The Joy and Challenge of Small Rings Metathesis**

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Olefins metathesis (the term is derived from the Greek word μεταθεσις with the same pronunciation, which means transposition) is basically an alkylidene exchange between two reacting fragments, mediated by transition metals alkylidene complexes.[1]

Recent decades have seen a burgeoning of interest in olefin metathesis, as witnessed by a rapidly growing number of elegant applications. Using this tool, chemists can now efficiently synthesize reactions of dienes and enynes represent an attractive and powerful tool for formation of medium and large cycles (≥5 members). However, it is generally acknowledged that small rings (three- and four-membered) and strained cannot be formed by RCM.[3] In such cases, the ring opening process can be far more thermodynamically favourable than ring closing. Indeed, various strained molecules, such as norbornene derivatives, are well known substrates for ring-opening metathesis polymerization (ROMP) reactions (Scheme 1).[4]

![Figure 1. Ruthenium catalysts commonly used in olefin metathesis.](image)

Metathesis reactions involving the opening of a small ring. Cyclopropenes and cyclobutenes may be polymerised via ring-opening in a similar fashion by the metathesis catalyst, although the examples of such transformations are less numerous than ROMP reactions of norbornene.[4] The driving force in these reactions is the relief of the enormous 3- and 4-membered ring strain. Another possible transformation for highly strained cyclic olefins is ROM/CM transformation Michaut, Parrain and Santelli showed that the Grubbs ruthenium complex Gru-I efficiently catalyses ring-opening metathesis/cross-metathesis (ROM/CM) of cyclopropenone ketal 1a to afford 1,4-divinyl ketone derivative 2 in good yields.[5]

![Scheme 2. ROM/CM of cyclopropenone ketal 1a. TMS = trimethylsilyl](image)

Kozmin and co-workers created a remarkably concise and efficient route to the protein kinase C activator, bistramide A (3), based on opening of strained cyclopropenone ring as one of the key steps.[6] The ROM/CM reaction of cyclopropene ketal 1b with alkene 4 led, after acidic hydrolysis, to divinyl ketone 5, a direct precursor of the key spiroketal domain of (+)-bistramide (Scheme 3).

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In addition to cyclopropenes, some cyclobutenes have also been used in ROMP and similar processes. One of the most impressive applications involving the ring-opening event is seen in the recent total synthesis of (+)-asteriscanolide (10) by Limanto and Snapper, where the ROM/CM sequence followed by divinyl cyclobutane rearrangement was used to fashion the cyclooctane ring of the core structure of the natural product (Scheme 6).[8a]

A similar ROM/CM reaction between substituted cyclobutene and gaseous ethylene was also used by Snaper in the preparation of series of isoprostane analogues[8b] and by Harrity and co-workers in synthesis of (+)-sporochnol A.[8c]

The Nicolaou group utilised similar sequence to open chiral cyclobutene-1,2-diol derivative 14 with achiral ruthenium catalyst Gru-II. The ring-opening event, followed by RCM resulted in smooth conversion of the strained cyclobutene 14 into the corresponding tetracyclic compound 15, with complete transfer of chirality (Scheme 8).[10]
The reason why at least 20 mol% of the catalyst is necessary to achieve the reasonable yield remains unclear. According to the authors, along with the expected cyclobutene 19b, only small amounts of the uncharacterised “CM dimers” (5%) and starting material 18a (10-15%) were identified in the crude reaction mixture. Interestingly, the formation of less strained cyclopentene 20, a product of an alternative cyclisation route,[14] was not observed. Campagne tested also the effect of ethylene (so called Mori’s conditions for enyne reaction).[15] Unfortunately the extensive byproduct formation was observed in this case.[16] Finally, the use of PtCl₂ as the catalyst was probed, but no reaction was observed (Scheme 10).[17]

Having the optimised reaction conditions, Debleds and Campagne attempted to define the scope of this transformation. Various 1,5-enyne substrates were tested, providing cyclobutene products 19a-19l in yields up to 58%, as shown in Figure 2. It was concluded that while the cyclobutene ring can be decorated with various substituents (R₁, R₃), only alkyl substituents are well-tolerated on the alkynyl part (R₂). A double cyclisation of a bis-enyne substrate was finally attempted, leading to the bis-cyclobutene 19l in a modest 19% yield (Figure 2). The moderate yields observed in these reactions were explained by the authors in part by wol complete conversions (the unreacted starting material was present in the most of the reaction mixtures) and by the formation of some unidentified by-products. In addition, difficulties in the purification of the sensitive highly strained cyclobutanes can also be responsible for diminishing the yield.

These results open a convenient new entry to functionalized cyclobutanes, which are useful building blocks in organic synthesis.
The 1,3-diene unit present in 19 can be further used in many transformations, such as Diels-Alder cycloaddition and others. Indeed, as it was shown by the authors, product 19a reacts with dienophile 21 at room temperature, to give the expected tricyclic compound 22 in respectable 80% yield and as a single diastereomer (Scheme 11).[12]

![Scheme 11. Diels-Alder reaction of N.](image)

In conclusion, Debleds and Campagne have opened a novel field in the area of metathesis technology by demonstrating that strained four-membered rings can be obtained by enyne reaction. At its current stage, the reaction suffers from rather mediocre yields and high catalyst loadings. The scope of substrates amenable for 1,5-enyne membered rings can be obtained by enyne reaction. At room temperature, to give the expected tricyclic strained cyclobutene product at metathetic cycloisomeration of 1,3-diene unit present in 19, similar to that one shown in Scheme 6, a byproduct bearing an external double bond and a bicyclic product, containing a cyclopropane unit. Compare [Ref. 2] and a) V. Sashuk, K. Grella J. Mol. Catal. A: Chem. 2006, 257, 59; b) K. Matsumotaa, S. A. Kozmin, J. Am. Chem. Soc. 2004, 126, 9546; c) J. Marjanovic, S. A. Kozmin, Angew. Chem. Int. Ed. 2007, 46, 9010; d) T. O. Schrader, M. L. Snapper, Tetrahedron Lett. 2000, 41, 9685; e) C. M. J. Bassindale, P. Hamley, J. P. A. Harity, Tetrahedron Lett. 2001, 42, 9055.


It is reasonable to expected that further optimisation of the reaction conditions or the application of more potent catalysts will allow to increase the reaction efficiency and scope. The simplicity of the transformation in combination with the synthetic importance of the obtained products suggests that this method can find numerous applications. Definitely, the preliminary results reported by Debleds and Campagne are worth further investigations.

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A molecular origami: metathetical opening of strained three- and four-membered rings is a well established transformation, successfully used in a number of total syntheses and in preparation of polymers. In the same time, it is generally considered that small cyclic products cannot be easily formed by RCM. The recent report on preparation of substituted cyclobutenes via 1,5-enzyme RCM creates a notable example of a process where a strained four-membered ring is created by olefin metathesis methodology.