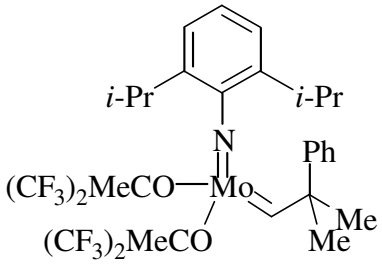
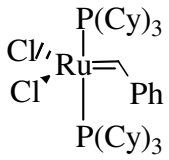
Olefin metathesis reactions: the synthetic tool of the decade?

Olefin metathesis is a fairly old reaction which was first observed in the 1950's when industrial chemists from Du Pont, Standard Oil and Phillips Petroleum reported that propene under heating with molybdenum on alumina led to ethylene and 2-butenes.[1] Almost half a century later, olefin metatheses have revolutionized the field of organic synthesis. Ring-closing metathesis (RCM), cross-metathesis (CM), ring-opening metathesis (ROM), asymmetric ring-closing metathesis (ARCM) and enyne metathesis as well as combinations of these transformations have emerged as extraordinarily powerful and general methods, giving new opportunities to synthesize a wide variety of organic molecules. This success is largely due to the introduction and the development of stable, reactive and functional group-tolerant metal alkylidenes as catalysts olefin metathesis. Of those catalysts described in the literature, the most popular are molybdenum-based **1** and ruthenium-derived catalysts **2** and **3** developed by Schrock[2] and Grubbs[3] respectively (see Figure 1**)**.

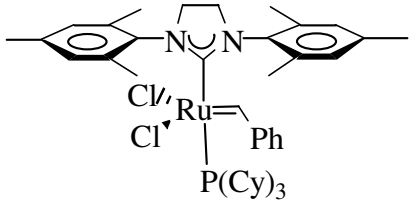
Figure 1



1



2



3

It should be pointed out that catalyst **3**[4] combines the qualities of both catalysts **1** and **2**: higher thermal stability, wider functional group tolerance and lower sensitivity to double bond substitution.

This overview will focus on the recent and relevant applications of metathesis in organic synthesis.

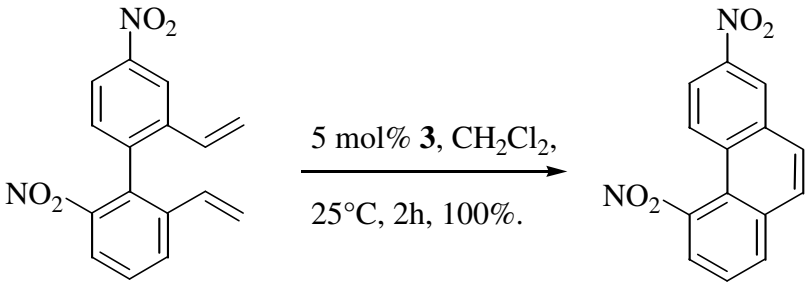
[1] D. Astruc, *New. J. Chem.* **2005**, *29*, 42-56.
[2] G. C. Bagan, J. H. Oskam, H.-N. Cho, L. Y. Park, R. R. Schrock, *J. Am. Chem. Soc.* **1991**, *113*, 6899-6907.
[3] E. L. Dias, S. T. Nguyen, R. H. Grubbs, *J. Am. Chem. Soc.* **1997**, *119*, 3887-3897.
[4] M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953-956.

RCM reactions[5]

The huge number of cyclic natural products which have been obtained using RCM as one of the key steps is an obvious proof of the synthetic efficiency of this methodology.

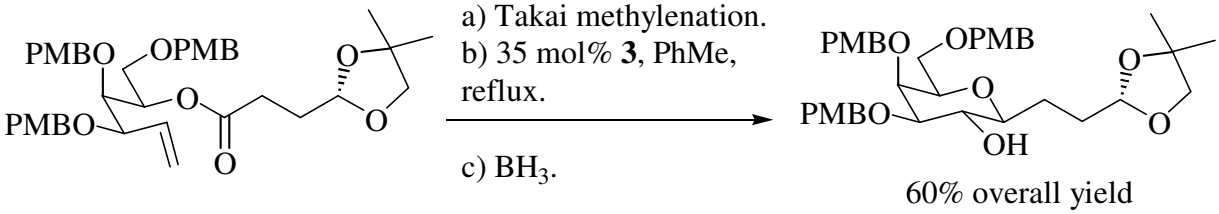
An original and efficient preparation of substituted phenanthrenes, a skeleton found in various biologically active compounds (antimalarial and anticancer compounds), has been published by Iuliano *et al.*[6] using RCM of 2,2'-divinylbiphenyl intermediates (see Scheme 1).

Scheme 1



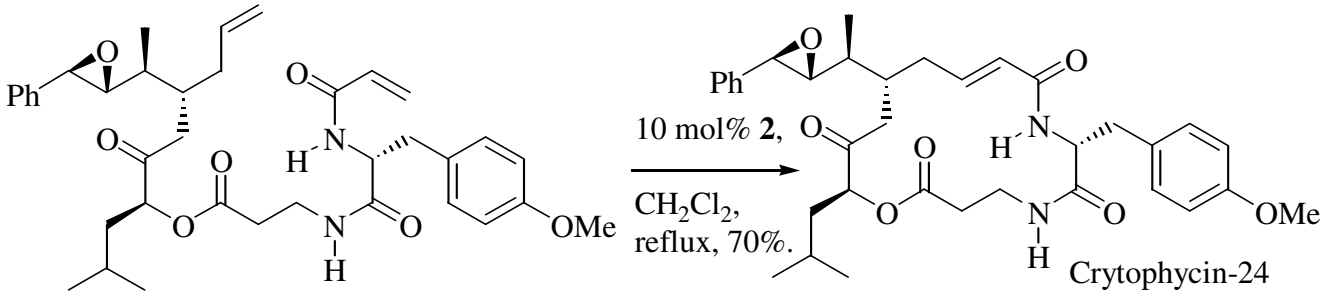
Postema *et al.*[7] have very recently disclosed an attractive access to a variety of □-*C*-glycosides based upon a Takai-reagent-mediated ester olefination-RCM sequence followed by hydroboration, as depicted in Scheme 2.

Scheme 2



RCM has been also used to prepare macrocyclic compounds, as illustrated by the total synthesis of crytophycin-24, disclosed by Georg *et al.* (see Scheme 3).[8] In this example only the *E*-isomer was formed.

Scheme 3



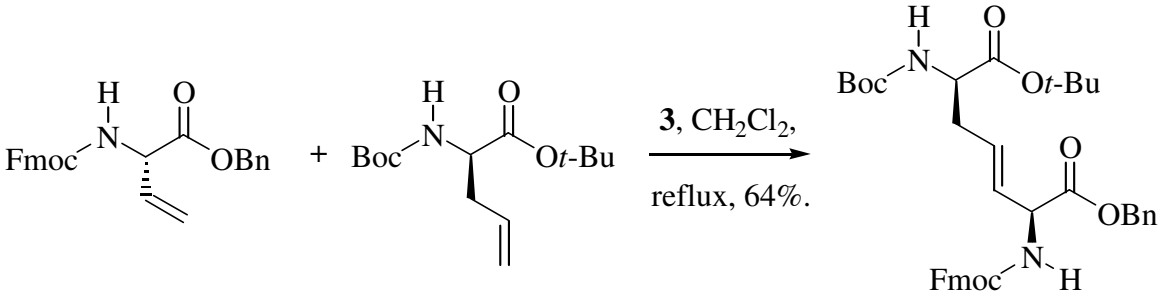
CM reactions[9]

The CM reactions are more complex due to competition between the desired CM reaction and the undesired self metathesis leading to homodimers. Nevertheless, with electronically different or with sterically hindered olefins, selective reactions were obtained, expanding the scope of olefin CM to complex substrates.

A particularly short synthesis of (*R*,*S*)-protected diaminopimelic acid was released by Boons *et al*[10] using a CM reaction between allyl and vinyl glycine derivatives as presented in Scheme 4. The use of an excess of the vinyl glycine, the lower reactive partner due probably to a combination of steric and electronics factors, led to a significant improvement of the yield.

[5] For recent a review on RCM reaction, see: A. Deiters, S. F. Martin, *Chem. Rev.* **2004**, *104*, 2199-2238.
[6] A. Lulino, P. Piccioli, D. Fabbri, *Org. Lett.* **2004**, *6*, 3711-3714.
[7] M. H. D. Postema, J. L. Piper, R. L. Betts, *J. Org. Chem.* **2005**, *70*, 829-836.
[8] N. K. Tripathy, G. I. Georg, *Tetrahedron Lett.* **2004**, *45*, 5309-5311.
[9] S. J Conner, S. Blechert, *Angew. Chem., Int. Ed.* **2003**, *42*, 1900-1923.
[10] A. R. Chowdhury, G.-J. Boons, *Tetrahedron Lett.* **2005**, *46*, 1675-1678.

Scheme 4

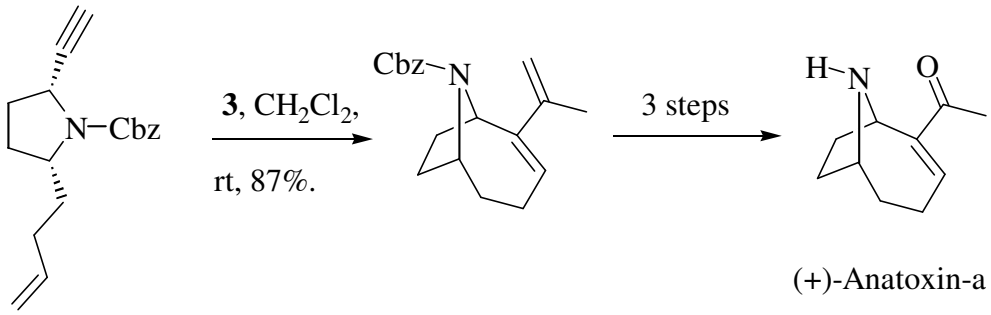


Enyne metathesis[11]

Intramolecular and cross enyne metatheses have also found nice applications in synthesis.

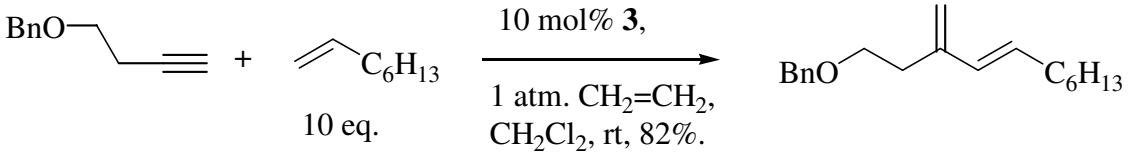
For example, a short synthesis of the potent nAChR agonist (+)-anatoxin-a was achieved in a elegant way (9 steps, 27% overall yield from commercially available D-pyroglutamate) by Martin *et al.*[12] with an intramolecular enyne metathesis to build the bridged azabicyclic key intermediate (see Scheme 5).

Scheme 5



Exposure of a large excess of olefins to alkynes under an ethylene atmosphere in the presence of catalyst **3** provided cleanly the 1,3-disubstituted butadienes with *E* stereochemistry as illustrated by the following example (see Scheme 6).[13]

Scheme 6



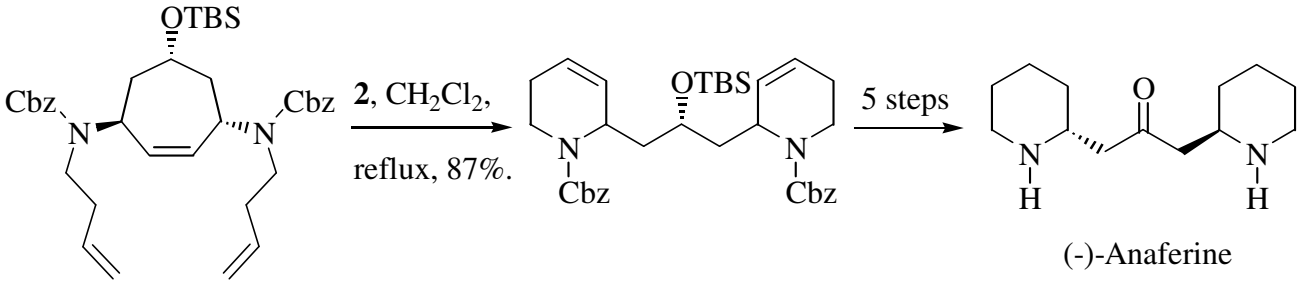
Tandem metathesis[14]

Intramolecular RCM-ROM or the RCM-ROM-CM domino process (so-called ring-rearrangement metathesis (RRM)) can shorten synthetic routes considerably and lead to complex structure from simple starting materials.

The Blechert group has made an important contribution in this field, as illustrated by the synthesis of (-)-anaferine [15] via a tandem RRM using a combination of ROM and two RCM (see Scheme 7).

Scheme 7

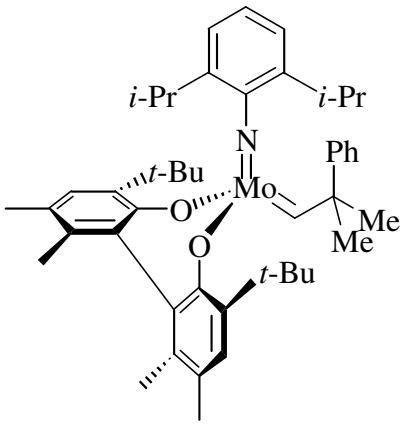
[11] For a review, see: C. Storm, R. Madsen, *Synthesis* **2003**, 1-19.
[12] J. B. Brenneman, S. F. Martin, *Org. Lett.* **2004**, *6*, 1329-1331.
[13] H.-Y. Lee, B. G. Kim, M. L. Snapper, *Org. Lett.* **2003**, *5*, 1855-1858.
[14] S. Randl, S. Blechert, in *Handbook of Metathesis. Applications in Organic Synthesis*, R. H. Grubbs, Ed.; Wiley-VCH: Morlenbach, 2003, Vol. 2.
[15] S. Blechert, C. Stapper, *Eur. J. Org. Chem.* **2002**, 2855-2858.



Asymmetric ring-closing and ring-opening metatheses[16]

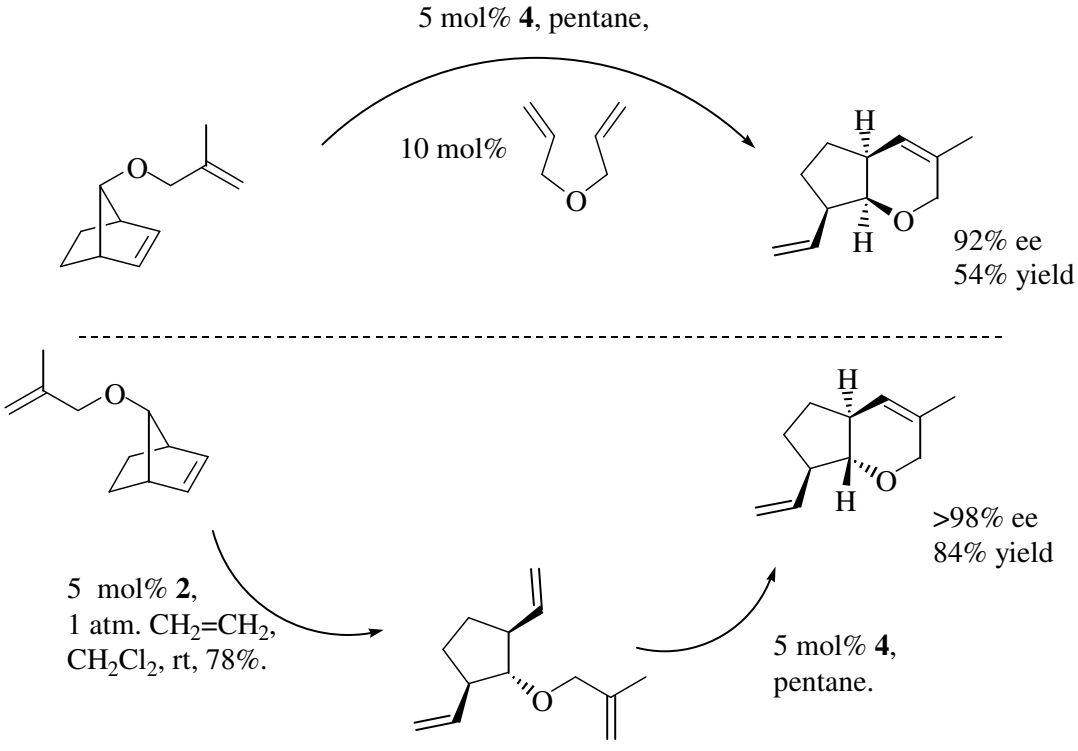
The development of effective chiral metathesis catalysts provides new opportunities for applications to enantioselective synthesis of biologically active compounds.

The new possibilities offered by these asymmetric processes are illustrated by a tandem AROM/RCM and ROM/ARCM carried on the two diastereomeric *meso*-bicylique substrates with the chiral molybdenum-based catalyst **4** (see Scheme 8).[17]



Chiral molybdenum-based catalyst **4**

Scheme 8



Outlook

[16] R. R. Schrock, A. H. Hoveyda, *Angew. Chem., Int. Ed.* **2003**, *42*, 4592-4633.

[17] G. S. Weatherhead, J. G. Ford, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *120*, 1828-1829.

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The increasing number of syntheses with olefin metathesis as a key step, the improvement of activity, stability and tolerance towards functional groups of the catalysts and the development of chiral catalysts predict a promising future for this reaction.