Ring closing metathesis

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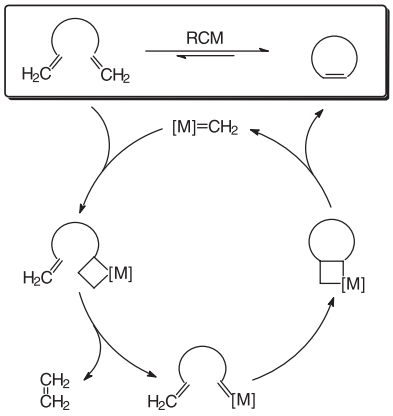
Résumé **Réaction de métathèse cyclisante**

Cet article présente un aperçu des plus récents développements en métathèse des alcènes et alcynes, en mettant particulièrement l'accent sur des nouvelles possibilités ouvertes en synthèse par les meilleurs catalyseurs actuels.

Mots-clés **Alcènes, alcynes, carbènes, métathèse, produits naturels.**

Key-words **Alkenes, alkynes, carbenes, metathesis, natural products.**



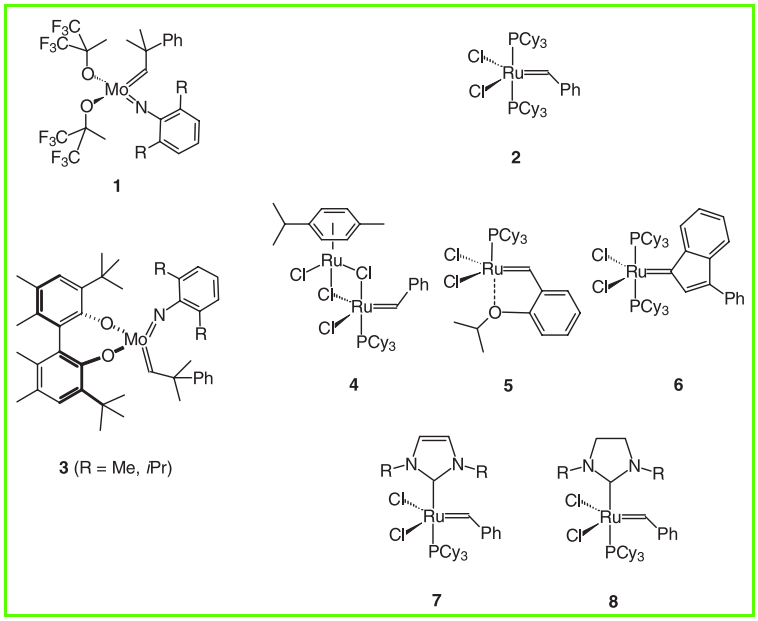
Scheme 1 - Basic catalytic cycle of RCM.
Although not specifically shown, all elementary steps – and hence the overall transformation – are reversible.

Although olefin metathesis has already been discovered during early studies on Ziegler polymerization and has found industrial applications shortly thereafter, it was not until the 90's that this transformation gained real significance for advanced organic synthesis [1]. The last decade, however, has seen an explosive growth of interest in metathetic conversions in general, making clear that this reaction is one of the most fascinating and versatile processes in the realm of homogeneous catalysis [2].

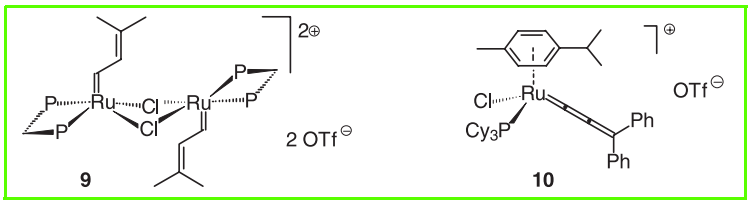
Alkene metathesis refers to the redistribution of the alkylidene moieties of a pair of olefins effected by catalysts that are able to cleave and to form C-C-double bonds under the chosen reaction conditions. This mutual alkylidene exchange occurs via a sequence of formal [2+2] cycloadditions/cycloreversions (Chauvin mechanism) [3] involving metal alkylidene and metallacyclobutane species as the catalytically competent intermediates. Among the many possible uses of metathesis, the ring closing olefin metathesis (RCM) of dienes to cycloalkenes depicted in *scheme 1* is certainly the most popular application.

It was the development of well defined metal alkylidene complexes combining high catalytic activity with an excellent tolerance towards polar functional groups that has triggered this avalanche of interest. The most prominent and versatile ones are the molybdenum alkylidene **1** developed by Schrock [4] and the ruthenium carbene **2** introduced by Grubbs (*scheme 2*) [5]. These commercially available complexes define the standard in this field and have reached an immense popularity as witnessed by a truly prolific number of successful applications. They also serve as « lead structures » for the development of even more powerful « second generation » catalysts such as **3**-**8** [6-9]. Among them, the heteroleptic ruthenium complexes **7** and **8** containing one N-heterocyclic carbene (NHC) ligand are particularly noteworthy because they exhibit activities similar to that of the molybdenum complex **1** while being highly robust and easy to use [10]. They effect even the formation of tetrasubstituted cycloalkenes and are sufficiently reactive to activate electron deficient (acrylates, vinyl sulfones, vinyl phosphonates etc.) [11] as well as certain electron rich alkenes (silylenol ethers, enamides) [12] that were beyond reach of the parent compound **2**. This panel of standard catalysts is further complemented by a set of additional metathesis (pre)catalysts such as the cationic complexes **9**-**10** that are similarly versatile tools (*scheme 3*) [13-14].

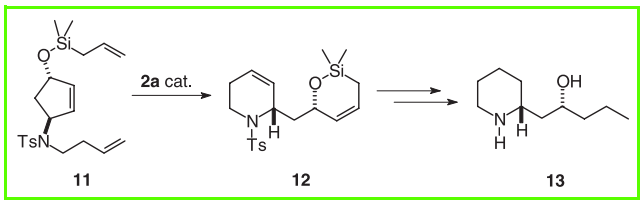
RCM is essentially driven by entropy; the ensuing equilibrium is constantly shifted towards the cycloalkene by loss of ethylene (or another volatile olefin) formed as the by-product (cf. *scheme 1*). The inherent competition between cyclization of a given diene and its polymerization via acyclic diene



Scheme 2 - Major metathesis (pre)catalysts.



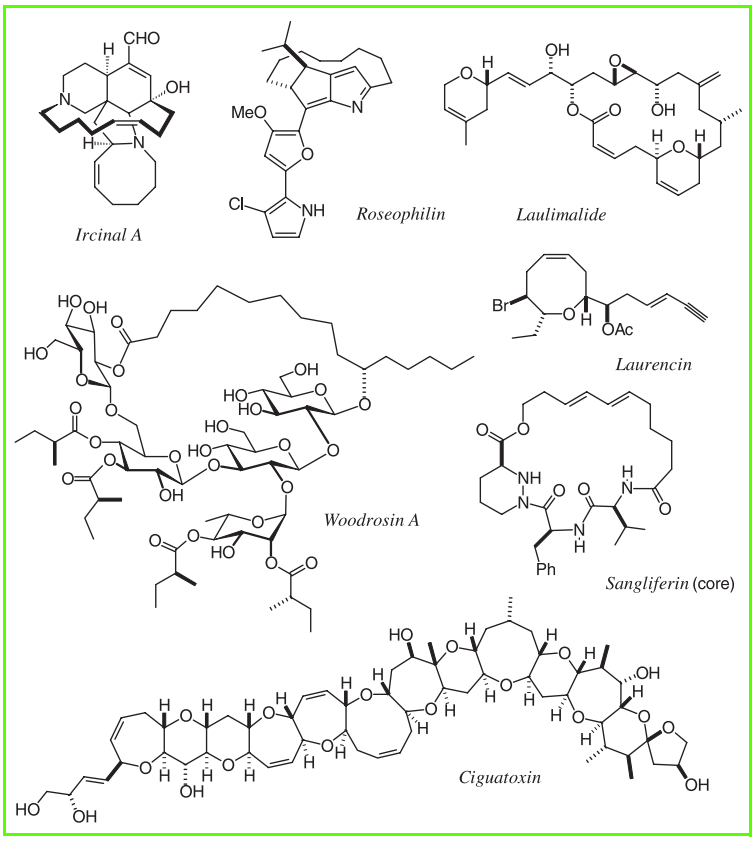
Scheme 3 - Cationic metathesis catalysts.



Scheme 5 - Key step of a total synthesis of (-)-halosaline.

metathesis (ADMET) strongly depends on the ring size formed as well as on pre-existing conformational constraints and can be influenced to some extent by adjusting the dilution. While 5-7 membered carbo- and heterocycles usually form without incident (sometimes even by adding the catalyst to the neat diene in the absence of any solvent), medium and large rings are more delicate and deserve careful consideration during retrosynthetic planning. It is known that chelation of the metal carbene intermediates by the polar substitutents in the substrates plays a decisive role for productive macrocyclization; hence, proper analysis of the donor strength of the heteroatoms, their distance and relative orientation towards the alkene groups allows for reliable planning even of complex target molecules of virtually any ring size [15]. A few recent highlights of bioactive compounds formed by RCM-based total synthesis protocols are shown in *scheme 4*.

A major advantage of RCM over more conventional approaches stems from the exceptional chemoselectivity of the available metathesis catalysts for the activation of olefins



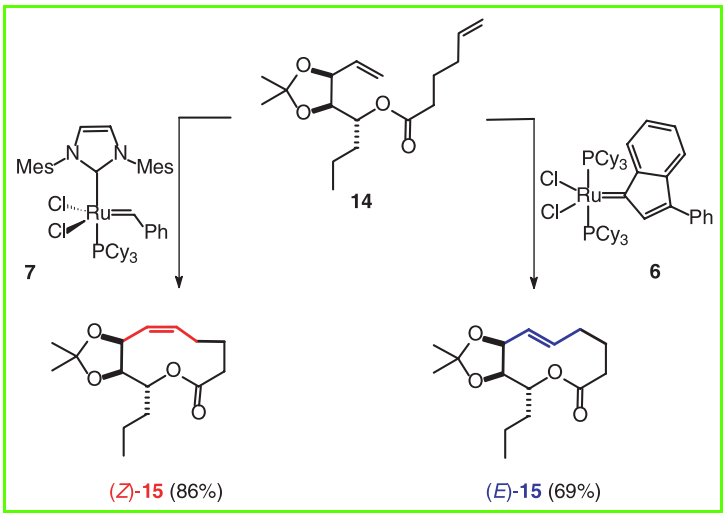
Scheme 4 - Recent examples of natural products prepared by RCM based approaches [16].

in the presence of most other functional groups. This, in turn, allows to avoid lengthy protecting group manipulations, thus rendering many metathesis based approaches unprecedentedly short and economic in the overall number of steps. As a consequence, modern metathesis chemistry has a profound impact on the logic of synthesis and might also reach industrial practice in the near future. This notion is further supported by the fact that the modern metathesis catalysts are fully operative under aqueous conditions [17] as well as in unconventional media such as ionic liquids [18] or supercritical CO_2 [19].

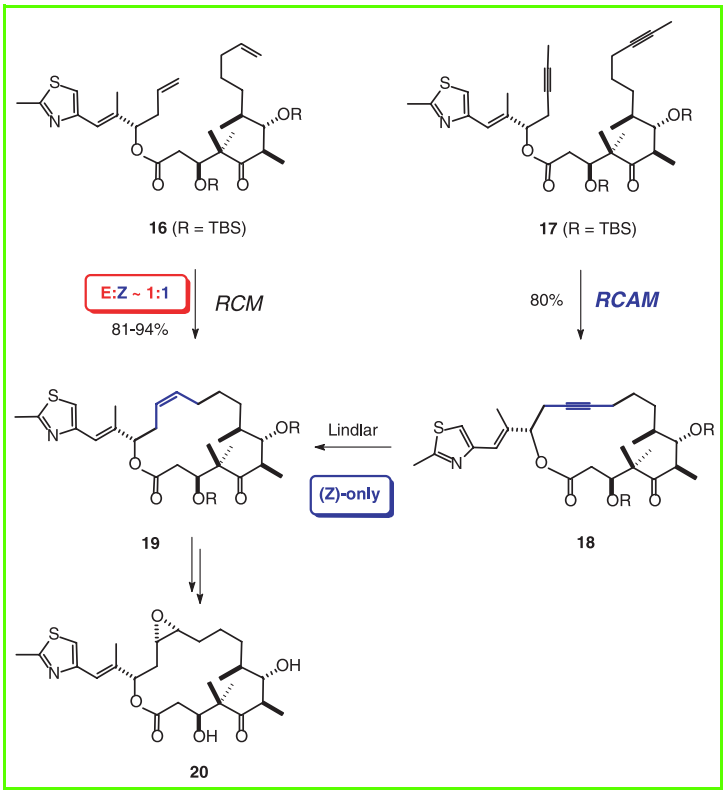
The seemingly trivial aspect that metathesis transforms olefins into olefins opens yet other vistas for advanced organic synthesis. Not only it is possible to convert the cycloalkenes obtained by RCM into a variety of different products by exploiting prototype alkene reactivity (cycloadditions, oxidations, reductions, isomerizations etc.) but imaginative and highly productive reaction cascades can also be performed. An illustrative example is shown in *scheme 5*, wherein a fully atom economical ring-closing/ring opening/ring closing manœuvre converts the readily accessible triene **11** into the key intermediate **12** of a total synthesis of the piperidine alkaloid (-)-halosaline **13** [20]. In view of the foregoing it comes as no surprise that metathesis is rapidly gaining importance in the context of combinatorial chemistry and diversity oriented synthesis [21].

Despite this highly attractive overall profile and the maturity reached in recent years, several problems remain to be solved. This does not only pertain to various practicality issues (price and lifetime of the catalyst, total turnover numbers etc.) but also to some inherent chemical aspects. A most prominent one is the missing control over the geometry of the emerging double bond during the formation of macrocycles as well as in cross metathesis reactions. However, the reaction depicted in *scheme 6*, the key step of the first total synthesis of the herbicidal lactone herbarumin I, shows that « catalyst tuning » can be a successful way to address this issue [22]. While treatment of diene **14** with the phenylindenylidene catalyst **6** [9] leads to the formation of the (*E*)-configured nonenolide, the « second generation » catalyst **7** delivers the (*Z*)-isomer with excellent selectivity. Since this outcome is deemed to reflect kinetic versus thermodynamic control, it holds the promise of being relevant wherever the stereoisomers are sufficiently different in energy.

Yet another way to form (*Z*)-alkenes in a predictable manner takes recourse to ring closing alkyne metathesis (RCAM) followed by Lindar reduction of the cycloalkynes thus formed (e.g. **17** → **18** → **19**) [23]. This indirect approach has been successfully implemented into various total syntheses, including a fully selective and high yielding route to the promising anti-cancer agent epothilone A **20** (*scheme 7*) [24-25].



Scheme 6 - First example of *E*/*Z*-control by « catalyst tuning ».



Scheme 7 - Comparison of the RCM and RCAM approaches to epothilone A.

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