most importantly—exceedingly tolerant catalysts or catalyst precursors. Scheme 2 depicts some of these catalysts (or precatalysts that convert into metal alkylidenes in situ),[6] among which the tungsten or molybdenum alkylidene complexes **1**[7] developed by Schrock and co-workers and the ruthenium carbene complexes **2** [8] introduced by Grubbs and co-workers are undoubtedly the most popular and versatile ones. Both reagents are now commercially available. The last decade has seen the rapid embrace of these tools by advanced organic synthesis as well as polymer chemistry, and the tremendous success of this development is documented in several excellent monographs and review articles.[9–11]

Although one might guess that the explosive growth of this field will now slowly cease after reaching a certain level of maturity, the very recent advent of even more advanced catalysts holds the promise of unabated pace for the next few

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[**] A list of abbreviations can be found at the end of this article.

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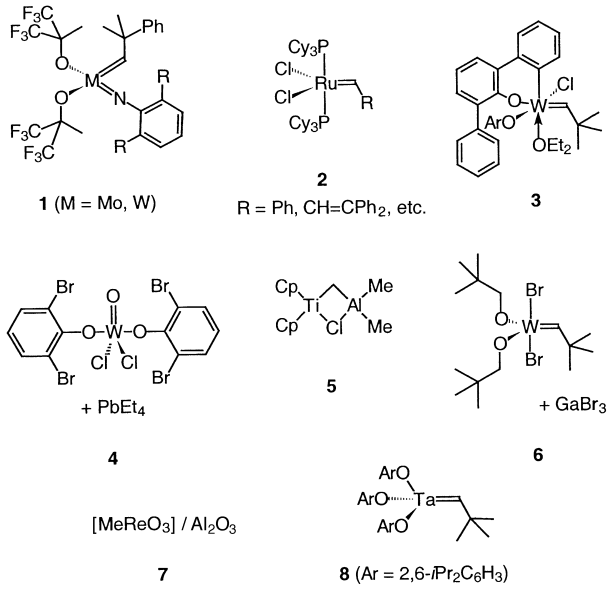
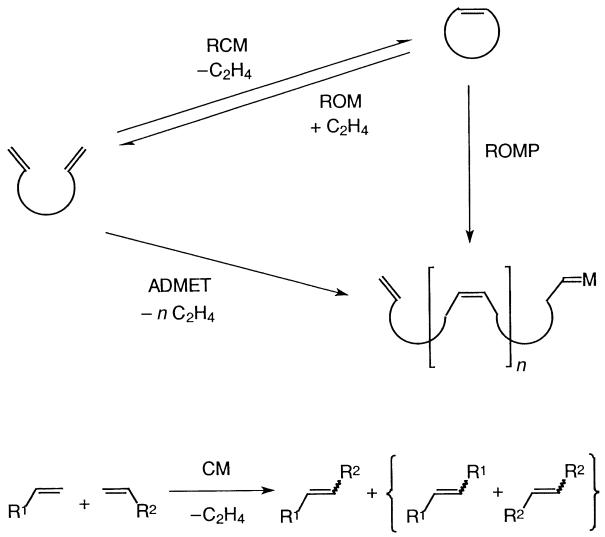


Scheme 2. Some typical metathesis catalysts and precatalysts.

years. The following review article is meant to delineate and accentuate this striking development and does not intend to provide a fully comprehensive treatise. The focus is on the advancements in catalyst design and on prototype applications illustrating the profound synthetic implications of metathesis on the logic of retrosynthetic planning. Finally, it will be shown that metathesis reactions of π systems other than olefins also bear great potential, and a short excursion into the, as yet hardly explored, "non-Chauvin world" will be undertaken. Despite the enormous relevance of metathesis for polymer chemistry, this field of applications will not be covered; the reader is referred to some authoritative review articles and monographs for further information in this respect.[9–12]

2. Mechanism and Fundamental Types of Applications

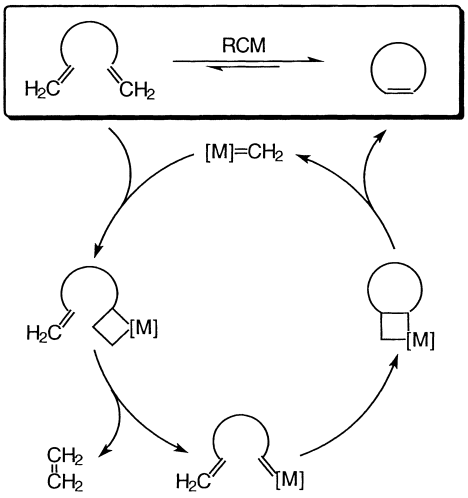
The generally accepted mechanism of metathesis reactions ("Chauvin mechanism")[5] consists of a sequence of formal [2+2] cycloadditions/cycloreversions involving alkenes, metal carbenes, and metallacyclobutane intermediates (for possible exceptions, see Section 8). Since all individual steps of the catalytic cycle are reversible, an equilibrium mixture of olefins is obtained. Therefore, it is necessary to shift this equilibrium in one direction in order to make metathesis productive in preparative terms. The major ways to do this are depicted in Scheme 3 and the mechanism of one such application, the ring-closing metathesis (RCM) of a diene, is shown in Scheme 4. In this particular case, the forward process is entropically driven because RCM cuts one substrate molecule into two products. If one of them is volatile (ethene, propene, etc.) the desired cycloalkene will accumulate in the reaction mixture.



Scheme 3. Important types of metathesis reactions: RCM = ring-closing metathesis; ROM = ring-opening metathesis; ROMP = ring-opening metathesis polymerization; ADMET = acyclic diene metathesis polymerization; CM = cross-metathesis.

Another important factor for productive RCM is the sensitivity of most metathesis catalysts to the substitution pattern of the olefin as this constitutes a kinetic obstacle for the retroreaction. This argument, however, does not apply to strained cycloalkenes because the release of ring strain provides a formidable driving force for ring-opening metathesis (ROM) or ring-opening metathesis polymerization

Alois Fürstner was born in 1962 in Austria. He studied chemistry at the Technical University of Graz and finished his PhD in 1987 under the supervision of Prof. Weidmann. After a period of postdoctoral study in the group of Prof. Oppolzer in Geneva, Switzerland, he obtained his Habilitation in 1992 in Graz. Subsequently he joined the Max-Planck-Institut für Kohlenforschung in Mülheim, Germany, as a group leader in 1993, was promoted to the rank of Director at that institute in 1998, and is also affiliated with the University of Dortmund. He has received several awards including the Dozentenstipendium of the German Chemical Industries (1994), the Ruhrpreis for Arts and Sciences (1998), the prestigious Leibniz Preis from the German Science Foundation (1999), and the Thieme–IUPAC prize in synthetic organic chemistry (2000). His research interests are presently focused on organometallic chemistry and homogeneous catalysis, in particular on applications thereof to the synthesis of bioactive target molecules.



Scheme 4. Basic catalytic cycle of RCM. Although not specifically shown in the scheme, all individual steps involved and, as a consequence, the overall transformation, are reversible; see text.

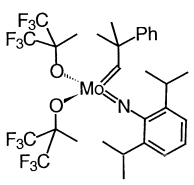
(ROMP).[12] Finally, it should be mentioned that the intrinsic competition between RCM and acyclic diene metathesis polymerization (ADMET)[12c] can be controlled to some extent by adjusting the dilution of the reaction mixure and is also strongly influenced by preexisiting conformational constraints in the substrate.

As metathesis necessarily converts one alkene into a new one, this reaction is predisposed for sequential transformations. Particularly attractive are domino processes incorporating different metathesis events (for example, RCM/ROM/CM or RCM/ROM/RCM) as they provide a tremendous increase in molecular complexity in a single catalytic and atom-economical step. Likewise, combinations of metathesis and other transformations of alkenes, such as Diels–Alder, Heck, Cope, or ene reactions, can be envisaged and hold an as yet largely unexplored, preparative potential. Some pioneering studies along these lines which feature the strategic advantages of such "orchestrated" maneuvers are included in different sections of this article.

3. Recent Advances in Catalyst Design

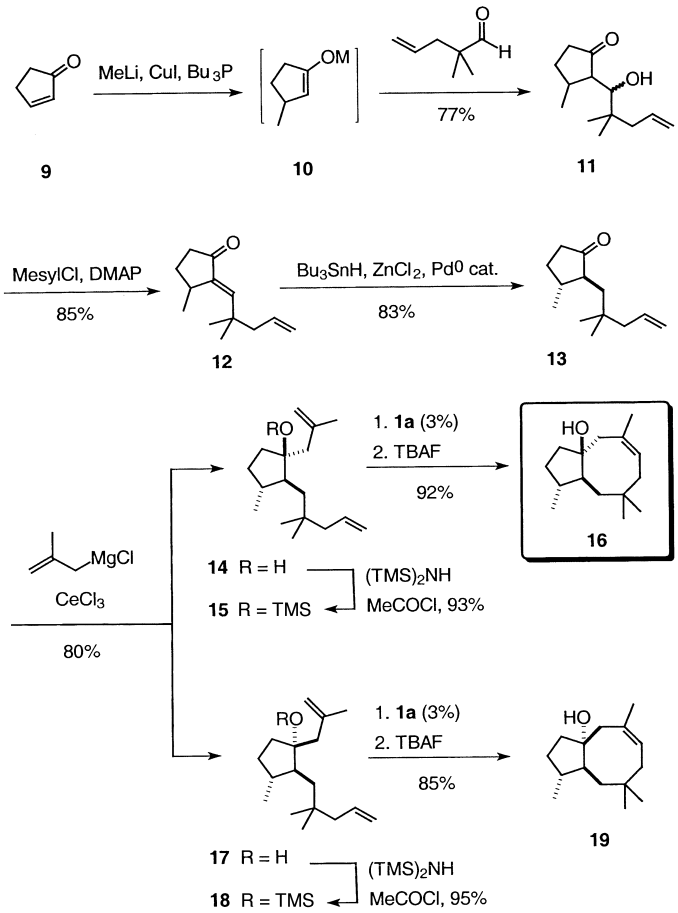
3.1. Molybdenum-Based Catalysts and Asymmetric Metathesis Reactions

Schrock's tetracoordinated alkylidene species of the general formula [M(=CHCMe$_2$Ph)(=NAr)(OR)$_2$] (M = Mo, W) with bulky substituents Ar and R on the imido and alkoxide ligands constitute potent and well behaved metathesis (pre)-catalysts which have been thoroughly studied from the mechanistic point of view.[7] Among them, compound **1a** turned out to be particularly active and is now commercially available. This and related complexes are quite sensitive toward oxygen and moisture and must be handled in rigorously dried solvents using Schlenck techniques. Their superb reactivity, however, compensates for this inconvenience and renders **1a** a calibration point for all studies on metathesis reactions.



1a

As the applications of **1a** in organic synthesis and polymer chemistry have recently been autoritatively reviewed,[13] a single example may suffice to illustrate this point. For a long time **1a** has been the only metathesis catalyst allowing the formation of tri- and even tetrasubstituted double bonds by RCM (only recently, a ruthenium-based system has been launched which allows to access these products as well; this development is summarized in Section 3.2.2).[14] Scheme 5 depicts a total synthesis of the terpene natural product

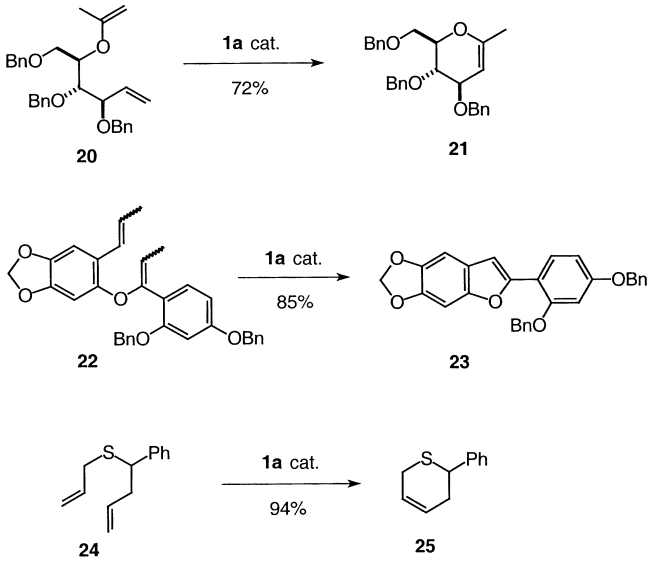


Scheme 5. Synthesis of dactylol (**16**) with RCM as the key step.

dactylol (**16**) based on RCM as the key step.[15] A three-component coupling triggered by addition of "MeCu" to cyclopentenone and subsequent alkylation of the resulting enolate **10** with 2,2-dimethyl-4-pentenal affords aldol **11** which is elaborated into the *trans*-disubstituted ketone **13** by standard means. Addition of methallylcerium dichloride provides a mixture of tertiary alcohols **14** and **17** which, after separation and O silylation, readily cyclize on exposure to catalyst **1a** and provide the targeted terpene **16** and its epimer **19**, respectively, upon desilylation of the crude product. Attempted ring closure of diene **15** with the ruthenium carbene **2** failed completely. This comparison illustrates the superior activity of **1a** in the preparation of tri- or tetrasubstituted products and shows that RCM can even be used for the synthesis of rather strained medium-sized rings if the

precursor is conformationally predisposed for ring closure (see also Ref. [161]). All previous syntheses of dactylol following more conventional routes are lengthy and very low yielding (9–20 steps with overall yields $< 0.1\%$). Therefore, this application (6 synthetic operations, 17% yield overall for **16** and 19% for epimer **19**)[15] gives a first impression of the advantages of metathesis in advanced organic synthesis.

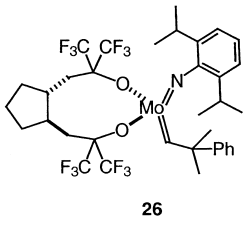
Additional advantages of the molybdenum complex **1a** reside in its tolerance towards certain functional groups which inhibit ruthenium-based metathesis catalysts. A mismatch of the "hard" Mo^{VI} center with "soft" sulfur or phosphine functionalities can explain why substrates such as **24** (Scheme 6) cyclize smoothly in the presence of **1a** but usually

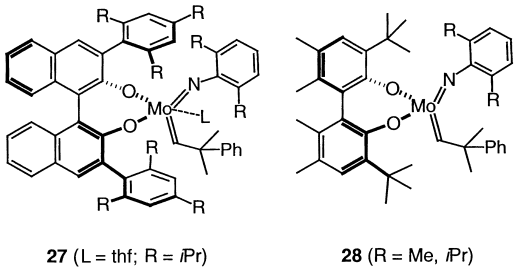


Scheme 6. RCM reactions which are only successful with the Schrock catalyst **1a**.

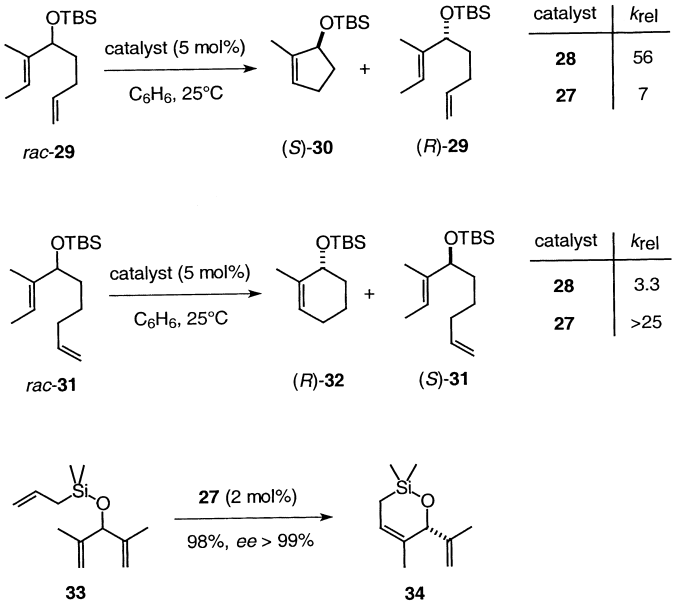
fail to react in the presence of the ruthenium carbene **2**.[16] Furthermore, catalyst **1a** is hardly affected by the electronic properties of the olefinic substrates and reacts even with electron-rich olefins (for example, enol ethers) and electron-poor olefins (such as acrylates, acrylonitrile).[17] Some examples are depicted in Scheme 6. Once again, the parent ruthenium carbene **2** is mostly unreactive towards these substrates,[18] but newly developed heteroleptic ruthenium species are now starting to compete with Schrock's complex **1a** in this particular field of applications as well (see Section 3.2.2).

In addition to the pronounced reactivity, the modular character of Schrock's molybdenum alkylidene complexes constitutes a particularly favorable feature. Specifically, various alkoxides can be readily introduced into the ligand sphere of the Mo center, including chiral scaffolds. This paves the way for different kinds of asymmetric metathesis reactions, such as asymmetric ring-closing metathesis (ARCM) or asymmetric ring-opening/cross metathesis (CM) cascades. Proof of principle has been achieved with catalyst **26** which contains an elaborate cyclic mimic of the $OCMe(CF_3)_2$ units of the parent compound **1a**.[19] Only recently, however,



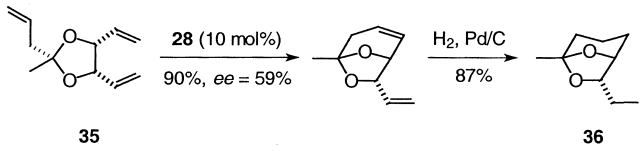


excellent levels of asymmetric induction have been reached with molybdenum complexes **27** and **28** carrying substituted BINOL- or BIPHEN-derived ligands.[20] Although it is too early to draw a fully comprehensive picture, the data presently available indicate that BIPHEN-derived species **28** are the catalysts of choice for the asymmetric formation of five-membered rings by ARCM, whereas the BINOL-derived analogues **27** give superior results in case of six-membered products.[20] However, the substitution pattern of the substrate must also be taken into account when choosing the best catalyst. Representative examples are compiled in Scheme 7.



Scheme 7. Examples for the application of **27** and **28**.

A synthesis of (+)-*endo*-brevicomin (**36**) based upon the desymmetrization of *meso*-triene **35** by means of complex **28** constitutes the first incorporation of this emerging new technology into target-oriented synthesis (Scheme 8).[21]

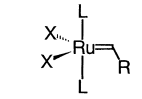


Scheme 8. Desymmetrization of the *meso* triene **35** through RCM in the synthesis of (+)-*endo*-brevicomin (**36**).

3.2. Ruthenium-Based Catalysts

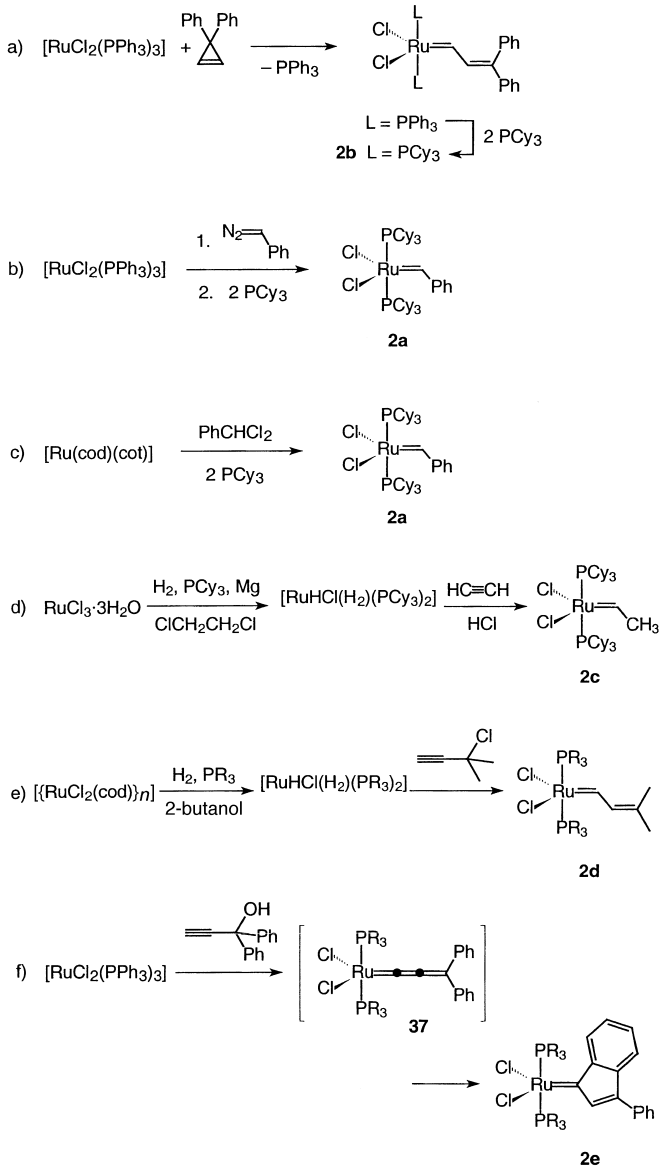
3.2.1. Variations on a Theme by Grubbs

The disclosure of Grubbs that ruthenium carbene complexes of the general type **2** are highly active single component (pre)catalysts for all types of alkene metathesis reactions denoted a real breaktrough and has triggered an avalanche of interest in this transformation.[8] Although their activity is usually lower than that of Schrock's molybdenum alkylidene **1a**, the spectacular tolerance of these "late" transition metal compounds toward an array of functional groups and the ease of handling caused by a reasonable stability against oxygen, water, and minor impurities in the solvents render them exceedingly practical tools and explain their unrivaled popularity in the organic and polymer chemists communities. Many elegant applications to the synthesis of complex target molecules highlight their truly remarkable scope. A wealth of information has accumulated which is summarized in several review articles and will therefore not be duplicated here.[9–11]



2
X = Cl, Br, OOCCF$_3$
L = PR$^i_3$

The rather cumbersome preparation of the diphenylvinylcarbene complex **2b** (R = CH=CPh$_2$), the first compound of this series historically, constituted a certain handicap. This catalyst is formed by an Ru^{II}-induced rearrangement of diphenylcyclopropene (Scheme 9a).[8a,b] Since the substituent R at the carbene unit of **2** itself, however, is irrelevant in many catalytic cycles,[22, 23] several carbene sources other than diphenylcyclopropene have been investigated in order to develop more convenient entries into this family of ruthenium compounds. The most important procedures described so far are summarized in Scheme 9. A significant improvement was achieved by the use of diazoalkenes instead of diphenylcyclopropene,[8c,e] although the hazardous nature of these reagents must be taken into account (Scheme 9b). Complex **2a** (R = Ph) thus obtained is now commercially available and has, therefore, found numerous applications. Other practical preparations that can be performed on industrially relevant scales either use *gem*-dihalides (Scheme 9c),[24] alkynes (Scheme 9d),[25] or propargyl chlorides (Scheme 9e)[26] as the actual carbene sources. Yet another convenient method is the treatment of commercially available [RuCl$_2$(PPh$_3$)$_3$] with diphenylpropargyl alcohol (Scheme 9f) to deliver phenylindenyl complex **2e** (rather than the allenylidene species **37** which was originally assumed to be the stable product of this reaction).[27] A detailed assessment of **2e** has shown that this complex is as good as or even slightly better than the

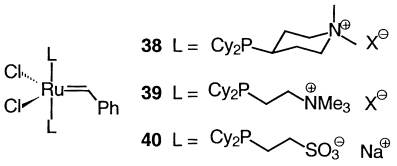


Scheme 9. Synthesis of some Grubbs-type catalysts.

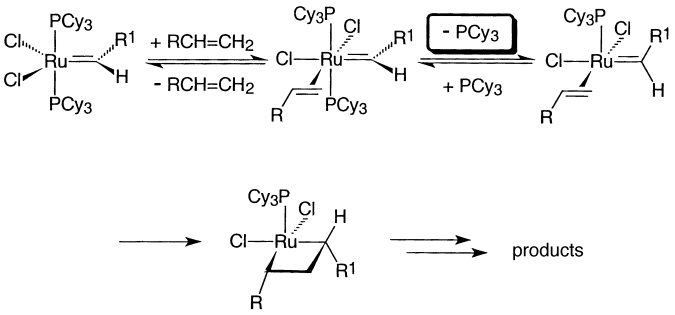
"standard" phenylcarbene **2a** in RCM (for an example, see Section 5.6).[28]

The influence of the ligands on the catalytic activity of 5-coordinate, 16-electron ruthenium complexes of type **2** has been systematically studied.[8, 29] With regard to the anionic substituent X, chloride seems to be optimal. The effect of this rather electron-withdrawing group, however, must be counterbalanced by electron-donating phosphines with large cone angles, such as PCy$_3$ or P(cyclopentyl)$_3$. Only a few other "designer" phosphines give similarly high activities.[30] Among them, bulky aliphatic phosphines incorporating either a quarternary ammonium or a sulfonate group are most remarkable.[31] The resulting catalysts **38**–**40** allow RCM of unprotected substrates in water or MeOH and enable emulsion polymerizations of appropriate substrates by ROMP in biphasic reaction media.

Detailed mechanistic studies allow the rationalization of the effect of the phosphines on the catalytic activity. It has been shown that the dominant pathway for productive



metathesis, which accounts for approximately 95% of the catalyst turnover in a typical RCM reaction, involves the dissociation of one of the two PCy_3 ligands from **2a**,[32] although it is not clear whether this dissociation occurs before or after the coordination of the alkene substrate (Scheme 10). The bulky and electron-donating character of the residual

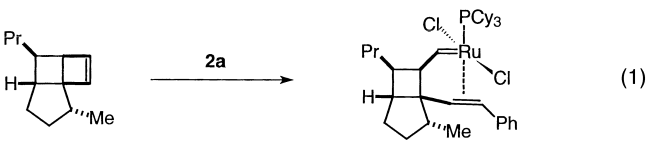


Scheme 10. Proposed dissociative mechanism for Grubbs-type catalysts.[32]

phosphine is decisive for stabilizing the reactive intermediates formed during this dissociative step. The alternative path in which both phosphines remain attached to the Ru center, though operative, is much less efficient. The olefin binding site is presumably *cis* to the carbene and *trans* to one of the chlorides and the subsequent formation of the metallacycle is believed to be rate determining.[32]

Recent investigations corroborate this picture, which was originally mainly based on the analysis of kinetic data. Supportive evidence comes from the inspection of reactive intermediates by electrospray-tandem-MS,[33] from theoretical studies of the reaction coordinate,[34] as well as from the following preparative results:

1) Snapper and co-workers were able to isolate and characterize a ruthenium catalyst "caught in the act".[35] Treatment of carbene **2a** with the strained olefin **41** provides complex **42** in which the tethered alkene moiety has replaced one of the PCy_3 groups. The authors have shown beyond doubt that **42** is a catalytically relevant species rather than a dead-end by-product [Eq. (1)].

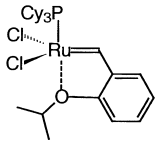


(1)

41 42

2) Additives, such as HCl (DCl) or Cu^I salts, that are able to abstract PCy_3 from the precatalyst or to intercept free PCy_3 in solution greatly enhance the reaction rate at the expense of the lifetime of the active species because they increase the concentration of reactive, but fragile, monophosphine metal fragments in solution.[32]

3) The clever design of complex **43** introduced by Hoveyda and co-workers also takes the mechanistic lessons into account.[36] The lateral O*i*Pr group on its phenylcarbene unit stabilizes the complex in its resting state, but readily opens a coordination site in the presence of the substrate. Moreover, this complex is able to regenerate itself once the substrate is depleted (Scheme 11) and can be recycled by conventional flash chromatography.



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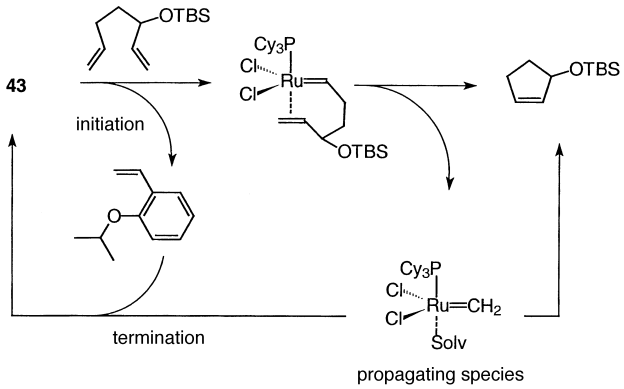
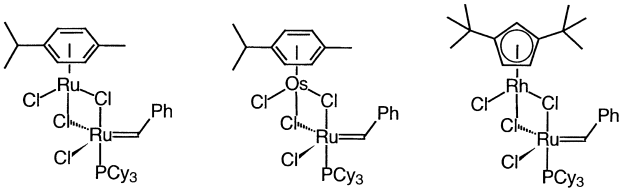


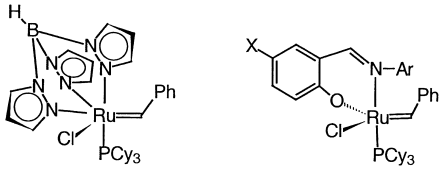
Scheme 11. Example of an RCM reaction catalyzed by complex **43**. Once the substrate is depleted, the active species is recaptured by *i*PrOC$_6$H$_4$CH=CH$_2$ and precatalyst **43** is, thereby, regenerated.

4) Similarly, replacement of one PCy_3 unit in the parent complex **2a** by a coordinatively labile metal fragment results in enhanced activity. This holds true, for example, for the dinuclear complexes **44**–**46**.[37] Once again, however, the lifespan of the catalyst in solution is relatively small because the metal fragment does not reassociate and, therefore, cannot protect the intermediates against decomposition.



44 45 46

5) In contrast, all strongly chelating entities that dissociate reluctantly from the Ru center enhance thermal stability but lower the performance. This holds true for complexes **47** and **48** which bear either tris(pyrazolyl)borate or



47 48

tethered Schiff base ligands.[38] While **48** shows appreciable activity at elevated temperatures, compound **47** is kinetically inert and cannot serve as a metathesis catalyst.

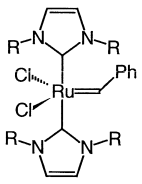
Further mechanistic studies have revealed the major decomposition pathways of complexes of type **2**.[39] Thus, substituted carbenes (R ≠ H) mainly decompose through bimolecular processes, whereas the methylidene complex (R = H)[22] that is responsible for 95 % of the turnover in RCM experiments decays unimolecularly. This dichotomy explains firstly, why high catalyst loadings are necessary for productive RCM of substrates with low intrinsic bias towards ring closure, and secondly, why ligands that accelerate ring closure as well as decomposition have no major preparative advantages.

Despite these important mechanistic lessons, not all intimate details of metathesis reactions catalyzed by **2** are clear yet. This refers, for example, to a recent publication showing that structurally unknown radical intermediates may intervene at some stage during the catalytic cycle.[40] The propensity of complex **2** to trigger radical processes such as Kharash additions of chloroform to alkenes or the radical polymerization of methyl methacrylate is well documented in the literature.[41]

3.2.2. *Ruthenium Complexes Containing* N-*Heterocyclic Carbene Ligands: Catalysts of Extended Scope and Increased Reactivity*

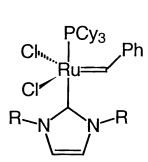
As outlined above, the steric and electronic properties of the residual neutral ligand in the catalytically relevant intermediates formed by the dissociative mechanism shown in Scheme 10 are decisive for the performance of the catalyst. They should be even more basic and sterically demanding than PCy_3 in order to increase its lifetime and reactivity. "Stable" *N*-heterocyclic carbenes (NHC) fall into this category.[42]

Herrmann and co-workers were the first to report on their use in the context of metathesis.[43] Complex **49**, in which both PCy_3 units of **2a** have been replaced by *N*,*N*′-disubstituted 2,3-dihydro-1*H*-imidazol-2-ylidene units, however, is rather stable but does not show an improved activity profile. This is mechanistically reassuring since the "sticky" NHC ligands render the dissociative pathway less likely and, therefore, result in a low concentration of the catalytically active ruthenium template in solution.

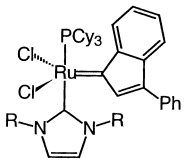


49

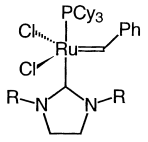
The use of one kinetically inert, electron-donating NHC ligand in combination with a coordinatively labile ligand on the other hand, however, should result in the desired synergetic effect. This idea was independently pursued by three different research groups which have almost simultaneously reported on the preparation and the catalytic properties of heteroleptic complexes such as **50**–**53**.[44–46] They differ 1) in the particular NHC ligand chosen, which can either be "unsaturated" or "saturated" (compare **50** with **52**), 2) in the substituents R on the *N* atoms, 3) in the complementary labile ligand, and 4) in the alkylidene fragment which does not necessarily have to be =CHPh (see compound **51**).



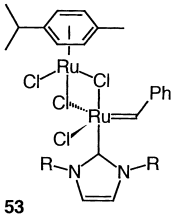
50



51



52



53

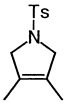
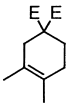
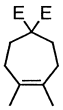
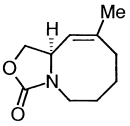
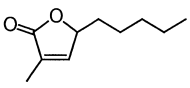
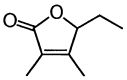
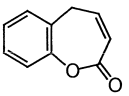
The results of solution calorimetry indicate that the NHC ligand with R = mesityl has a significantly stronger bonding (by approximately 5 kcal mol^{-1}) to ruthenium than PCy_3.[44] Furthermore, X-ray analysis shows that by virtue of the short metal–NHC bond length the bulky ligand is brought close to the metal center which is, therefore, effectively shielded against bimolecular decomposition. The Ru–NHC bond is formally best represented as a "single" bond since the ligand merely acts as a strong σ donor and has almost no π acceptor properties; rotation, however, is largely restricted for steric reasons.[43, 44, 46b]

Although it is too early to give a fully comprehensive analysis of the catalytic properties of these "second-generation" ruthenium carbene complexes, the data presently available make clear that they open new vistas for preparative chemistry. Most importantly, their activity is significantly higher than that of the parent Grubbs carbene **2a** and comes close to or even surpasses that of Schrock's molybdenum alkylidene complex **1a** discussed in Section 3.1. In combination with the exceptional thermal stability and the resistance toward oxygen and moisture, as well as the compatibility with many functional groups, these complexes are exceedingly useful tools for the practicioner and may well define new standards in this field.

The following examples from the recent literature substantiate this claim. One of the most notable features of these heteroleptic complexes is the ease of formation of tri- and even tetrasubstituted double bonds in RCM and CM reactions.[45, 46a, 47] Representative examples, including bicyclic compounds formed by annulation reactions, are displayed in Table 1. Note that products of this type have been beyond reach of **2a** and could previously only be made using molybdenum alkylidene **1a**. Similarly, acrylates constitute problematic substrates for the parent ruthenium carbene **2a** but were found to cyclize smoothly in the presence of complex **50**, even if ring closure was additionally hampered by a high degree of substitution.[45d, 47]

Another informative example is the formation of the conduritol derivative **55** shown in [Eq. (2)] and Table 2.[48] Attempted cyclization of diene **54** derived from D-glucose with the parent Grubbs carbene **2a** turned out to be rather difficult; high concentrations of the catalyst and unacceptably long reaction times were required in order to reach complete

Table 1. RCM reactions catalyzed by ruthenium complexes with NHC ligands.[a]

Product	Cat.	R	Yield [%]	Ref.
	**50**	Mesityl	96	[47]
	50	CHMePh	80	[46b]
	51	Mesityl	97	[47]
	53	C_6H_{11}	63	[46b]
	**50**	CHMePh	96	[46b]
	51	Mesityl	89	[47]
	53	C_6H_{11}	88	[46b]
	**50**	Mesityl	98	[47]
	**51**	Mesityl	71	[47]
	53	C_6H_{11}	65	[46b]
	**50**	Mesityl	95	[47]
	**50**	Mesityl	92	[47]
	**50**	Mesityl	63	[47]
	**50**	Mesityl	89	[47]

[a] (E = COOEt).

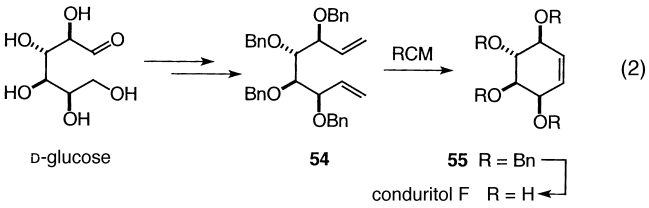


Table 2. Comparison of the reactivity of different metathesis catalysts in the RCM reaction shown in Equation (2).

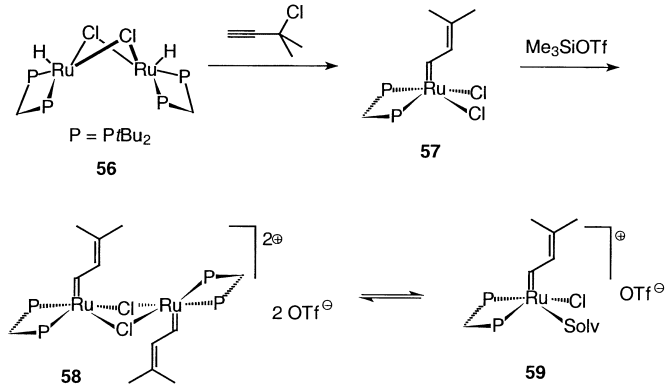
Catalyst	Reaction time [h]	Yield of **55** [%]
2a	60	32 (GC)
1a	1	92
50 (R = mesityl)	2	89

conversion.[48, 49] The second entry shows the significantly higher reactivity of Schrock's catalyst **1a** which depletes the substrate within one hour and gives the desired cyclohexene derivative in excellent yield.[48] As can be seen from the third entry, however, the fairly air-stable ruthenium complex **50** is similarly effective. This outcome illustrates the big increase in reactivity engendered by the NHC ligand and pinpoints the notion that these new heteroleptic complexes are most practical alternatives to the sensitive molybdenum catalyst **1a**.

Finally, it should be pointed out that the reactivity of **50** can be tuned to some extent by the proper choice of the substituents R on nitrogen as well as by the reaction medium,[47] although this cooperative effect is not yet well understood. Moreover, complexes such as **52** containing "saturated" Wanzlick-type HNC ligands seem to be even more reactive than their "unsaturated" Arduengo-type analogues **50**.[45b,c] This can be explained by an increased basicity of the former, in which the carbene center is less stabilized. These ligands also allow incorporation of chirality in their carbon backbone as well as in the *N*-substituents and may, therefore, become useful for asymmetric metathesis reactions as well.

3.2.3. A Cationic Scenario: Ruthenium Carbene Complexes Activated by Chloride rather than Phosphine Abstraction

As summarized above, dissociation of one of the two neutral ligands from precatalysts of the Grubbs-type is believed to open the productive pathway for metathesis. Recent studies from Hofmann and co-workers show, however, that other options can also be pursued. Thus, exposure of $[\{Ru(cod)Cl_2\}_n]$ to bis(di-*tert*-butylphosphino)methane (dtbpm) and Et_3N under an atmosphere of H_2 delivers the dinuclear hydridocomplex **56** which reacts with dimethylpropargyl chloride to give the monomeric carbene complex **57** in which the phosphine ligands are *cis* rather than *trans* to one another (Scheme 12).[50] Although these neutral complexes

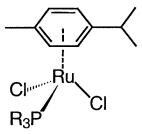


Scheme 12. Formation of the neutral carbene complex **57**, which can be further transformed into the cationic complex **59**.

themselves initiate ROMP of suitable cycloalkene substrates, they convert into much more active species upon treatment with TMSOTf.[51] The irreversible formation of TMSCl forces the generation of cationic intermediates **58**. The latter are dimeric in the solid state, but the association is readily reversible in solution as shown by NMR spectroscopy (Scheme 12). The resulting monomeric and cationic carbenes **59**, which bear a bulky neutral chelate ligand but only one chloride in the coordination sphere of Ru, are very active catalysts for ROMP and effect RCM of 1,7-octadiene even at $-40\,^{\circ}C$.[51] A full assessment of their preparative potential, however, is still pending.

3.2.4. Other Ruthenium-Based Metathesis Catalysts

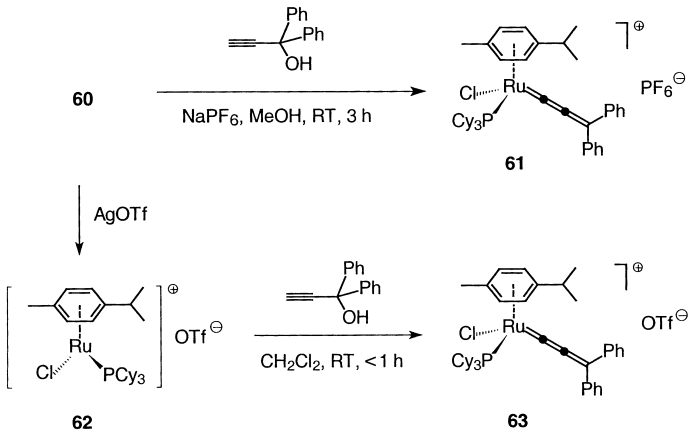
Despite the tremendous success of the Grubbs carbenes and derivatives thereof, the recent literature also documents a



60

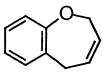
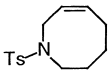
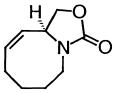
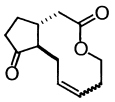
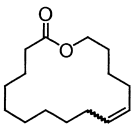
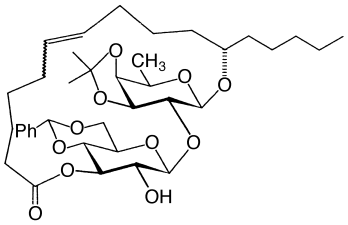
search for alternative metathesis catalysts of comparable performance and scope.[52] Among them, the mononuclear 18-electron complex $[(\eta^6\text{-cymene})RuCl_2(PR_3)]$ (**60**) deserves particular mention. Although this complex per se exhibits only moderate metathesis activity ($R = Cy > i\text{Pr} \gg Ph$), it constitutes a versatile and convenient precatalyst that can be activated by various means:

1) In the presence of catalytic amounts of trimethylsilyldiazomethane or diazoacetate, complex **60** efficiently catalyzes ROMP of cyclooctene and other cyclic monomers. The polymers formed have high molecular weight and low polydispersities.[53] Esters, ethers, epoxides, and alkyl bromides turned out to be compatible with this system. Applications to RCM, however, have not yet been reported.
2) Compound **60**, as well as its osmium analogue, respond to photochemical activation. Irradiation with a UV lamp (200 W Hg lamp) leads to very active systems for the technically important polymerization of dicyclopentadiene ("Photo-ROMP"), most likely with decoordination of the arene ligand as the triggering event.[54] Since then, it has been found that no special photochemical equipment is necessary for the activation of **60**. Thus, heating of a solution of this complex and a suitable diene substrate results in clean and high yielding RCM provided that the reaction is exposed to neon light (common neon tubes) or strong daylight.[55] Although cyclization proceeds more slowly than with the Grubbs carbene **2a**, the yields obtained and the tolerance towards functional groups are comparable, as can be seen from the results compiled in Table 3. Since **60** can be conveniently formed in situ from the commercially available dimer $[\{(\eta^6\text{-cymene})RuCl_2\}_2]$ and PCy_3, this "low-tech" procedure is highly user-friendly and deserves consideration in advanced organic synthesis.
3) Reaction of **60** with propargyl alcohols in the presence of a suitable chloride trap results in the formation of cationic ruthenium allenylidene complexes such as **61** or **63**, which are active metathesis catalysts (Scheme 13).[56] Systematic variations of their basic structural motif have shown that the phosphine plays the most important role ($PCy_3 > Pi\text{Pr}_3 \gg PPh_3$), but the escorting counterion X is also involved in determining the rate and selectivity of the reaction, with X = OTf being the most appropriate choice. Prototype cyclizations effected by **61** and a comparison with other metathesis catalysts are given in Table 3, which illustrate the wide scope and excellent overall application profile of these allenylidene catalysts.



Scheme 13. Formation of the metathesis catalysts **61** and **63**.

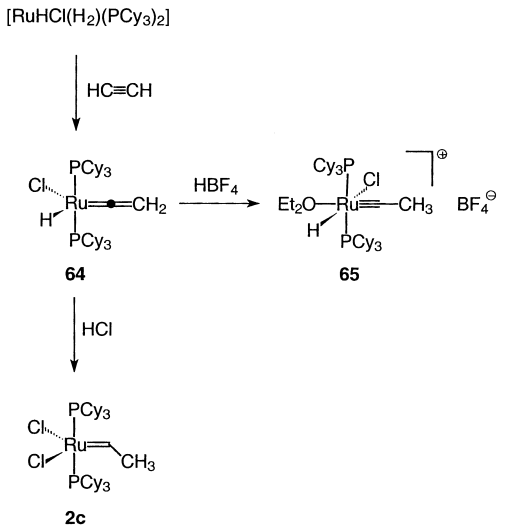
Table 3. Comparison of the reactivity of different ruthenium-based metathesis catalysts in typical RCM reactions.

Product	Yield [%]		
	2a	**60**/*hν*	**61**
	93	90	83
	–	78	86
	68	77	75
	76	72	66
	86	65	40
	79	80	90
	77	70	85

Another interesting system is the cationic ruthenium alkylidyne complex **65** described by Werner and co-workers.[57] This rather unstable complex is formed by protonation of the hydridovinylidene species **64** with HBF_4 and was found to effect ROMP of cyclooctene approximately 20 times faster than the standard Grubbs carbene **2a** does. (Note that protonation of **64** with HCl instead of HBF_4 leads to standard Grubbs-type carbene complex **2c**, see Scheme 14.) Although electron deficient alkenes in general are poor substrates for ruthenium-based metathesis catalysts (for exceptions, see Section 3.2.2.), **65** allows efficient ROM/CM between cyclopentene and methyl acrylate to form acyclic, unsaturated esters.[57]

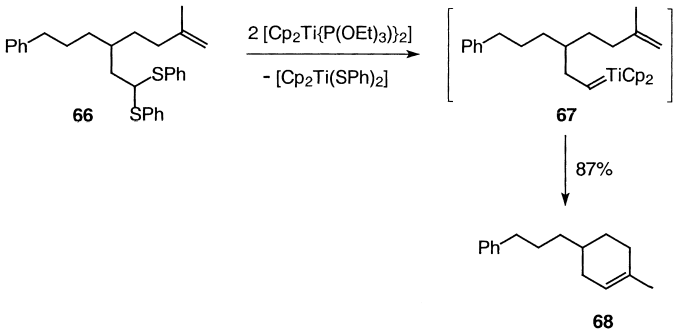
3.3. Development of New Metathesis Catalysts Based on Other Transition Metals

The development of the Tebbe reagent **5** (Scheme 2) was an early landmark which shows the link between metathesis and



Scheme 14. The choice of the proton source is important for the synthesis of **65**.

carbonyl olefination.[6c, 58] This reagent has seen a renaissance in preparative organic chemistry in recent years (for an example, see Section 5.3). Quite interestingly, a second titanium-based procedure for metathesis has been disclosed which generates metal carbene intermediates from dithioacetals and low-valent titanium reagents [Ti], formed in situ from $[Cp_2TiCl_2]$, $P(OEt)_3$, and Mg (Scheme 15).[59] Although this methodology requires (over)stoichiometric amounts of [Ti], it widens the set of substrates amenable to metathesis beyond simple alkenes.



Scheme 15. Olefin metathesis with a titanium reagent.

4. General Preparative Aspects

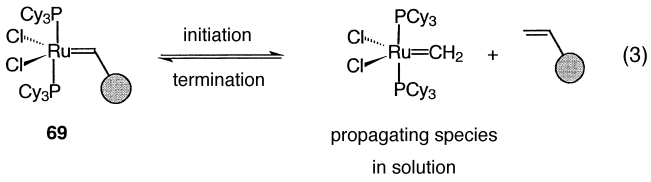
4.1. Purification of the Reaction Mixtures

Standard work-up of a metathesis reaction followed by purification of the crude material with flash chromatography, recrystallization, distillation, etc. usually affords pure compounds which may, however, still contain traces of metal salts derived from the catalyst. The latter are problematic in subsequent transformations or in pharmacological studies of the products. Therefore, Grubbs has recently developed an improved work-up procedure which is particularly useful for reactions on a larger scale.[60] It comprises the addition of excess tris(hydroxymethyl)phosphine to the crude mixture. By virtue of the polar character of this commercially available ligand, the resulting ruthenium complexes can either be extracted during a standard aqueous work-up, or can be deposited on silica and then filtered off. This simple procedure reduces the ruthenium impurities in the products by factors of 10 – 100.[60]

4.2. Recovery and Immobilization of the Catalyst

Several attempts have been made to immobilize Grubbs-type catalysts on solid supports to facilitate the work-up and to make this reaction even more attractive for industrial applications. An obvious possibility uses moderately cross-linked polystyrene that is functionalized with PCy_2 units. Stirring of a solution of **2a** with such a polymer leads to its immobilization through ligand exhange.[61] The loaded polymer, however, was found to be at least two orders of magnitude less active than homogeneous solutions of **2a** and leaching of the active metal template from the polymer matrix could not be suppressed.

Another innovative possibility was explored by Barrett and co-workers who used the carbene rather than the phosphine as the anchor group [Eq. (3)].[62] The carbene substituent of

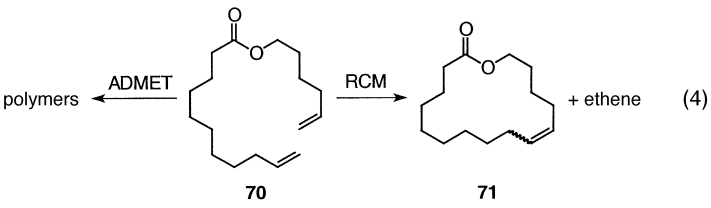


the immobilized precatalyst **69** is cleaved off during the first turn of the catalytic cycle and the ruthenium template is, thereby, released from the polymer and acts as a homogeneous catalyst; it is, however, recaptured by the resin once the substrate in solution has been consumed. The authors have coined the expression "boomerang catalyst" which nicely describes this overall behavior.[62] Since unimolecular decomposition of the active methylidene complex **2** in solution cannot be avoided, however, the activity of the polymer catalyst becomes insufficient after a few runs. It is obvious that replacement of the "standard" Grubbs carbene entity by more highly stabilized ruthenium catalysts (for example, the new generation of NHC-containing complexes) may significantly upgrade this creative design in the future.

4.3. Unconventional Media: Metathesis in Supercritical CO_2

Yet another way to achieve easy separation of the products from the catalyst is the use of supercritical CO_2 ($scCO_2$) as the reaction medium. Both, the molybdenum alkylidene complex **1a** and the ruthenium carbenes **2** turned out to catalyze RCM, ADMET, or ROMP in this environmentally benign medium.[63] It is interesting to note that the course of the reaction strongly depends on the density of $scCO_2$. Thus, it was found

that diene **70** cyclizes selectively to the musk-odored lactone **71** at densities of $\rho \geq 0.65\ g\,cm^{-3}$, whereas ADMET dominates below this threshold ([Eq. (4)] and Figure 1). In addition, product **71** is removed when the autoclave is vented, by virtue



(4)

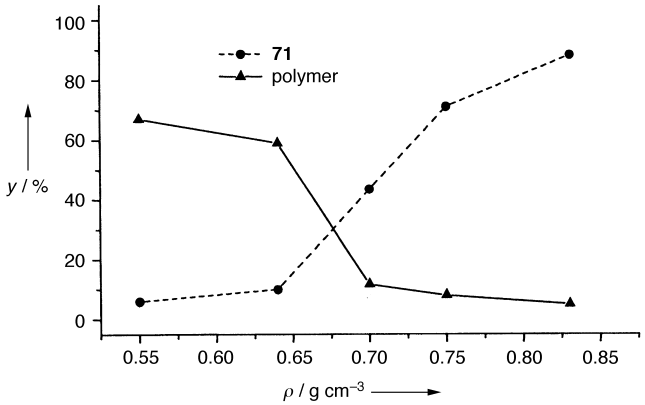


Figure 1. Effect of the density (ρ) of $scCO_2$ on the outcome of the reaction depicted in Equation (4).

of the extractive properties of $scCO_2$. The product can be collected in an appropriate trap; the metal residue remaining in the reactor was found to be still active and can be directly used in the next run.[63] This easy separation technique may upgrade the industrial application profile of metathesis and, hence, render this transformation useful for fine chemical production.

Finally, it should be mentioned that $scCO_2$ can also be used as a "protective medium" for certain functional groups.[63] Thus, unprotected amines can be used as substrates due to the reversible formation of the corresponding carbaminic acid, whereas they must be protected if RCM is carried out in conventional organic solvents in order to avoid deactivation of the ruthenium catalyst.

4.4. Parallel Screening of Metathesis Catalysts

The impact of combinatorial chemistry on the advancement of life sciences inspires many attempts to exploit this technique in the context of catalysis as well. The successful examples reported to date highlight the crucial role of analytical techniques that allow rapid and parallel screening of potential catalysts. In view of the large number of metathesis-active complexes published during the last few years and the prospect that many still remain to be discovered, methods allowing a semiquantitative assessment in a parallel mode are called for.

An exploratory study has recently shown that high precision IR-thermography is a useful tool in this context.[64] Catalytic activity is identified by heat uptake from the medium as monitored by the appearance of "cold spots". It is likely that the heat of vaporization of the gaseous by-product ethylene (or other volatile alkenes) formed upon productive RCM plays a pivotal role, since RCM itself is only slightly endothermic or even thermoneutral. Control experiments and comparison with preparative data have unequivocally shown that this method constitutes a rapid, convenient, and reliable way to 1) assess the relative rate of initiation of RCM by different precatalysts, and 2) determine the inherent reactivity of various substrates towards a given metal complex. Figure 2 depicts a typical example of the time-resolved imaging of RCM of 1,7-octadiene catalyzed by four different ruthenium complexes.[64]

4.5. Metathesis on Solid Supports and Applications to Combinatorial Chemistry

Organic chemistry on solid supports has gained tremendous importance during the last decade, mainly driven by the needs of pharmaceutical sciences. Metathesis was soon recognized as a useful technique in this context because of the robust and tolerant nature of the available catalysts.

The conceptually most simple application makes use of alkenes as covalent linkers for solid-phase synthesis. An illustrative example (Scheme 16) deals with oligosaccharide synthesis in which the first sugar unit is attached to the

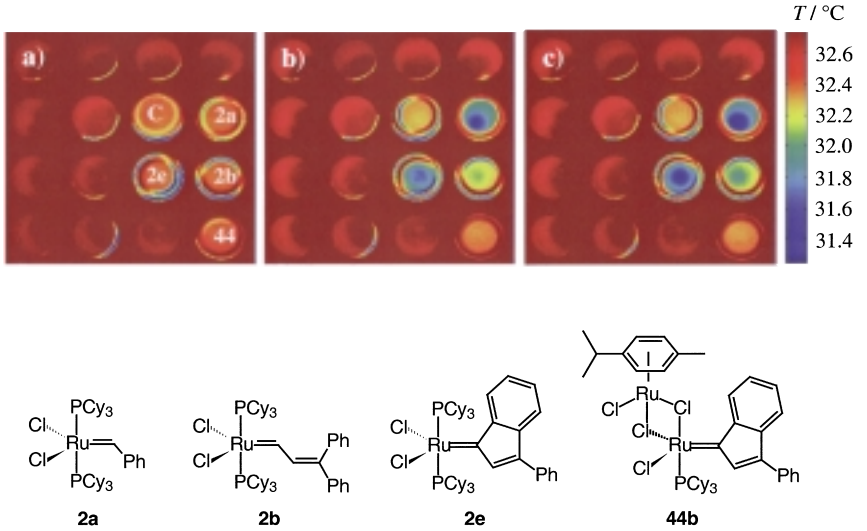
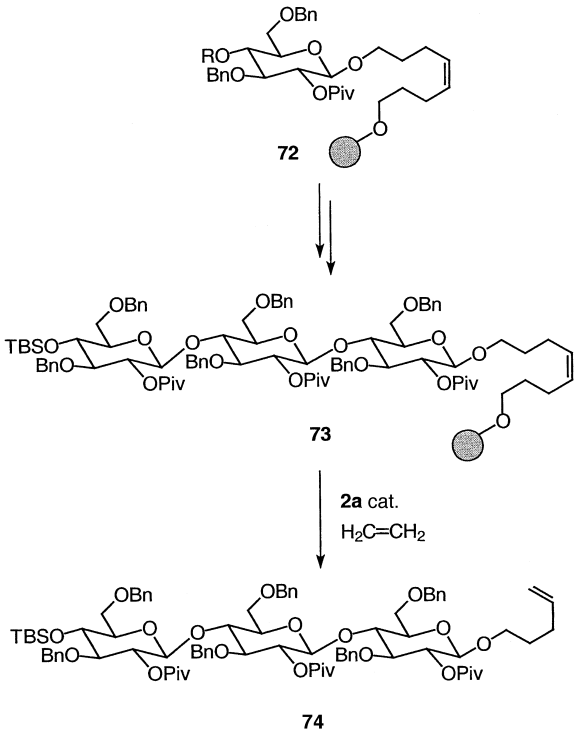


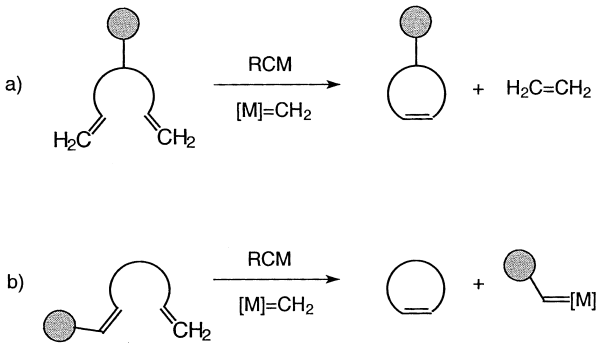
Figure 2. Parallel screening of four different ruthenium catalysts with IR-thermography as the detection method.[64] The test reaction is the cyclization of 1,7-octadiene to cyclohexene. The tube marked "**C**" shows a control experiment in which catalyst **2a** is added to octane instead of the octadiene. a) Before addition of the catalysts; b) after 1 min of reaction time; c) after 2 min of reaction time.



Scheme 16. Alkene groups as covalent linkers in the solid-phase synthesis of oligosaccharides.

support through an unsaturated linkage.[65] After a series of subsequent glycosylation reactions, the product is cleaved off the resin by cross metathesis with ethylene.

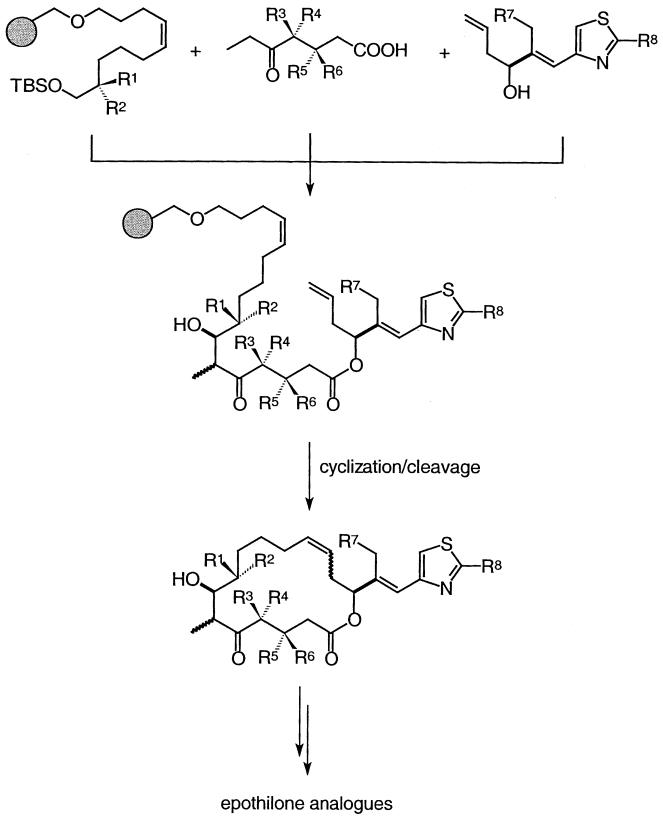
Metathesis can also be employed as a tool for the elaboration of immobilized compounds.[66] Thus, a suitable alkene (diene, enyne, etc.) is covalently attached to the resin, metathesis is carried out, and the products formed are cleaved off by conventional methodology (Scheme 17a). Alternatively, the metathesis event itself can be used to form the product



Scheme 17. Typical applications of RCM to polymer-bound substrates: a) The product is cleaved from the resin after the metathesis reaction; b) the product is released by the metathesis reaction.

and to release it simultaneously from the solid support (Scheme 17b). This strategy has the inherent advantage that only compounds with the correct functionality will be liberated, whereas any unwanted by-products remain bound to the polymer. Note, however, that the catalyst is captured by the polymer matrix during each productive "cyclization/cleavage" event. Therefore, one has to use either very high catalyst loadings or "ancillary" terminal alkenes which liberate the catalyst from the bead by subsequent cross metathesis and reconvert it into a soluble species.

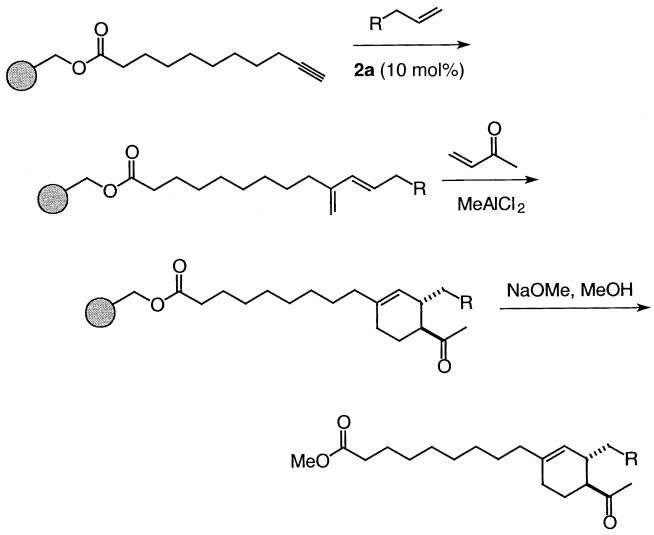
A typical application of the "cyclization/cleavage" technique is the synthesis of a library of epothilone analogues which enabled a synthesis-driven mapping of the pharmacophore of this promising anticancer agent (Scheme 18).[67] Other applications follow a similar rationale.[68]



Scheme 18. Outline of an epothilone-library synthesis by the cyclization/cleavage strategy.[67]

Solid-phase synthesis also provides advantages in cross-metathesis reactions. Due to the compartmentalization of the reaction partners it is possible to drive the conversion by using an excess of the soluble component. Various successful applications illustrate this idea, among which the synthesis of a muscone library[69] and the elegant use of intermolecular cross metathesis or crossed enyne metathesis reactions are most noteworthy.[70, 71] In the latter case, the 1,3-diene formed by enyne metathesis is amenable to post-metathesis elaboration, for example, by Diels–Alder cycloadditions (Scheme 19).

In addition to these metathesis reactions using polymer-bound substrates, some examples of solution-phase combinatorial chemistry have also been reported. They span a wide range of applications including the preparation of "alkene libraries" by simple scrambling of a set of olefinic substrates[72] and rather sophisiticated studies into biased macrocycle synthesis,[73] just to mention a few typical cases.



Scheme 19. Enyne cross metathesis and post-metathesis functionalization of polymer-bound substrates.[70]

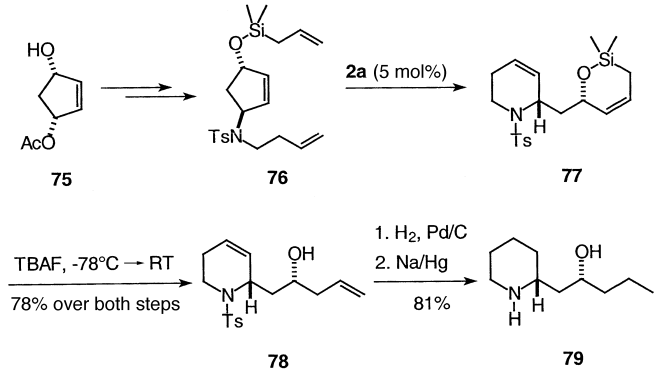
5. Selected Applications to Natural Product Synthesis

Once it became clear that the new catalysts tolerate a wide spectrum of polar functional groups due to their remarkable chemoselectivity profile, metathesis rapidly evolved into a relevant and mature tool for target-oriented synthesis. A proliferating number of applications substantiates this notion and makes the following treatise necessarily selective rather than comprehensive. The examples described below are meant to demonstrate some of the "strategic" advantages of this transformation such as high overall efficiency, inherent flexibility, practicality, atom economy, and an unrivaled "economy of steps" even in multiplex synthesis manoeuvers.

5.1. Ring Shuffling by Metathesis Cascades: Synthesis of (−)-Halosaline

Ring-opening metathesis is usually driven by the release of ring strain and has mainly been applied to the formation of speciality polymers by ROMP. However, it is possible to avoid polymerization by combining ROM with CM or RCM into suitable reaction dominos.[74] This constitutes an elegant way, for example, to transfer stereochemical information from one ring to another, as illustrated by the total synthesis of the piperidine alkaloid (−)-halosaline (**79**) summarized in Scheme 20.[75]

Acetate **75** is available in excellent optical purity (*ee* > 99%) by enzyme-catalyzed desymmetrization of the *meso*-diacetate precursor. Protection of the OH function with allyldimethylchlorosilane and cleavage of the remaining OAc group followed by introduction of a *N*-butenyl side chain by a Mitsunobu reaction delivers triene **76** as the key precursor for the subsequent domino event. Exposure of this substrate to catalytic amounts of the ruthenium carbene **2a** reorganizes the ring system and provides compound **78** in good yield after



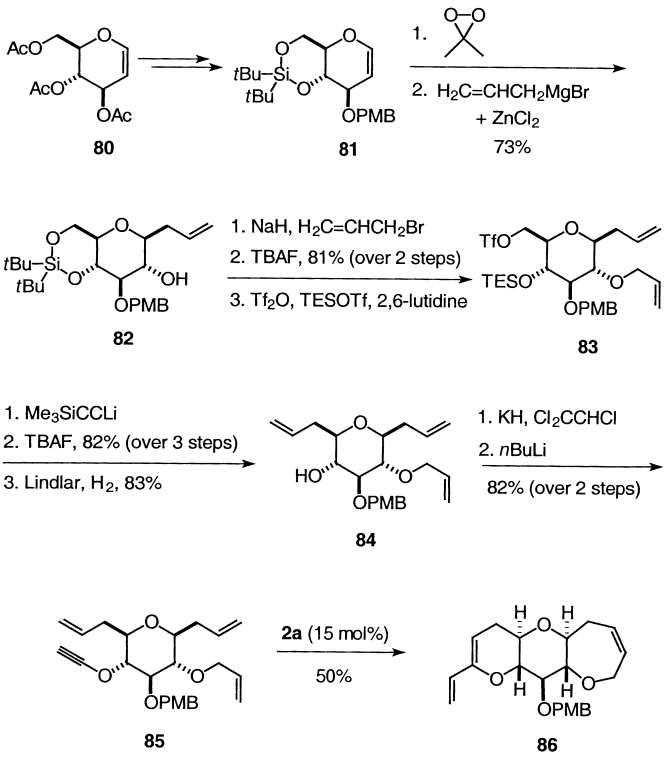
Scheme 20. A ROM/RCM domino reaction is employed in the synthesis of (−)-halosalin (**79**).

desilylation of the crude bicyclic product **77**. Note that the outcome of the crucial metathetic ring shuffling is independent of the site of initiation; it can be rationalized in terms of initial formation of a ruthenium carbene at one of the unsaturated appendages which opens the preexisting cyclopentene ring and, thereby, translates the carbene functionality such that it undergoes RCM with the other side chain. Hydrogenation of diene **78** under standard conditions and cleavage of the *N*-Ts group with Na/Hg in methanolic phosphate buffer delivers enantiomerically pure (−)-halosaline (**79**) in excellent overall yield.[75] The enormous potential of such atom economical skeletal reorganizations has yet to be explored in detail and further elegant applications of this principle can be expected.

5.2. Two-Directional Metathesis: Polyether Syntheses

The structural complexity of brevetoxin or ciguatoxin and related polyether natural products consitutes an ideal forum to scrutinize the preparative potential of RCM. Many studies have been devoted to these targets;[76] among them, two independent reports on two-directional strategies for the construction of the ABC ring framework of ciguatoxin are noteworthy from the conceptual standpoint.[77, 78]

Both syntheses start from easily accessible tri-*O*-acetyl-D-glucal (**80**) and pursue similar routes. One of them is depicted in Scheme 21.[77] Thus, epoxidation of the electron-rich double bond of **81** using dimethyldioxirane, followed by opening of the resulting epoxide with allylmagnesium bromide in the presence of $ZnCl_2$, provides alcohol **82** in a highly diastereoselective manner. Allylation followed by routine protecting-group manipulations lead to primary triflate **83** which allows chain extension upon treatment with lithium trimethylsilylacetylide. Desilylation and subsequent Lindlar reduction delivers alcohol **84** which is readily converted into alkynyl ether **85** according to a literature method. This sets the stage for the crucial two-directional ring closure. Exposure of this substrate to the Grubbs catalyst **2a** affords product **86** in respectable 50% yield which corresponds to the ABC ring system of ciguatoxin-3C. This transformation is noteworthy because it comprises a regular RCM on one side of the molecule and a simultaneous but independent enyne meta-



Scheme 21. Compound **85** is transformed into **86** in one step through RCM and enyne metathesis.

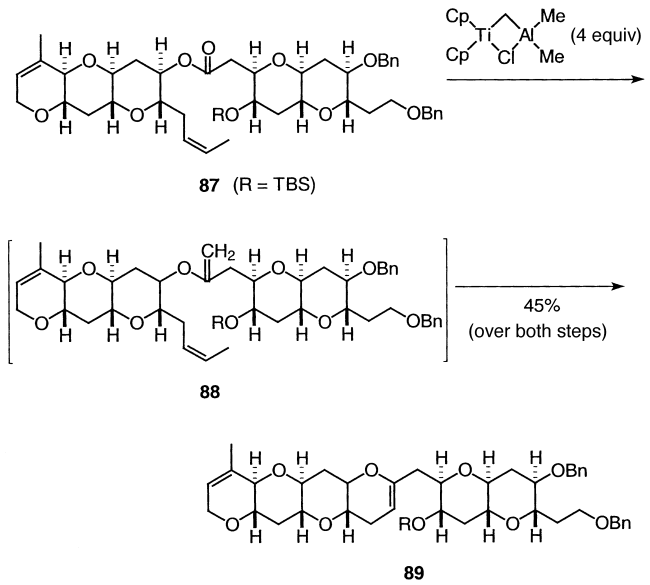
thesis on the other end which do not interfere with one another. This example is also one of the rare cases in which an electron-rich alkyne is subjected to ruthenium-catalyzed enyne metathesis, a yet largely unexplored arena.[77]

5.3. Carbonyl Olefination/RCM Cascades: Polyether Syntheses

A complementary approach to the formation of cyclic ether skeletons takes advantage of the fact that the Tebbe reagent (or its more convenient surrogate [Cp_2TiMe_2]) is nucleophilic enough to effect Wittig-type olefination even of ester carbonyl groups and can also catalyze regular alkene metathesis.[6c, 58] These two properties were cleverly combined into a domino process which allows the transformation of acyclic olefinic esters into cyclic enol ethers. The efficacy of this technique is illustrated by the preparation of various polyether domains of maitotoxin.[79] A representative example is depicted in Scheme 22.

5.4. Carbocycles from Carbohydrates

The widespread occurrence and biological significance of polyoxygenated carbocycles provide constant impetus for the development of flexible methods for the synthesis of these compounds. RCM constitutes a valuable tool that supplements the existing arsenal. Therefore, many applications have been reported in which sugar-derived dienes are transformed into enantiomerically pure carbocycle derivatives by RCM.



Scheme 22. Methylenation and subsequent RCM with the Tebbe reagent.

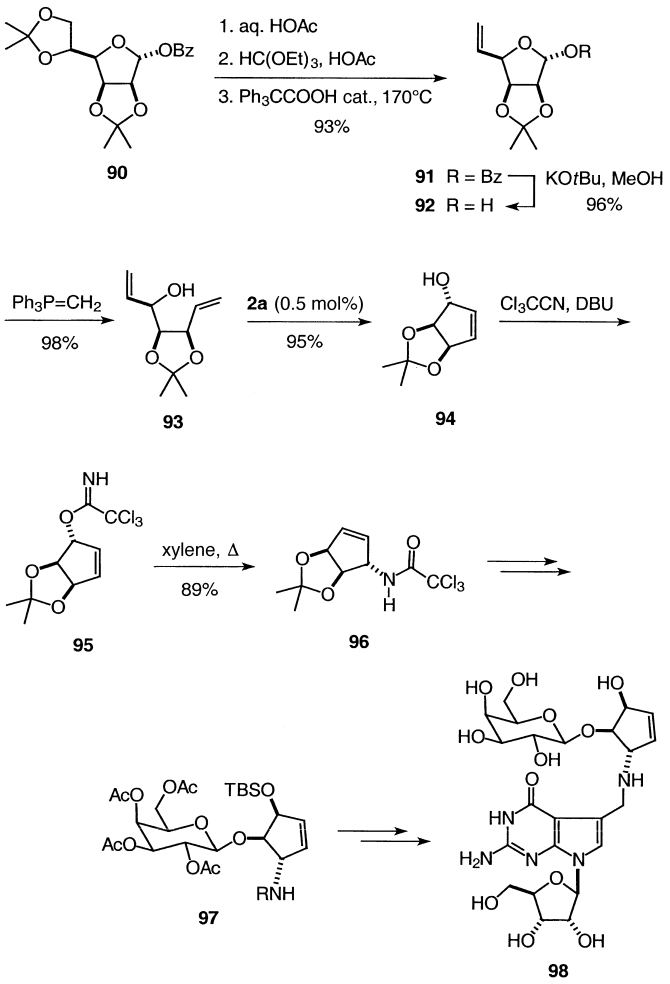
Most notable among them are syntheses of various conduritol derivatives (see also Chapter 3.2.2.),[48, 49] (+)-valienamine,[80] as well as various azasugars,[81] carbasugars, and sugar mimics.[82, 83]

A nice illustration is shown in Scheme 23, which summarizes the preparation of the unusual cyclopentene appendix of nucleoside Q **98**.[84] The mannofuranose derivative **90** is easily accessible on large scale from the parent sugar. Regioselective cleavage of the 5,6-*O*-isopropylidene acetal, treatment of the crude diol derivative with $HC(OEt)_3$, and acid-catalyzed thermal rearrangement of the resulting orthoester deliver alkene **91** in excellent yield; this is converted into diene **93** by cleavage of the anomeric benzoyl group and subsequent Wittig olefination of the resulting hemiacetal **92**. RCM of **93** catalyzed by ruthenium carbene **2a** gives 95% of the desired cyclopentene derivative **94**. Introduction of the missing amino group is elegantly achieved by a [3,3]-sigmatropic Overman rearrangement of the trichloroacetimidate **95** derived thereof. Standard protecting-group manipulations of compound **96** thus obtained, followed by β-galactosylation, provide the desired product **97** suitable for incorporation into nucleoside Q.[84]

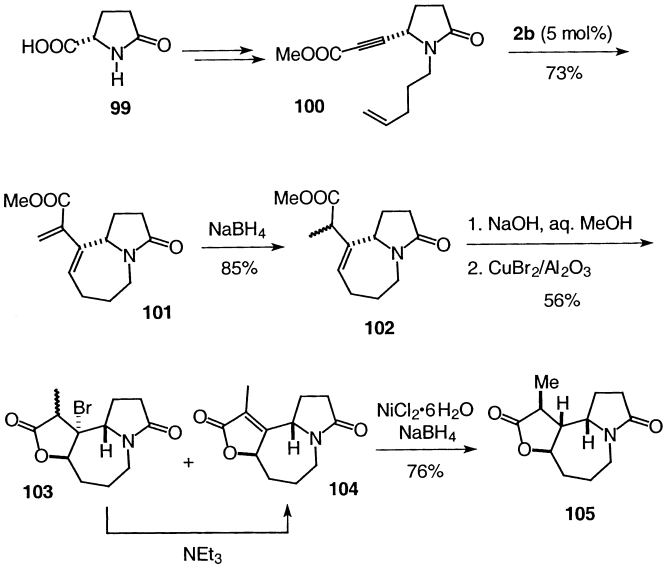
5.5. Enyne Metathesis: (−)-Stemoamide

Although many studies have demonstrated the preparative potential of inter- as well as intramolecular enyne metathesis in general,[85, 86] applications to natural product synthesis are still relatively scarce. A nice exception is the synthesis of (−)-stemoamide (**105**) reported by Kinoshita and Mori (Scheme 24).[87]

Pyroglutamic acid **99** is converted by conventional means into enyne **100** which undergoes a high yielding cyclization to the corresponding diene **101** on exposure to catalytic amounts of ruthenium carbene **2b**. Regioselective reduction of the conjugated double bond, followed by bromolactonization of



Scheme 23. RCM is the key step in the synthesis of the cyclopentene fragment of nucleoside Q (**98**).

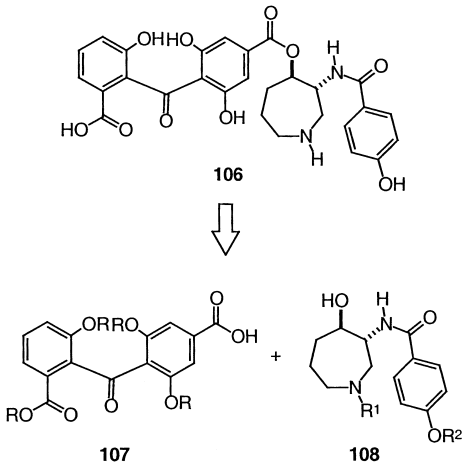


Scheme 24. An enyne metathesis in the early stages of a natural product synthesis.

102, delivers a mixture of bromide **103** and the elimination product thereof. Treatment with base drives the elimination process to completion and gives lactone **104** as the sole product. This is finally reduced with $NaBH_4$ in the presence of $NiCl_2 \cdot 6H_2O$ to afford the natural product in good overall yield.[87]

5.6. (−)-Balanol

The structurally rather unusual alkaloid balanol (**106**) represents an important new lead structure in the quest for selective inhibitors of protein kinase C. All syntheses of **106** reported to date assemble the product by esterification of the benzophenone carboxylic acid fragment **107** with the hexahydroazepine domain **108** (Scheme 25). Although the latter is a

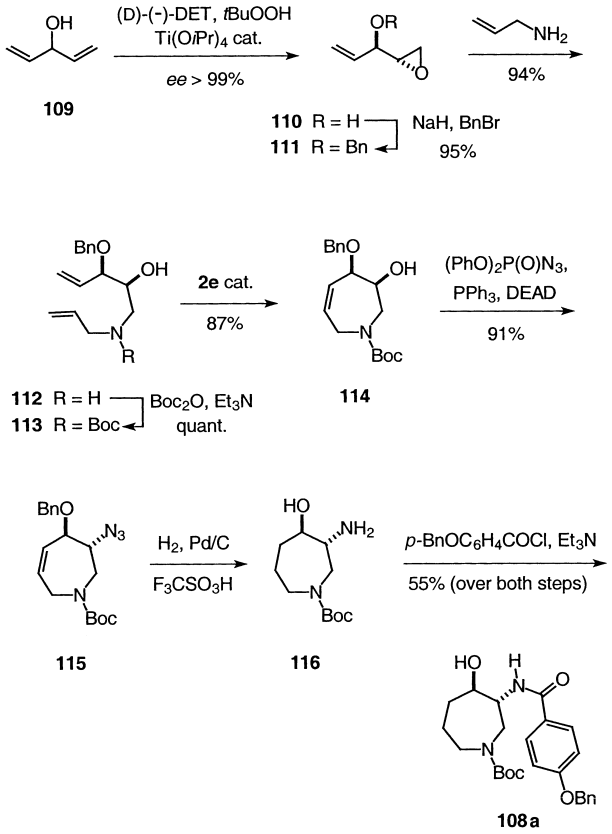


Scheme 25. Retrosynthesis of balanol (**106**).

relatively simple structure, all but one syntheses of enantiomerically pure **108** reported to date require more than 12 steps, independent of whether they rely upon 1) the exploitation of the chiral pool, 2) ligand-controlled enantioselective transformations, or 3) the resolution of racemates. Only recently, a much shorter route to this key intermediate has been described which is based on RCM as one of the key steps.[88]

Sharpless epoxidation of divinylcarbinol **109** affords epoxide **110** in good chemical yield and excellent optical purity (Scheme 26). *O*-Benzylation followed by regioselective opening of the oxirane ring of **111** with allylamine gives diene **112** which is protected with an *N*-Boc group and subsequently submitted to ring closure. The ruthenium indenylidene complex **2e**[27, 28] was found to be the best choice, although the "standard" Grubbs carbene **2a** also provides respectable yields of the desired seven-membered ring **114**. Conversion of the free OH group into azide **115** under Mitsunobu conditions followed by hydrogenation and *N*-acylation of the crude amine **116** thus formed delivers compound **108a** which is amenable to (−)-balanol according to literature procedure.[88]

It is worth mentioning that the order of azide formation and RCM can also be reversed. In this case, however, only Schrock's molybdenum alkylidene **1a** allows productive RCM,[88] whereas all ruthenium-based initiators, which require higher reaction temperatures, led to decomposition of the azide moiety.



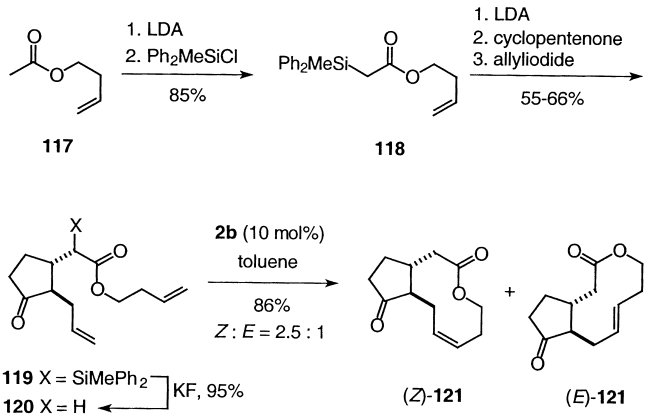
Scheme 26. Synthesis of the balanol precursor **108a**.

To date, this approach constitutes the shortest (eight steps) synthesis of the hexahydroazepine domain of (−)-**106** in enantiomerically pure form. All key operations of this sequence are catalytic in nature (epoxidation, RCM, hydrogenolysis, hydrogenation) and scale-up seems to be possible. Finally, the route can be adapted to the synthesis of the antipode of balanol simply by switching from (D)-(−)-DET to (L)-(+)-DET in the initial Sharpless epoxidation reaction and it provides ample opportunity for the preparation of analogues by deviating from the blueprint outlined above at different stages of the synthesis.

5.7. Three-Component Coupling/RCM: Synthesis of Jasmine Ketolactone

Due to the inherent strain of medium-sized rings, eight- to eleven-membered cycloalkenes are excellent substrates for ROMP but constitute particularly challenging targets for RCM. If preexisting conformational constraints, however, force the substrates to adopt a favorable conformation for ring closure, even this class of compounds is within reach, as witnessed by a rapidly growing number of successful applications.[89] In this context, a recent report deserved particular emphasis in which an eight-membered ring incorporating an *E*-configured double bond has been formed by RCM.[89b]

A typical example that illustrates the efficiency as well as the limitations of RCM in this arena is a synthesis of jasmine ketolactone ((*Z*)-**121**; Scheme 27).[90, 91] A three-component



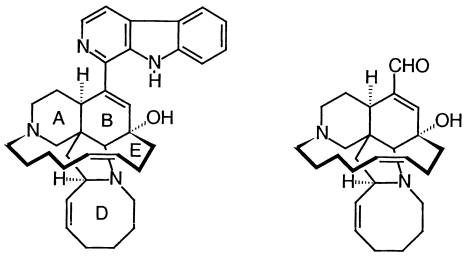
Scheme 27. Synthesis of (*Z*)-**121** and (*E*)-**121** through a three-component coupling with subsequent RCM.

coupling comprising 1,4-addition of the lithium enolate of butenyl (diphenylmethylsilyl)acetate (**118**) to cyclopentenone, followed by alkylation of the resulting ketone enolate with allyl iodide, delivers compound **119**. Subsequent protodesilylation followed by RCM of the resulting diene **120** under high dilution conditions affords the targeted ten-membered lactone **121** in remarkable 86% yield. The efficiency of this five-step sequence, however, is compromised by the fact that both geometrical isomers of the product are formed, although the required *Z* isomer is slightly favored (*Z*:*E* = 2.5:1).

In general, it is not yet possible to predict or control the stereochemistry of the newly formed double bond of cycloalkenes with more than ten ring atoms. This important limitation is evident from many other syntheses as well, among which the epothilone case is certainly the most prominent one. Approaches to this anticancer agent based on RCM are not discussed in detail in this article, because several timely and comprehensive review articles are available.[92, 93] However, these examples make clear that it is a prime strategic goal for future investigations to gain control over the *E*:*Z* ratio in metathesis reactions. As will be shown in Section 7, alkyne metathesis followed by partial reduction of the cycloalkynes thus formed is presently the only viable solution for this stereochemical problem.

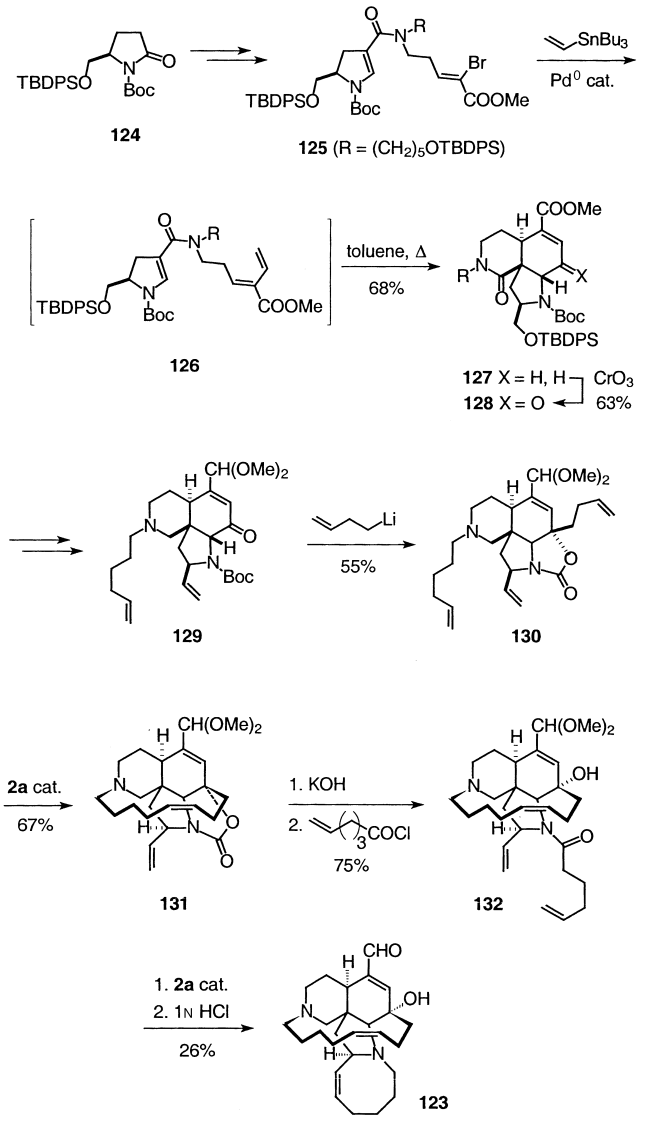
5.8. Ircinal A and Related Manzamine Alkaloids

The intricate polycyclic structure of the potent antitumor agent manzamine A (**122**) was soon recognized as an excellent testing ground for RCM. Several model studies have shown



that the macrocyclic E ring, as well as the eight-membered D ring, can be accessed by this technique.[94] It was only recently, however, that a concise total synthesis of enantiomerically pure ircinal A (**123**), a biosynthetic precursor to manzamine A, has been completed which makes strategic use of this transformation.[95]

Starting from the easily accessible imide **124**, a cleverly designed domino Stille/Diels–Alder strategy leads to the tricyclic core **127** which is elaborated into compound **130** by routine functionalizations of the carbon backbone (Scheme 28). A facile macrocyclization of **130** to product **131** takes place (67%, $Z{:}E = 8{:}1$) on exposure to Grubbs

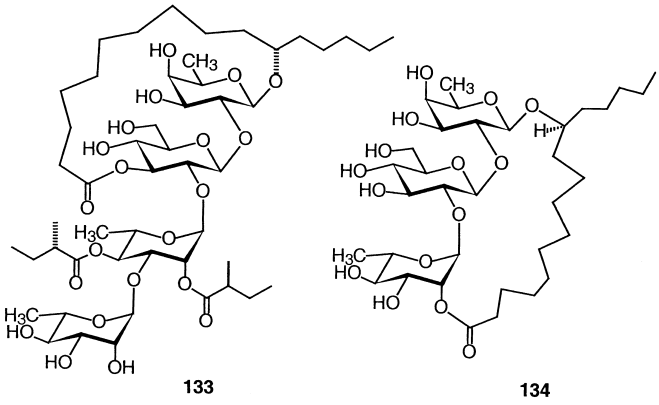


Scheme 28. Synthesis of ircinal A (**123**) with two RCM steps.

carbene **2a** under high dilution conditions even without protonation of the tertiary amine function. The regioselectivity of this RCM step may be interpreted in terms of different steric hindrance close to the alkene moieties of substrate **130**. While the two unhindered ones result in the formation of the thirteen-membered ring, the third olefin is sterically encumbered and, therefore, does not interfere. In turn, however, this crowded situation renders the final formation of the eight-membered D ring (**132** → **123**) highly problematic and results in only 26% isolated yield of the desired product. Despite this unfavorable outcome, the iricinal A synthesis summarized in Scheme 28 constitutes a nice example for the cooperative use of transition metal catalyzed reactions in advanced natural product synthesis.[95]

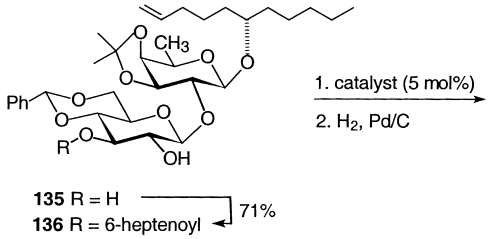
5.9. Inherent Flexibility: Total Synthesis of Tricolorin A and Related Glycolipids

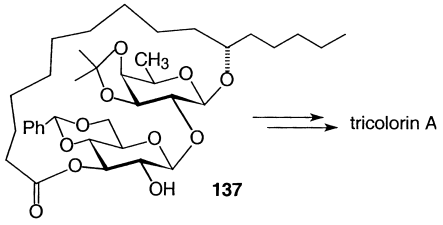
A detailed analysis of the amazing structures of resin glycosides such as tricolorin A (**133**), tricolorin G (**134**), and other members of this series shows that all of them contain 11(*S*)-hydroxyhexadecanoic acid as the aglycon which forms a macrolactone ring by spanning two or more sugar units of the oligosaccharide backbone. Although these glycolipids exhibit promising biological activities including cytotoxicity against human cancer cell lines, systematic structure/activity correlation studies are difficult as long as each analogue requires a labour intense independent synthesis.



The inherently modular character of metathesis allows the problem to be circumvented.[96] Specifically, esterification of the more reactive 3′-OH group of the disaccharide diol derivative **135** with 6-heptenoic acid followed by RCM of the resulting diene **136** and hydrogenation of the *E*,*Z* mixture thus formed gives macrolide **137** that can be elaborated into tricolorin A according to a literature procedure (Scheme 29). The cationic ruthenium allenylidene complex **61**[56] and the photochemically driven procedure using [(η^6-cymene)Ru$Cl_2(PCy_3)$] (**60**)[55] as a catalyst precursor perform similarly well as the "standard" Grubbs carbene **2b**[8] which serves as the calibration point in this investigation.

More importantly, however, diol **135** can be used as a common platform for the preparation of many analogues and positional isomers simply 1) by incorporating unsaturated acids other than 6-heptanoic acid; 2) by attaching the unsaturated moieties to the 2′-OH instead of the 3′-OH group; 3) by replacing the ester linkage with, for example, ether, carbonate, or carbamate functionalities; or 4) by incorporating further carbohydrate residues into the back-

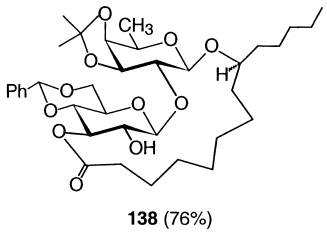


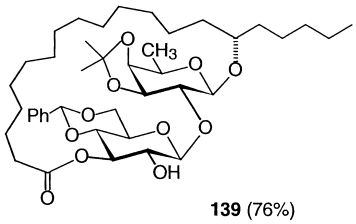


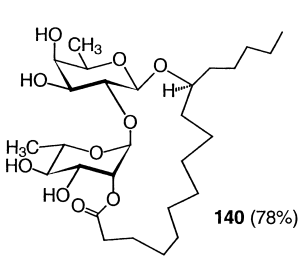
catalyst	yield
2b	77%
60/*hν*	70%
61	85%

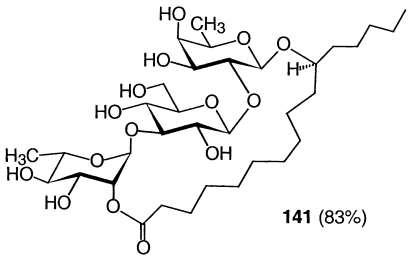
Scheme 29. Synthesis of the tricolorin A precursor **137** by RCM.

bone prior to ring closure. In fact, an array of products (for example, **138**–**141**) has been obtained in excellent yields by this strategy including tricolorin G (**134**) which had not been synthesized before.[96]





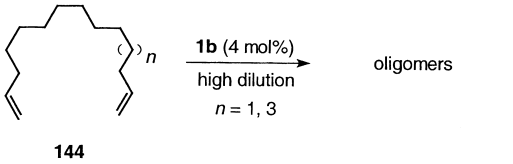




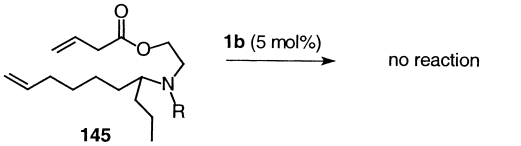
5.10. Inherent Flexibility: The Roseophilin Case

From the large set of data available on macrocyclizations with RCM it was possible to deduce some basic rules which help to identify the proper site within a given target molecule where productive formation of a large ring can be expected.[97] According to this rationale, a suitably biased ground state conformation is not required as can be seen, for example, from the successful preparation of the 16-membered ring **143** from diene **142** [Eq. (5)].[98] However, a well balanced interaction of Lewis-basic heteroatoms of the diene substrate with the emerging Lewis-acidic carbene intermediates is crucial for efficient macrocyclizations [see Eqs. (5)–(8)].[97, 98] If such

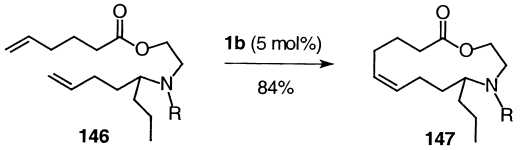
(5)



(6)



(7)

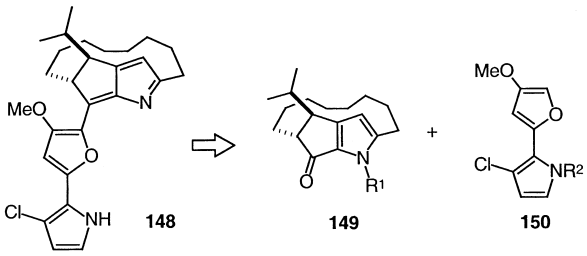


(8)

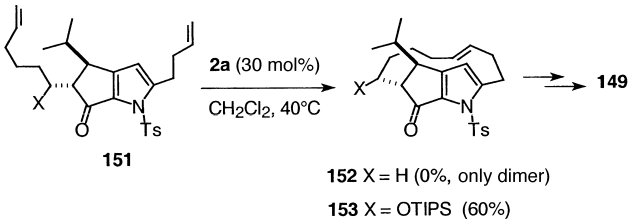
chelation becomes too strong, the activity of the metal carbene is attenuated and RCM is likely to cease; this may explain why the attempted cyclization of diene **145** has failed.[98b] Therefore, it is of utmost importance in retrosynthetic planning to assess the distance as well as the affinity of the polar groups towards the catalytically active metal species. One must keep in mind, however, that RCM-based macrocycle formations are mainly entropically driven and will hardly overcome large enthalpic barriers. The formation of highly strained products will, therefore, be problematic unless preexisting conformational constraints help to shape the substrate and, thereby, facilitate the ring-closing reaction.

These notions are illustrated by three different approaches directed toward roseophilin (**148**), a structurally unique, cytotoxic alkaloid of marine origin. The only total synthesis of this deeply red-colored pigment reported so far assembles the azafulvene chromophore by combining the heteroaromatic side chain **150** with the rather strained macrotricyclic ketone derivative **149** (Scheme 30).[99] The latter constitutes an obvious target for RCM; it has been made by three different RCM-based routes. A comparison of these strategies is quite informative.

Fuchs and co-workers form both five-membered rings prior to the cyclization of the ansa chain (Scheme 31).[100] Attempted RCM of diene **151** (X = H), however, turned out to be unsuccessful even under very high dilution conditions (0.0005 M) because all the strain in the product must be built up during macrocyclization. Only after the introduction of an



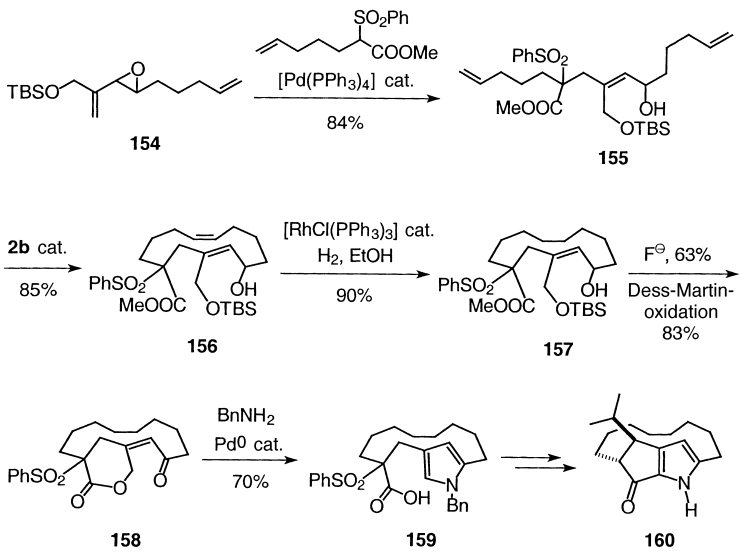
Scheme 30. Retrosynthesis of roseophilin (**148**).



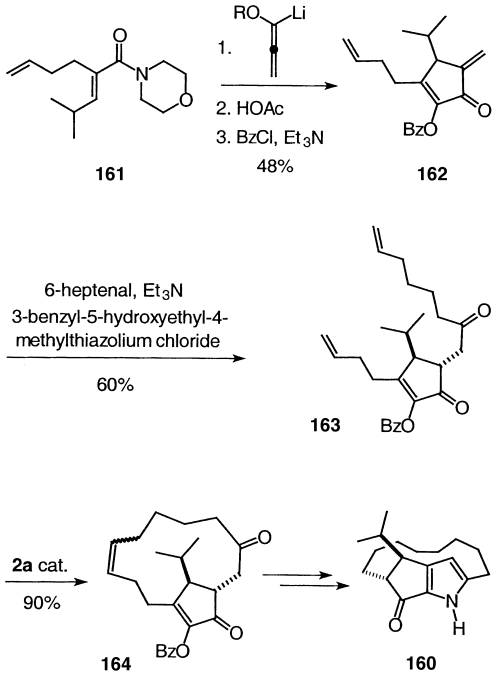
Scheme 31. On route to roseophilin: The ring closure to macrocycle **149** only occurs after the introduction of a group to aid the conformational preorganization.

ancillary group (X = triisopropylsiloxy) as a conformational control element which forces the unsaturated side chains into closer proximity was it possible to accomplish the reaction in 60% yield by using a rather high catalyst loading.[100]

In contrast to this result, the large ring forms without difficulties if the order of events is inversed.[101] Specifically, treatment of triene **155** with Grubbs carbene **2b** delivers, in 85% yield, the desired thirteen-membered ring **156** which is then converted into the ketopyrrole entity as shown in Scheme 32; note that the strain in the molecule is now introduced during the kinetically more favorable closure of the five-membered rings.[101] This example also highlights the excellent compatibility of the ruthenium complex with various functional groups and shows that this catalyst rigorously distinguishes between the terminal and the trisubstituted alkene groups of substrate **155**. In line with this finding, macrocyclization also proceeds uneventfully with the monocyclic diene **163** (Scheme 33).[102] The resulting product **164** is then converted into the target by a conventional Paal–Knorr pyrrole synthesis.



Scheme 32. On route to roseophilin: It is advantageous to perform the RCM-based macrocyclization at an early stage of the synthesis of **160**.



Scheme 33. On route to roseophilin: An alternative route to **160**.

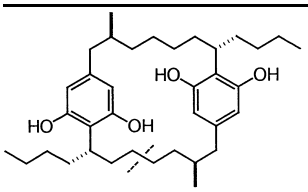
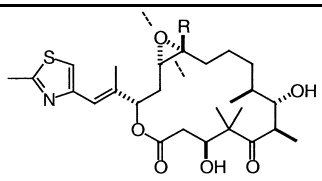
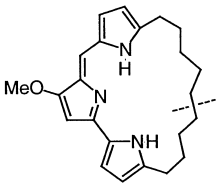
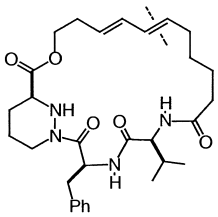
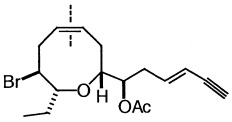
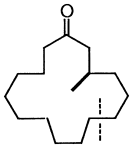
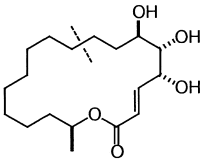
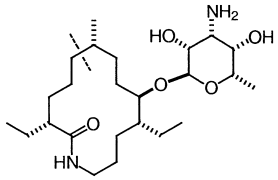
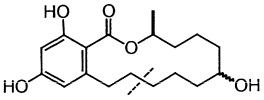
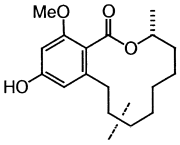
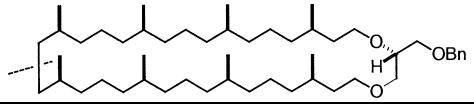
Irrespective of the individual features of each route, the roseophilin case exemplifies the flexibility and liberty in retrosynthetic planning that is made possible by the truly remarkable application profile of modern metathesis catalysts. More examples of RCM-based syntheses of macrocyclic natural products are compiled in Table 4.[92, 93, 103–112]

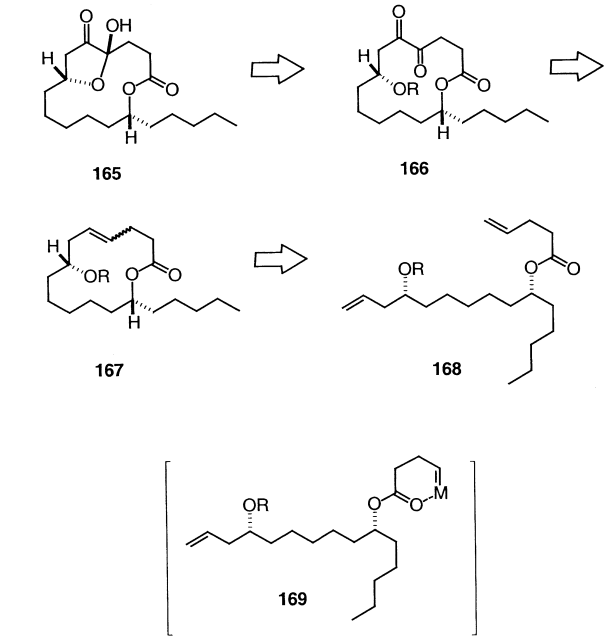
5.11. Binary Catalyst System: (−)-Gloeosporone

The retrosynthetic analysis for (−)-gloeosporone (**165**) depicted in Scheme 34 suggests that RCM may open an unprecedentedly short entry into this macrolide antibiotic, which has previously been prepared by lengthy lactonization strategies. Bearing in mind, however, that the distance and the affinity of the polar groups of a given substrate toward the emerging carbene entities during RCM play a decisive role for productive macrocyclization,[97, 98] diene **168** may be a problematic substrate. If the catalyst attacks the 4-pentenoate entity, a fairly stable six-membered chelate **169** may evolve which can potentially intercept the catalyst in an unproductive form.

The required diene **168** is readily obtained in enantiomerically pure form starting from cycloheptene as shown in Scheme 35. In line with the rationale presented above, this substrate fails to afford any cyclized product on exposure to catalytic amounts of ruthenium carbene **2a**. This outcome, however, can be easily rectified upon addition of Ti(O*i*Pr)$_4$ to the reaction mixture. The binary system comprising catalytic amounts of **2a** and substoichiometric

Table 4. Macrocyclic natural products prepared by RCM. The site of ring closure is indicated by a dotted line.

Product	Ref.	Product	Ref.
	[103]		[92, 93]
	[104]		[105]
	[106]		[111]
	[107]		[108]
	[109]		[109]
			[110]

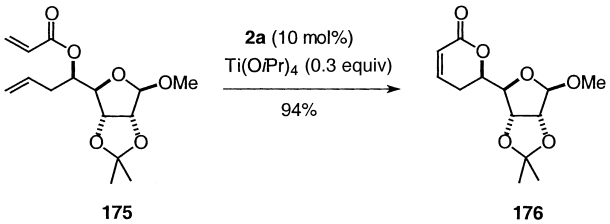


Scheme 34. Retrosynthesis of (−)-gloeosporone (**165**).

amounts of Ti(O*i*Pr)$_4$ results in a clean and high yielding formation of the desired macrocycle **167**, which is then converted into gloeosporone by oxidation of the alkene and cleavage of the silyl group during work-up.[113]

From the conceptual point of view, several aspects of this approach are noteworthy. It is significantly shorter than all previous syntheses of **165** reported in the literature due to the highly chemoselective character of metathesis allowing structurally unproductive protecting-group manipulations to be minimized.[114] Specifically, enantiomerically pure gloeosporone is obtained in only eight steps with an overall yield of 18% starting from cycloheptene. Note that all C–C-bond formations are transition-metal catalyzed and that the chiral centers are concomittantly formed in a ligand-controlled manner. This gives maximum flexibility for the preparation of analogues of this bioactive target and illustrates the relevance of catalysis in general and of metathesis in particular for natural product chemistry.

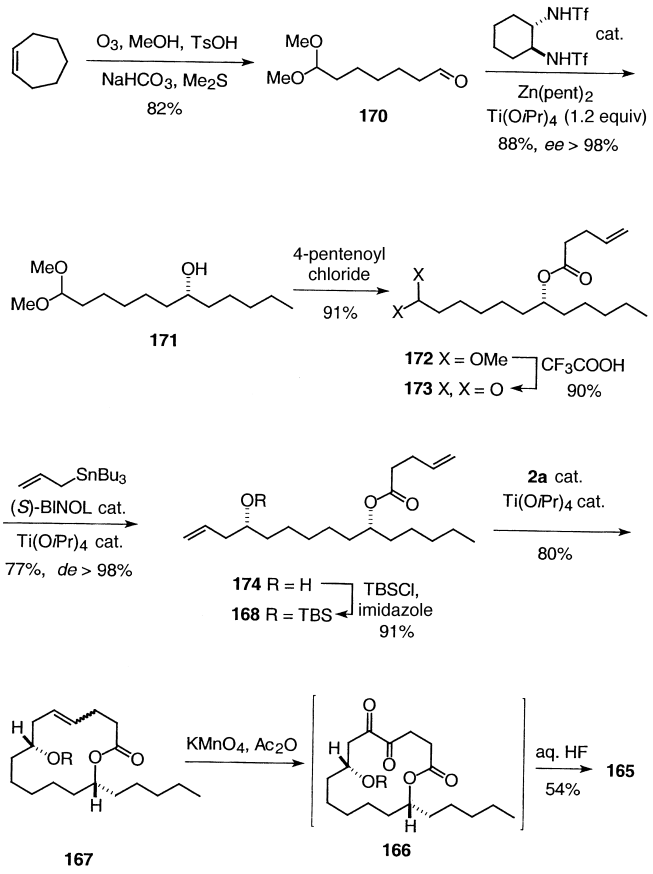
Although the precise mode of action of Ti(O*i*Pr)$_4$ is not yet clear, one can envisage three different possibilities: 1) This weakly Lewis-acidic additive competes with the emerging ruthenium carbene for a kinetically labile coordination onto the ester and, thereby, avoids the formation of unreactive intermediates such as chelate **169**. 2) Alternatively, Ti(O*i*Pr)$_4$ may coordinate onto the ester and, hence, direct the initiation of RCM to the other olefinic site of the molecule. 3) Finally, one can envisage that the Lewis-acidic Ti(O*i*Pr)$_4$ abstracts one of the basic PCy$_3$ ligands from **2a** and, thereby, activates the catalyst. The data presently available do not allow one to decide which of these effects is operative.[113] The beneficial influence of Ti(O*i*Pr)$_4$ on RCM, however, seems to be quite general as witnessed by a rapidly growing number of successful applications reported in the literature.[115] Problematic substrates such as acrylates were shown to react efficiently if the binary system **2a**/Ti(O*i*Pr)$_4$ is employed as a metathesis catalyst mixture. A typical example is shown in Equation (9).



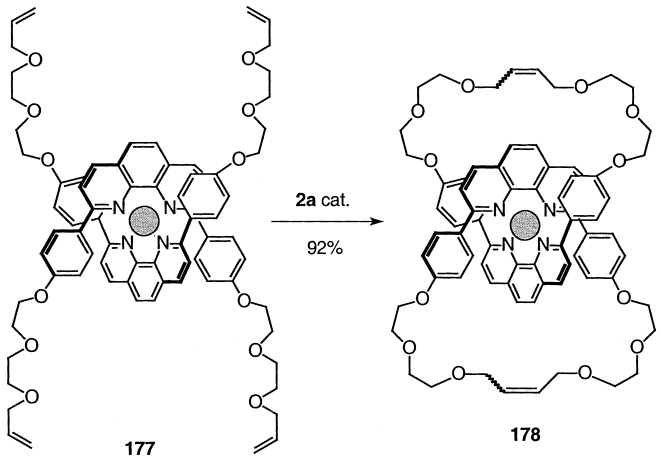
(9)

6. Highlights from the Nonnatural Product Series

Metathesis has also seen a prolific use in the nonnatural product series and this section must, therefore, be restricted to a few recent highlights. Among them, several reports on the efficient formation of catenanes by means of RCM have to be mentioned.[116] A representative example is displayed in Scheme 36, which shows the self assembly of two 1,10-phenanthroline molecules bearing unsaturated appendages



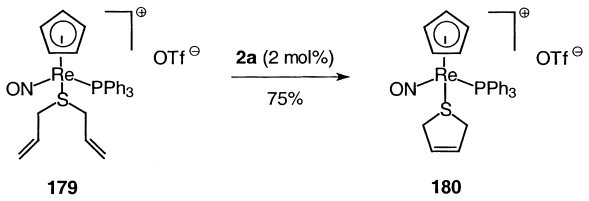
Scheme 35. Synthesis of (−)-gloeosporone (**165**) from cycloheptene with the use of a binary catalyst system in the metathesis step.



Scheme 36. Synthesis of a [2]catenane by double RCM.

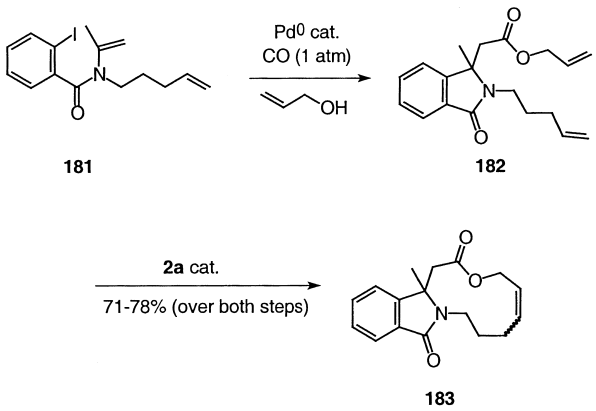
on a Cu^{I}-template followed by RCM of the resulting tetraene **177**. This reaction provides the interlocked complex **178** in 92% yield as the only reaction product which can be quantitatively demetalated with KCN to afford the corresponding [2]catenand. The basic principle of this approach was later extended to the preparation of even more sophisticated structures such as molecular knots.[117] In addition to the use of metal templates such as Cu^{I}, hydrogen bond directed assembly and templating π-acceptor/π-donor interactions have also been exploited for the formation of complex catenane structures by RCM-based ring closure.[118]

Superb examples for metathesis in metal coordination spheres have been reported by Gladysz and co-workers.[119] These authors succeeded in cyclizing various unsaturated metal complexes such as the cationic rhenium compound **179** shown in Equation 10. In this particular case, the metal atom simultaneously acts as a "protecting group" for the sulfide, because RCM of free thioethers is known to be unproductive if the Grubbs catalyst **2a** is used.[16]



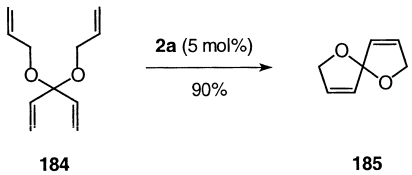
(10)

An illustration of how metathesis can be employed in concert with other transition metal catalyzed processes has been described by Grigg and co-workers.[120] They invented a domino process resulting in the formation of four bonds, two rings, and one tetrasubstituted C atom by means of a palladium-catalyzed Heck reaction/carbonylation followed by RCM (Scheme 37).



Scheme 37. RCM as the last step of a domino process.

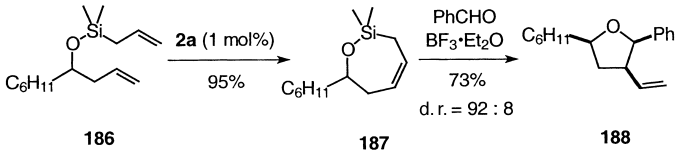
Two or more simultaneous RCM events can be surprisingly selective as shown, for example, by the high yielding formation of spirocyclic arrays such as **185** from the tetraene precursor **184** [Eq. (11)].[121] The observed selectivity in



(11)

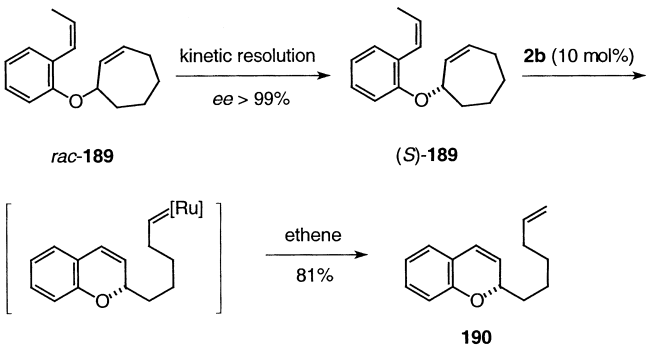
this particular case is probably the result of a kinetic preference for the formation of the five-membered rings in combination with a slow reversibility of the reaction which avoids undue scrambling. Similar ideas have been pursued by Lautens et al. en route to various bicyclodiene derivatives.[122]

Yet another general synthesis method makes use of temporary linkers which enable directed cross metathesis of different olefins.[123, 124] As has been independently shown by several research groups, silicon-based linkers are particularly useful in this context due to the ease of preparation and cleavage.[125] The silicon moiety can even be exploited for subsequent transformations as exemplified by cleverly designed RCM/Sakurai reaction sequences (Scheme 38).[126] Likewise, an efficient approach to D-altritol is based on temporary silicon-tethered RCM followed by dihydroxylation of the resulting alkene product.[127]



Scheme 38. A sequence of RCM and a Sakurai reaction.

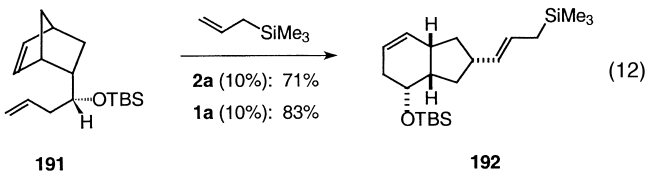
Hoveyda and co-workers have developed a Zr-catalyzed kinetic resolution protocol providing good access to cyclic diene derivatives such as (*S*)-**189**, which serve as starting materials for imaginative ROM/RCM/CM cascades.[128] Upon treatment with a suitable metathesis catalyst they convert into 2-substituted chromenes (Scheme 39) and they have been



Scheme 39. An ROM/RCM/CM cascade which leads to a chromene derivative.

used for an efficient synthesis of the antihypertensive agent (*S,R,R,R*)-nebivolol.[129] Depending on the level of substitution, the domino process may either be triggered by interaction of the catalyst with the styrenyl or with the carbocyclic alkene; the outcome of the reaction, however, is independent of the site of initiation. Note that an ethylene atmosphere is imperative for the typical transformation displayed in Scheme 39 as it terminates the reaction domino by cross metathesis and, thereby, avoids the formation of dimeric products.

Other variants of ROM/RCM/CM cascades have been reported which take advantage from the high reactivity of norbornene or 7-oxanorbornene substrates in metathesis reactions [Eq. (12)].[130] Furthermore, multicyclization reactions of polyunsaturated precursors containing acetylenes or cyclic olefins as relays should also be mentioned in this context.[131]

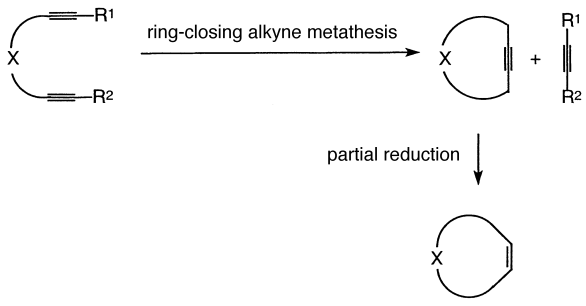


Metathesis has been used to capture and covalently stabilize certain conformations of more or less flexible backbones. Ramification of β-sheet peptide assemblies[132] or the intramolecular cross-linking of the α-helix structure of peptides are highlights in this field.[133] Furthermore, a cleverly designed "rolling loop scan" should also be mentioned which allows the preparation of small libraries of compounds which have the same peptide sequence but different active conformations locked in by RCM.[134, 135] Moreover, an interesting application to medicinal chemistry deserves mentioning, in which taxol hybrids with restricted conformations are prepared by RCM.[136] All of these applications are made possible by the excellent tolerance of Grubbs-type catalysts towards densely functionalized molecules.

7. Beyond Alkenes: Alkyne Metathesis and Ring-Closing Diyne Metathesis

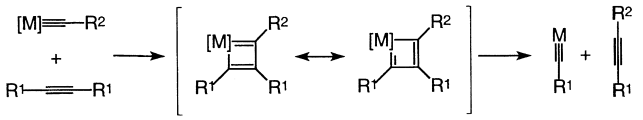
Among the few shortcomings that infringe upon the superb overall application profile of RCM, the lack of control over the configuration of the newly formed double bond is most noteworthy if the reaction is applied to the macrocyclic series. The products formed are usually obtained as mixtures of the *E* and *Z* isomers, with the former dominating in most of the recorded cases. This constitutes an obvious drawback in target-oriented synthesis, as can be seen from many examples reported in the literature.

In the long term, this fundamental problem calls for the development of stereoselective RCM catalysts. One may, however, contemplate that ring-closing alkyne metathesis followed by partial reduction of the resulting cycloalkyne also provides a viable solution (Scheme 40), in particular since several alkyne metathesis catalysts are known. They fall into two categories. Schrock-type alkylidyne complexes of various transition metals are particularly attractive because they are structurally well defined, show high catalytic activity, and have been thoroughly studied from the mechanistic point of



Scheme 40. Formation of stereochemically defined cycloalkenes by ring-closing alkyne metathesis and subsequent Lindlar hydrogenation.

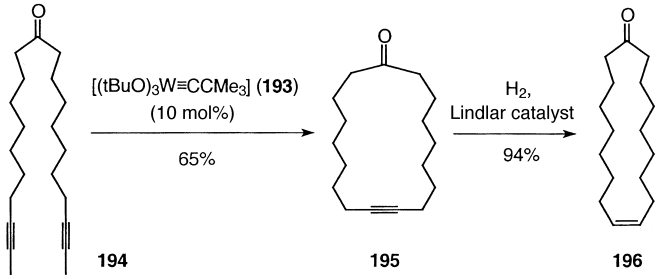
view.[137] They react by a Chauvin-like mechanism as depicted in Scheme 41.[138] The other class comprises multicomponent initiator systems in which a structurally unknown catalyst is formed in situ from different ingredients. For example, the combination of $[Mo(CO)_6]$ and phenol additives (p-ClC_6H_4OH, p-$(F_3C)C_6H_4OH$, etc.) was introduced early on, although catalytic activity is observed only at rather elevated temperatures.[139, 140]



Scheme 41. Mechanism of alkyne metathesis.

Surprisingly, however, applications of these alkyne metathesis catalysts have been very limited and were essentially confined to the preparation of a few speciality polymers[141] and to the dimerization or cross-metathesis of simple acetylene derivatives.[142]

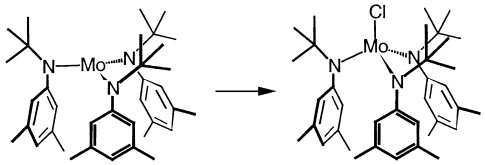
The first application of alkyne metathesis to the formation of large rings has been reported in 1998 using Schrocks tungsten alkylidyne complex $[(tBuO)_3W{\equiv}CCMe_3]$ **193** as the catalyst.[143, 144] This study made clear that: 1) rings with more than 12 atoms—even including very large rings—are readily accessible by this method in good to excellent yields; 2) ring-closing diyne metathesis proceeds even faster than RCM of the corresponding dienes; 3) the reaction tolerates ethers, esters, silyl ethers, amides, urethanes, ketones, enones, sulfones, furans, etc.; 4) the catalyst rigorously distinguishes between alkynes (reactive) and preexisiting alkene groups in the substrate, which were found to be inert; and 5) this method provides an excellent entry into macrocyclic (*Z*)-alkenes if combined with a Lindlar reduction of the cycloalkyne products. This two-step strategy constitutes an indirect but convenient solution for the stereochemical shortcomings of RCM mentioned above.[143, 144] A typical example, the stereoselective synthesis of the macrocyclic musk civetone (**196**) is displayed in Scheme 42.[145]



Scheme 42. Synthesis of civetone (**196**) by the alkyne metathesis/Lindlar strategy.

The $[Mo(CO)_6]$/p-chlorophenol initiator system has also been applied to various ring-closure reactions.[144–146] Although this user-friendly "instant" system optimized by Bunz and co-workers,[140] which requires no particular precautions as to handling and drying of the reagents and solvents used, gives satisfactory results in many cases, its scope is somehow limited and the quite harsh conditions (130–150 °C in dichloro- or trichlorobenzene) prevent applications to sensitive substrates.

Very recently, yet another alkyne metathesis catalyst has been developed which is formed in situ from the trisamidomolybdenum complex **197** and halide sources such as CH_2Cl_2 or TMSCl [Eq. (13)].[147, 148] Among various molybdenum

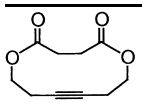
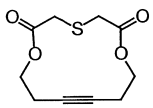
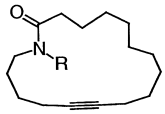
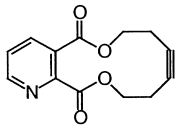
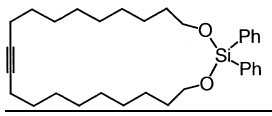


197 **198** (13)

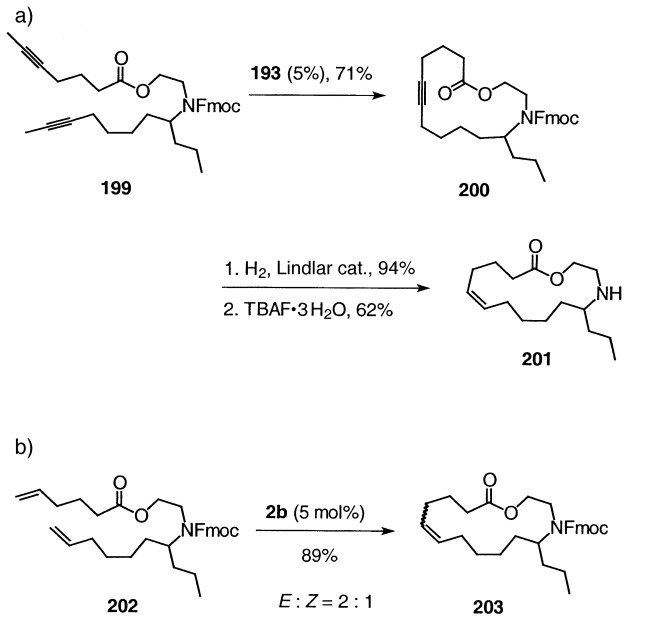
compounds formed during this activation phase, chloride **198** was identified as a catalytically relevant species although it is presently not clear how this compound interacts with the substrates and what the intermediates along the ensuing alkyne metathesis pathway look like. The preparative data, however, show the excellent performance of this novel initiator which tolerates even "soft" donors such as thioethers, crown ether segments, and pyridine rings that are incompatible with $[(tBuO)_3W{\equiv}CCMe_3]$ (**193**).[147] Table 5 provides a comparison of the three catalyst systems used so far for ring-closing alkyne metathesis.

With these tools in hand, several applications of alkyne metathesis/Lindlar reduction sequences to the synthesis of bioactive targets have been accomplished, including stereoselective syntheses of musk-odored perfume ingredients (civetone, ambrettolide, yuzu lactone),[144, 145] as well as an application to the insect-repellant azamacrolides epilachnene

Table 5. Comparison of the yields in ring-closing alkyne metathesis reactions with three different catalysts.

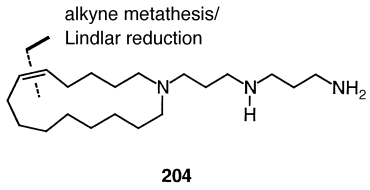
Product		**193**	$[Mo(CO)_6]$ + ClC_6H_4OH	**197** + CH_2Cl_2
		73	64	91
		0		84
	R = H	62	0	0
	R = Me	72	64	72
		0		88
		55	(decomp)	74

and homoepilachnene.[144] It is interesting to note that the latter compounds had previously been targeted by conventional RCM (Scheme 43 b).[98b] Although the macrocyclization **202** → **203** proceeds uneventfully, a mixture of both stereoisomers is obtained, with the unnatural *E* alkene dominating.

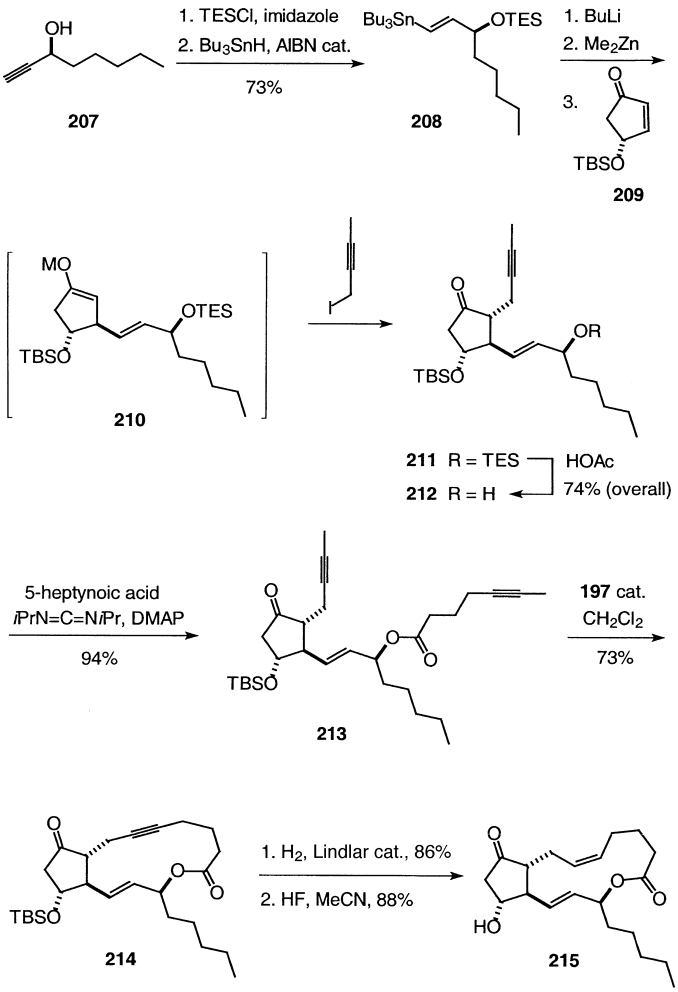


Scheme 43. a) Epilachnene (**201**) is obtained as a pure diastereomer through use of the alkyne metathesis/Lindlar strategy. b) When conventional RCM is employed in the synthesis, the precursor **203** is formed as a mixture of diastereomers.

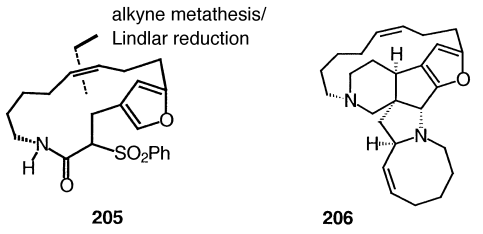
The use of the alkyne metathesis/Lindlar strategy solves this problem and delivers pure epilachnene (**201**) via cycloalkyne **200** as the key intermediate (Scheme 43 a).[144] The same holds true for a synthesis of motuporamine C (**204**), a cytotoxic spermine-type alkaloid. While RCM affords a mixture of *E* and *Z* alkenes,[149] ring-closing diyne metathesis followed by Lindlar reduction stereoselectively delivers this natural product in excellent overall yield.[150]



The most advanced applications of alkyne metathesis reported to date are the preparation of the macrocyclic perimeter **205** of the polycyclic marine alkaloid nakadomarin A (**206**),[144] as well as an efficient total synthesis of prostaglandin E_2-1,15-lactone (**215**; Scheme 44).[151] The latter comprises a three-component coupling reaction for the assembly of compound **211**, ring-closing alkyne metathesis of diyne **213** derived thereof by means of the molybdenum-based catalyst **197**/CH_2Cl_2, followed by Lindlar reduction of the resulting cycloalkyne **214** and fluoride-mediated deprotection of the *Z* alkene thus formed. The fact that the labile



Scheme 44. Total synthesis of prostaglandin-E_2-1,15-lactone (**215**) with the alkyne metathesis/Lindlar strategy.



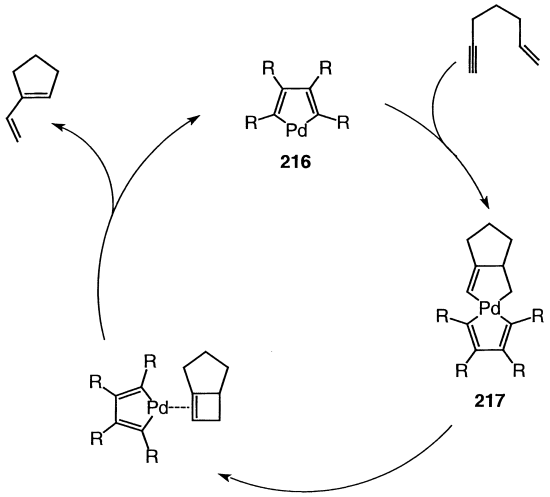
aldol substructure of **213** remains intact and that no epimerization or racemization was observed attest to the mildness of the ring-closing alkyne metathesis step and corroborate the notion that this transformation qualifies for applications to even more advanced targets.[151]

8. Excursion into the "Non-Chauvin" World

As outlined in the Introduction, metathesis usually follows the mechanistic rationale originally proposed by Chauvin,[5] who was the first to interpret this reaction as a sequence of formal [2+2] cycloaddition/cycloreversion steps of metal

carbene and metallacyclobutane intermediates. An analogous pathway has been proposed and experimentally corroborated for alkyne metathesis, comprising metal alkylidynes and metallacyclobutadiene derivatives as the relevant species.[138]

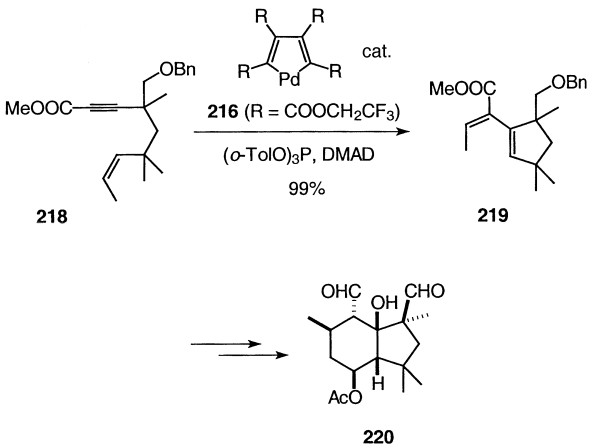
One can, however, envisage other scenarios resulting in formal metathesis events. Redox chemistry such as the Pd^{II}/Pd^{IV} system proposed by Trost and Krische leads to "metathesis" of 1,6- or 1,7-enyne substrates (Scheme 45).[152] In this



Scheme 45. Formal enyne metathesis by a Pd^{II}/Pd^{IV} system.

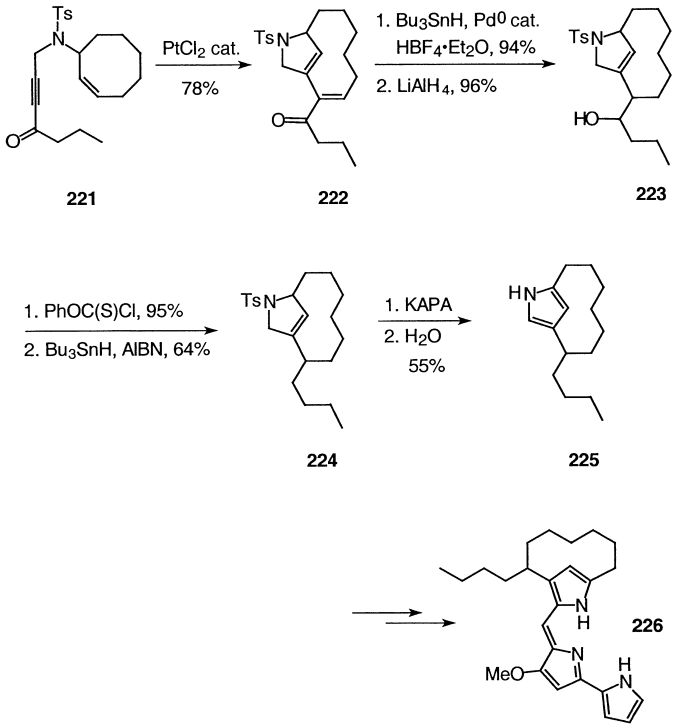
particular case, the metallacyclopentene derivative **217** initially formed undergoes reductive elimination with formation of a cyclobutene which delivers the expected product by electrocyclic ring opening. Evidence for this mechanism comes from the fact that cyclobutene derivatives are occasionally isolable.[153] A multicomponent catalyst system comprising palladacycle **216** ($R = COOCH_2CF_3$), tris(*o*-tolyl)-phosphite, and dimethyl acetylenedicarboxylate (DMAD) effects this transformation, provided that the alkyne entity of the substrate bears an electron-withdrawing group.[154] This reaction has been employed as a key step in an approach to the botrydiane natural product **220** shown in Scheme 46.[155]

Murai and co-workers have found that $PtCl_2$ or $[\{RuCl_2(CO)_3\}_2]$ are even more practical and atom-economical catalysts for the same type of transformation.[156] If substrates containing cyclic alkene entities are employed, the preexisting



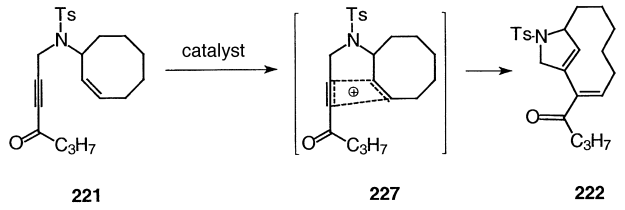
Scheme 46. Enyne metathesis in a natural product synthesis.

ring is expanded and bridged bicyclic products are formed. This reaction has been employed as a key step (**221** → **222**) in a recent total synthesis of the immunosuppressive alkaloid streptorubin B (**226**; Scheme 47).[157] During the course of this



Scheme 47. Ring expansion by metathesis in the total synthesis of streptorubin B (**226**).

study, it was also possible to shed light onto the mechanism of this unusual transformation which formally cleaves a C=C bond, forms two new C=C bonds, and concomittantly installs a bridgehead alkene function. Thus, careful analysis of some very minor by-products suggests that a carbocation such as **227** is responsible for the formation of product **222**. The formation of this reactive intermediate, however, is not only triggered by coordination of $PtCl_2$ onto the π system of substrate **221**, but can also ensue from coordination of hard Lewis or Bronsted acids onto the adjacent carbonyl group. In fact, $BF_3 \cdot Et_2O$ or even HBF_4 were found to be efficient catalysts for the conversion of substrate **221** into the bicyclic product **222** (Scheme 48). This result can be formally inter-



catalyst	yield
$PtCl_2$	79%
$BF_3•Et_2O$	64%
HBF_4	57%

Scheme 48.

preted as the first example of a "proton-catalyzed enyne metathesis", although the actual mechanism is a complex Wagner–Meerwein rearrangement.[157] In any case, it shows that "metathesis" is by no means restricted to anionic systems.[158] Totally different but largely unexplored scenarios can be envisaged that hold great promise for preparative chemistry.

9. Conclusions and Outlook

Tremendous progress in catalyst design has firmly established metathesis as a mature tool for advanced organic synthesis and polymer chemistry, but this development is not yet over. During the last year, new complexes have been introduced that allow applications which were previously either impossible or, at least, very difficult to achieve. Moreover, the logic of retrosynthetic planning is strongly affected by metathesis since this transformation can be used in a strategic manner for the design of unprecedentedly short and efficient synthesis routes. This is particularly true if it is cleverly combined with other transition metal catalyzed reactions for the formation of the required alkene, diene, or polyene substrates. Likewise, metathesis cascades are highly promising and will almost certainly gain great importance in the near future.

Although metathesis of alkenes will remain the core business, recent developments pinpoint the notion that metathesis of other π systems may also fertilize advanced organic synthesis. This refers in particular to enynes, alkynes, allenes,[159] and, very probably, even to heterodouble and heterotriple bond systems.[160] Investigations into this area are just starting. The same holds true for metathesis reactions deviating from the classical Chauvin pathway. In any case, it can be concluded that metathesis in general and olefin metathesis in particular are among the most important advancements in preparative chemistry seen in recent years, although many stimulating discoveries certainly still lay ahead.

Abbreviations

Ac	acetyl
ADMET	acyclic diene metathesis polymerisation
AIBN	2,2′-azobisisobutyronitrile
ARCM	asymmetric ring-closing metathesis
BINOL	2,2′-dihydroxy-1,1′-binaphthyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bz	benzoyl
CM	cross-metathesis
cod	cycloocta-1,5-diene
cot	cycloocta-1,3,5,7-tetraene
Cp	cyclopentadienyl
Cy	cyclohexyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DEAD	diethylazodicarboxylate
DET	diethyltartrate
DMAD	dimethylazodicarboxylate
DMAP	4-dimethylaminopyridine
dtbpm	bis(di-*tert*-butylphosphino)methane
Fmoc	9-fluorenylmethoxycarbonyl
KAPA	potassium 3-aminopropylamide
LDA	lithium diisopropylamide
NHC	*N*-heterocyclic carbene
Piv	pivaloyl
PMB	*para*-methoxybenzyl
RCM	ring-closing metathesis
ROM	ring-opening metathesis
ROMP	ring-opening metathesis polymerisation
solv	solvent
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TIPS	triisopropylsilyl
TMS	trimethylsilyl
Tol	tolyl
Ts	tosyl (4-toluenesulfonyl)

I sincerely thank all my co-workers in the metathesis team for their high motivation, their excellent intellectual contributions, and their skillful work. Their names appear in the references. The constant and generous financial support of our projects provided by the Max-Planck-Gesellschaft, the Deutsche Forschungsgemeinschaft (Leibniz program), the Fonds der Chemischen Industrie, the Deutsche Akademische Austauschdienst, and the European Union is acknowledged with gratitude.

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