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Preparation of macrocyclic musks *via* olefin metathesis: comparison with classical syntheses and recent advances

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Recent advances in the synthesis of macrocycles with musk scent *via* catalytic olefin metathesis are presented with a particular emphasis on advantages offered by the metathesis technology. The review includes short historical background about musks and olefin metathesis to introduce the subject. Substantial emphasis is given on ring-closing metathesis (RCM) as a tool for the synthesis of cyclic compounds such as civetone, muscone, exaltolide, ambrettolide/isoambrettolide, and yuzu lactone. The bibliography includes 106 references.

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List of abbreviations used in manuscript:
ADMET — acyclic diene metathesis,
AIBN — azobisisobutyronitrile,
BB-RCM — back-biting ring-closing metathesis,
CAAC — cyclic (alkyl)(amino)carbene,
CALB — lipase *Candida antarctica*,
CM — cross metathesis,
9-DA — 9-decenoic acid,
9-DAEE — 9-decenoic acid ethyl ester,
DCC — *N*,*N*′-dicyclohexylcarbodiimide,
DIBAL — diisobutylaluminium hydride,
DIPEA — *N*,*N*-diisopropylethylamine,
DIPP — 2,6-diisopropylphenyl,
DMAP — 4-(dimethylamino)pyridine,
2-DTC — di-2-thienyl carbonate,
ENE-YNE — alkene – alkyne metathesis,
HFIP — hexafluoro-2-propanol,
HMPA — hexamethylphosphoric triamide,

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ICI — iodine monochloride,
KHMDS — potassium bis(trimethylsilyl)amide,
MCF — mesocellular siliceous foam,
MOF — metal-organic framework,
Mes — mesityl,
NHC — *N*-heterocyclic carbene,
NHPI — *N*-hydroxyphthalimide,
PAO — poly-alpha-olefins,
PCC — pyridinium chlorochromate,
PDC — pyridinium dichromate,
PyClU — chlorodipyrrolidinocarbenium hexafluorophosphate,
RCM — ring-closing metathesis,
ROM — ring-opening metathesis,
ROMP — ring-opening metathesis polymerisation,
SBA-15 — mesoporous form of silica,
SM — self metathesis,
TBAF — tetra-*n*-butylammonium fluoride,
TBDPSCl — *tert*-butyl(chloro)diphenylsilane,
TBDMSCl — *tert*-butyldimethylsilyl chloride,
TBS — *tert*-butylsilyl group,
TES — triethylsilyl group,
TFBQ — tetrafluoro-1,4-benzoquinone.

1. Musk smelling macrocycles

Back in ancient times some unique substances harvested from animals or plants were already highly valued and used in manufacturing of perfumes.[1] During the Sung dynasty (10 to 13 century CE), Chinese merchants exchanged precious goods for various substances possessing attractive smell. These highly desirable fragrances may be found both in the plant kingdom, as components of essential oils, and also in the animal kingdom, produced by appropriate glands as pheromones for luring the opposite sex. This class of compounds with rare fragrance properties is called musks, named after a Siberian musk deer (*Moschus moschiferus*), from which this substance was harvested for the first time.

1.1. Naturally occurring musks

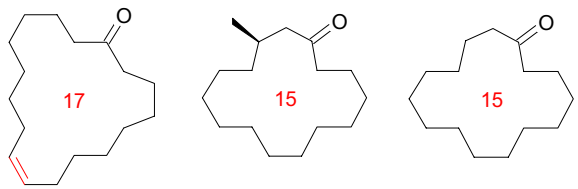
In a novel by Polish writer Igor Abramow–Newerly '*The taiga sea*', the action of which takes place in Imperial Japan-invaded Manchuria, there is a thrilling scene of wild musk deer hunting and selling the obtained glands to a Chinese merchant in Harbin.[2] The males of Siberian musk deer, a species occurring in the Tibetan highlands, China and Mongolia, produce musky secretion to lure females. Although Siberian musk deer gland secretions can be acquired without killing an animal, in some countries (*e.g.*, China), animals are bred or hunted for meat, skins and also precious musk. Approximately, 35 adult male deer are needed to obtain only one kilogram of raw material.[1]

Musk can also be obtained from the African civet (*Civettictis civetta*) living in Sahara and the muskrat (*Ondatra zibethicus*) living in North America (Fig. 1). Musk is a brittle mass with a strong ammonia odour and, after being dissolved in an alcohol solution, it acquires a sensual, animal-like aroma.



Figure 1. (*a*) Siberian musk deer [photo by Nikolai Usik (CC BY-SA 3.0)]; (*b*) African civet [photo by Nikolai Usik (CC BY-SA 3.0)]; (*c*) Muskrat [photo by James Phelps (CC BY 2.0)].

In 1926, a Nobel Prize laureate Leopold Ružička described the first musk ketone and named it civetone (**1**).[3] Analysis of the natural substance isolated from civet glands allowed him to confirm the macrocyclic structure of this compound. This discovery led to subsequent finding of other macrocyclic ketones, such as muscone (**2**) (Walbaum [4] and Ružička [5]) from Siberian musk deer, and exaltone (**3**) (Stevens and Erickson) [6] from muskrat (Fig. 2). Nowadays these compounds are produced on an industrial scale and are used as perfume additives in the flavour and fragrance industry (F&F).



1 (civetone) **2** [(–)-R-muscone] **3** (exaltone®)

Figure 2. Macrocyclic ketone musks.

In the plant kingdom, fragrance compounds of the musky smell are present as components of essential oils. Exaltolide and ambrettolide are mostly extracted from garden angelica (*Angelica archangelica*). This plant not only exhibits many medicinal properties but also contains a valued essential oil which includes, in addition to the most valuable exaltolide, also other substances such as α-D-phellandrene, α-pinene, ostenol, angelicin, diacetyl, furfural, and others.[7] In turn, the musk mallow (*Abelmoschus moschatus*) is valued for the seeds that are used to make perfumes (Fig. 3). Historically, the first macrocyclic lactone, which was ambrettolide, was described in 1927 by Kerschbaum.[8] Another interesting macrolide with pleasant citrus-like aroma is yuzu lactone (**4**) found in yuzu citrus fruit, which grows in China, Japan, and Korea. Its fruits look like oranges, are acidic in taste, and are mostly used as additives and aroma boosters.[9]

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Current research interests of the authors: organic and organometallic chemistry, olefin metathesis, design of new ruthenium complexes and their utilization in synthesis of natural products and pharmaceuticals, valorization of biomass.

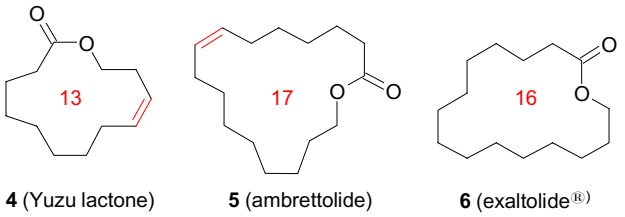


Figure 3. Examples of macrocyclic lactones.

1.2. Nitro musks

In 1888, Baur nitrated *meta-tert*-butyltoluene and synthesised a derivative bearing three nitro groups and exhibiting pleasant musky smell.[10] As it turned out later, it was the beginning of a new class of compounds, nowadays known as nitro musks. The most common representatives of this class are shown in Fig. 4.

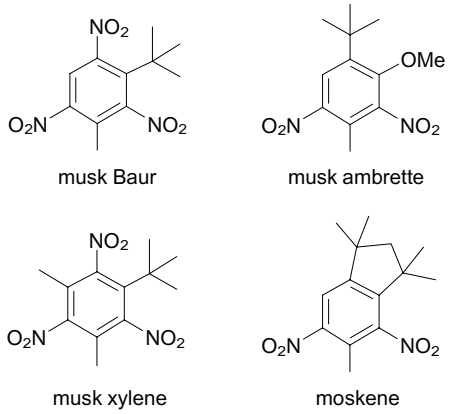


Figure 4. Examples of so-called nitro musks.

1.3. Polycyclic musks

The low stability of nitro musks in the presence of light, their explosive properties, as well as possible neurotoxic effects have become a reason to search for new classes of compounds with promising properties as fragrances. In the 1950s, a new group of non-nitro musky smelling compounds that contained two, or less often, three condensed rings was synthesised. They are usually tetraline or indane derivatives,[11] and the most recognised representative — phantolide, also known as musk indane — is shown below (Fig. 5). Unfortunately, reports of possible bioaccumulation in adipose tissue or blood plasma as well as carcinogenic properties[12] again resulted in ceasing polycyclic musk utilisation in the F& F industry.

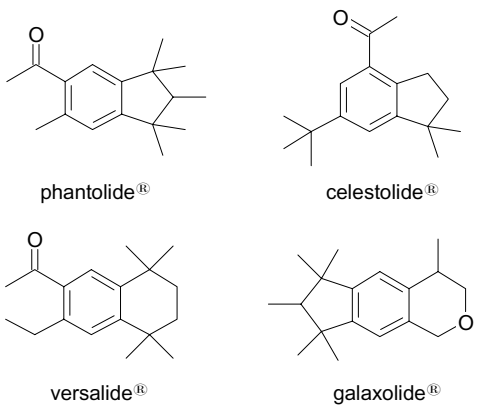


Figure 5. Examples of polycyclic musk.

1.4. Linear musks

In 1975,[13] BASF established the so-called fourth generation of musk compounds. Hoffman and von Fraunberg were the first to publish a musky smelling molecule called cyclomusk.[14] It is a cyclopentenyl ester possessing an intense musky aroma with a slight note of strawberry. Fifteen years later, Giersh and Schulte – Elte from the Swiss company Firmenich published a synthesis of helvetolide — a substance with a strong musky smell combined with a floral note.[14, 15] In 2000, more 'musky' romandolide was synthesised (Fig. 6).[16]

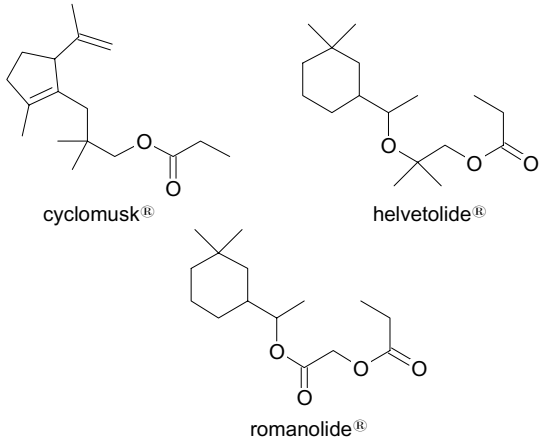


Figure 6. Examples of linear musks.

1.5. Synthetic analogues of macrocyclic musks

Because of the high bioaccumulation in the human tissues and plasma, nitro and polycyclic musks were banned from the flavours and fragrances market, which strengthened the privileged position of macrocyclic compounds. This situation imposed, however, the search for new possibilities to acquire the latter, because their extraction from the natural sources is not only expensive, but also has a devastating effect on fauna and flora, *e.g.*, by bringing a number of species to the verge of extinction.[17] The solution to this vital problem was the implementation of organic synthesis, which made it possible not only to prepare naturally occurring musks, but also to introduce numerous structural modifications leading to compounds with improved olfactory properties.

Most of the naturally occurring macrocyclic musks are based on skeletons of ketones and lactones, varying in ring size, number of multiple bonds, and additional substituents. Furthermore, modern organic synthesis has allowed the introduction to newer macrocycle core structural motifs, whereby the limit of its diversity is the sky (Fig. 7).

The presence of a C – C double bond in macrocyclic musks makes them prone to cyclopropanation reaction. The resulting molecules gain more and more popularity due to

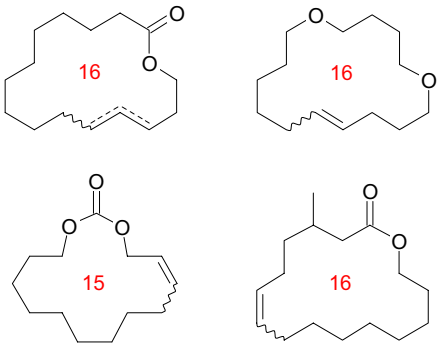


Figure 7. Examples of macrolides with musk scent synthesized *via* metathesis.

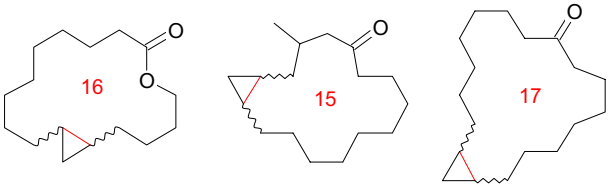


Figure 8. Examples of cyclopropanated macrocycles.

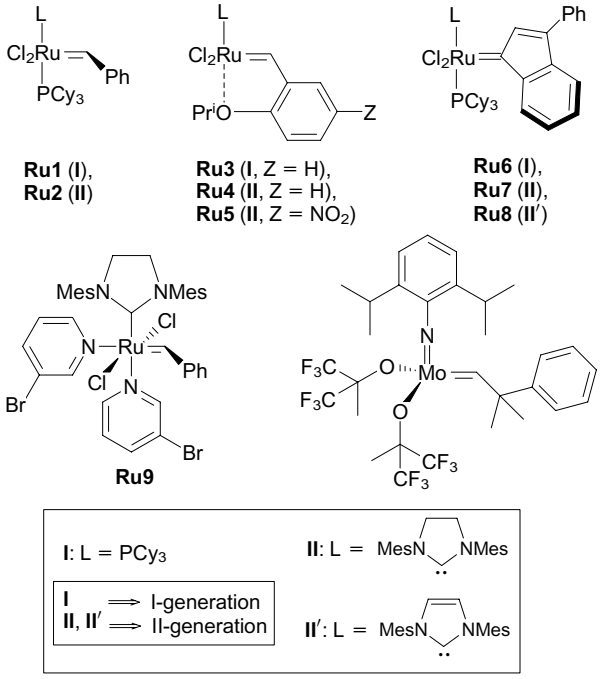


Figure 9. Popular, well-defined molybdenum and ruthenium olefin metathesis catalysts.

interesting flavour they possess, which often differs significantly from that of parental compounds (Fig. 8).[18,19]

It is well known that the olfactive strength of the unsaturated macrocyclic musks is much higher[20] than that of saturated ones, which have been used for decades, such as muscone, exaltone, exaltolide; therefore, recently a lot of efforts have been invested into production of unsaturated musks *via* olefin metathesis.

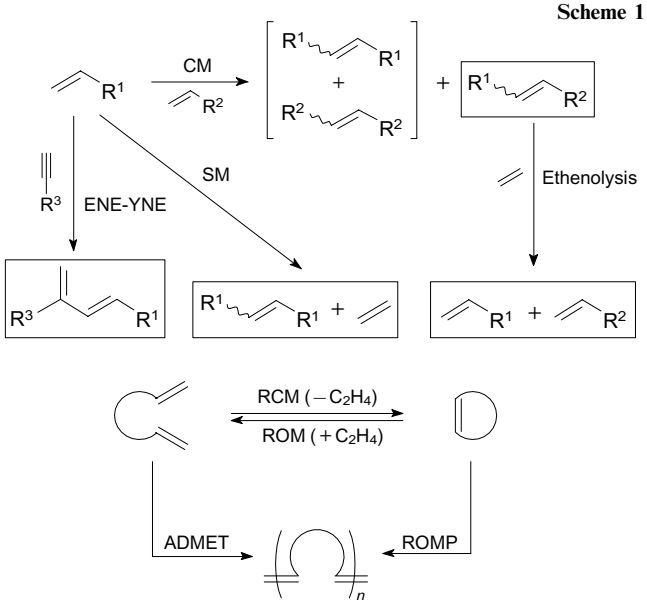
2. Use of olefin metathesis in synthesis of musk macrocycles

2.1. History of olefin metathesis

The origins of the olefin metathesis reaction can be traced back to the mid-1950s where disproportionation of propylene was studied in several research laboratories belonging to various corporations, such as DuPont, Standard Oil, and Phillips Petroleum.[21–23] Exposure of propene to high temperature in the presence of molybdenum catalyst deposited on a solid carrier lead this olefin into transformation that resulted in a mixture of ethylene and two geometric isomers of 2-butene. In 1967, Calderon used the term 'olefin metathesis' to define the catalytic redistribution of C–C double bonds in a pair of olefins, which affords new alkenes.

Due to the introduction of well-defined molybdenum and ruthenium complexes (Fig. 9), which significantly broadened the scope of application of this methodology, including target oriented synthesis, polymerisation, and even modification of biomolecules in aqueous media, metathesis has become one of the most frequently used reactions in the process of C–C double bond formation (Scheme 1).[24] The potential of this transformation was perfectly emphasised by the Nobel Prize awarded to three chemists, Yves Chauvin, Robert H. Grubbs, and Richard R. Schrock, for the '*development of the metathesis method in organic synthesis*'.[25]

Scheme 1



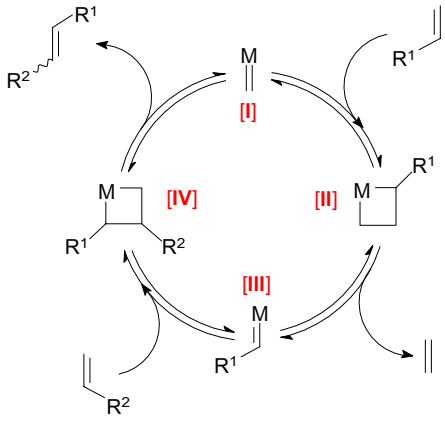
2.2. Mechanism of olefin metathesis

The possibility of selective functionalisation of the molecules under mild conditions is extremely important. This, combined with the use of advanced, highly selective and productive catalysts, allowed olefin metathesis to compete with other well-established carbon–carbon bond-forming reactions, such as Negishi, Suzuki, and Stille couplings. Another benefit is high atom economy of this process, especially when substrates with terminal C–C double bonds are used. Here, ethylene is produced as the only by-product, making the whole methodology compatible with the principles of green chemistry.[26] Moreover, the volatility of this by-product shifts the reaction equilibrium to the right, providing the desired products in high yields. These

are the main reasons why olefin metathesis gains more and more applications and is widely used in both industry [27] and academic research.[28–30]

For many years attempts to explain the mechanism of this reaction were not successful, also because the catalysts that were used till 1970s were poorly defined. In 1971, Yves Chauvin and his student Jean-Louis Hérisson, based on the work of Fischer, Natta, Banks, and Bailey, proposed a process composed of a sequence of reversible cycloaddition–cycloelimination reactions with an alkylidene-based metal complex (Scheme 2).[31]

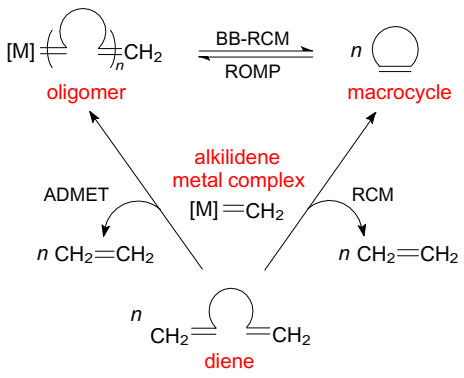
Scheme 2



According to the proposed mechanism, complex [**I**] forms metallacyclobutane [**II**] with the olefin molecule by [2 + 2] cycloaddition. Then the mechanism predicts two ways for the degradation of the unstable intermediate [**II**]. One of them is the restoration of [**I**] and the initial olefin, and in the second case, decomposition of the metallacyclobutane leads to liberation of ethylene and formation of new complex [**III**]. The resulting compound may react with a new molecule of olefin, once again forming metallacyclobutane [**IV**], which may also break down in two ways. In the first case, [**III**] and the olefin are reconstructed. However, if metallacyclobutane [**IV**] transforms *via* the second possible route, a new olefin is formed and [**I**] is restored. All steps in the catalytic cycle are reversible, resulting in a state of equilibrium at some point in time. In practice, very often one of the products is ethylene or reaction is carried out with an excess of one olefinic partners to shift the equilibrium to the products.

The above considerations have interesting consequences in the RCM macrocyclisation reaction. Oligomers formed by the ADMET (Acyclic diene metathesis polymerisation) process, can also be formed by ROMP process (ring-opening metathesis polymerisation) of macrocycle. However, due to the reversibility of the metathesis reaction, oligomers can be consumed in so-called 'back-biting' process (BB-RCM, Scheme 3) and the desired macrocyclisation product might be formed as long as strict control of the concentration is ensured. If the dilution is too high, the catalyst will be deactivated before the entire oligomer will be processed.

Scheme 3



2.3. Factors influencing the efficiency of formation of macrocyclic compounds in ring-closing metathesis

Ring-closing metathesis (RCM) is currently one of the most important tools for the production of cyclic compounds: musk macrolactones, drugs, natural products, *etc*. One of the first literature reports of 1980 deals with synthesis of civetone (**1**) [32] and exaltolide (**6**) [33] *via* RCM. Almost four decades have passed since then, and the number of publications about applications of RCM is steadily increasing, as evidenced by numerous reviews.[34–37]

Unlike the small rings, the synthesis of macrocycles by RCM is extremely demanding. The efficiency of formation of larger rings depends on many factors that must be precisely controlled. The most important are: concentration, time, temperature, and catalyst and solvent nature.

2.3.1. Ring size and strain

Cyclic molecules with a small number of atoms in a ring (5 to 7) are thermodynamically privileged. In the case of medium rings (about 8 to 13 atoms), the strain resulting from unfavourable arrangement in space is high and makes these compounds prone to competitive polymerisation reaction. For large rings, containing more than 13 atoms, a drop in strain is observed, which allows for their cyclisation at high dilution. Fogg investigated the relationship between the ring size and the yield of cyclic esters by analysing a

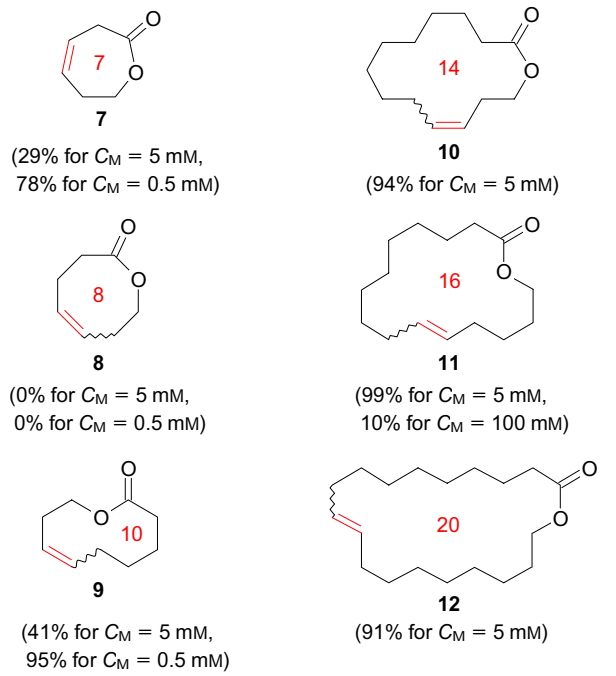


Figure 10. Effect of the ring size and concentration on the yield of macrocyclic products.[24]

series of dienes subjected to RCM reaction and leading to lactones containing 7 to 20 atoms in the ring.[38] Depending on the molar concentration of the substrate (C_M), authors identified a correlation between the ring size and the product yield (Fig. 10).

The intramolecular reaction can be accelerated when a diene contains a certain structural bias, for example is decorated with polar substituents, which increase the probability of encounter of terminal bonds *via* so-called templating (pre-organisation) effect.[39] Thus, RCM can be facilitated in the presence of various fused rings that stiffen the structure of the diene, or Lewis basic and mildly coordinating substituents.[40,41] In the example shown below (Scheme 4), the position of carbonyl group greatly influences the total yield of the macrocyclisation reaction.

Utilisation of the Thorpe–Ingold effect is another possibility to force effective cyclisation; however, it requires a specific construction of the substrate. Some examples of this effect are shown below (Fig. 11).

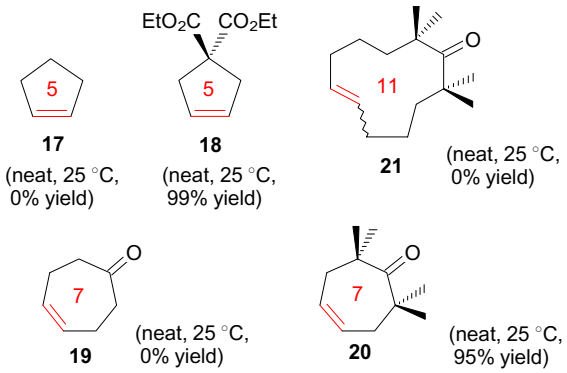
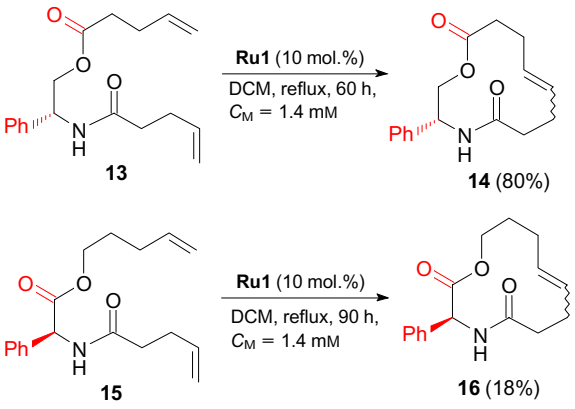


Figure 11. Thorpe–Ingold effect in RCM.[24]

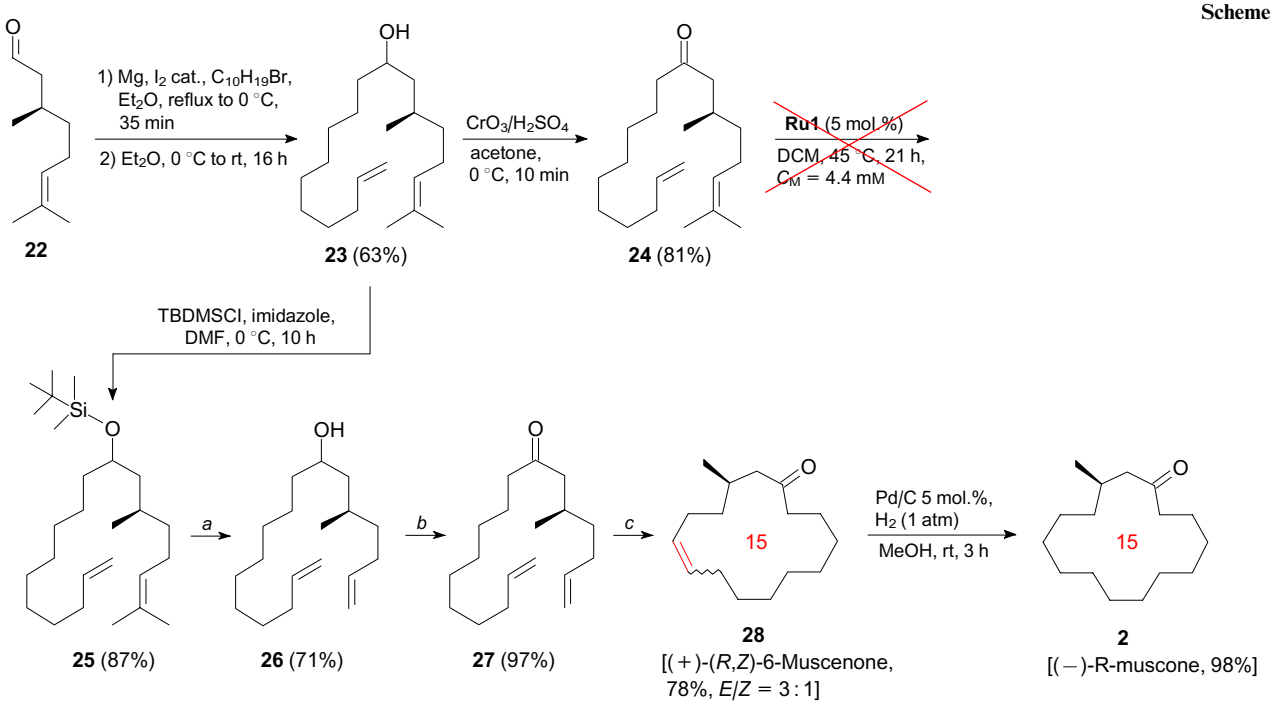
2.3.2. Steric hindrance around the C–C double bond

The next factor which determines the reactivity of a given substrate is an accessibility of its reacting C–C double bonds to the catalytic centre, mostly dependent on steric hindrance of double bond's substituents. This issue is of high importance, since many natural products which can be utilised as building blocks in synthesis of macrocycles contain an isoprene moiety — a rather challenging structural motif in olefin metathesis. In the example shown below, authors attempted the synthesis of muscone (**2**) starting from (*R*)-(+)-citronellal, which is an inexpensive starting material (Scheme 5). In two-step reaction, they prepared the starting diene, but utilisation of Grubbs first generation catalyst in refluxing DCM was completely ineffective towards trisubstituted double bond. Therefore, the authors were forced in four-step sequence to re-synthesise the substrate, this time being a *terminal* diene and finally

Scheme 4



Scheme 5



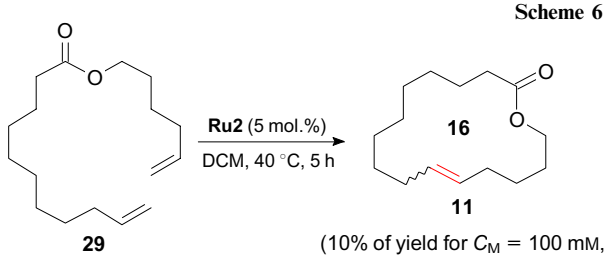
(*a*) 1) O_3, DCM, −78 °C, 15 min, Me_2S, −78 °C to rt, 21 h; 2) Ph_3PMeBr, Bu^nLi, THF, −78 °C to rt, 3 h; 3) TBAF, THF, rt, 3 h;
(*b*) CrO_3/H_2SO_4, acetone, 0 °C, 5 min; (*c*) 5 mol.% **Ru1**, DCM, 45 °C, 21 h, C_M = 4.4 mM

managed to perform successful ring-closing metathesis in good yield (78%).

2.3.3. Diene concentration

Dienes subjected to RCM reactions, depending on the chosen reaction conditions, may have a tendency to undergo polymerisation or macrocyclisation, which strictly depends on the ratio between the substrate and the solvent. For small rings, the effective concentration is within the 0.1 to 0.2 M,[42] although solvent-free reactions are also possible.[43] When the size of the ring increases, the cyclisation becomes less favoured and high dilution, up to 0.5 mM, is necessary to minimise intermolecular interactions leading to metathesis-based dimerisation and oligomerisation processes. A good illustration of this correlation is the study conducted by Bach in 2002.[44] Reducing the substrate concentration from 6 to 0.5 mM, while maintaining the remaining conditions unchanged, allowed for a threefold increase of the yield of macrocyclic product. Similar study conducted by Fogg, which focused on the synthesis of unsaturated exaltolide analogue **11**, led to an indication of optimal molar concentration. The RCM reaction of **29** at 5 mM concentration gave quantitative yield, leading to 16-membered macrolactone **11**, while the increase of concentration to 100 mM caused almost exclusively the formation of oligomers, leading to only 10% of the desired product **11** (Scheme 6).[38]

Scheme 6



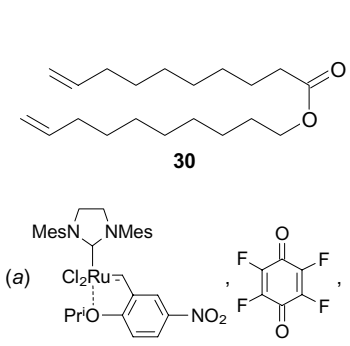
2.3.4. Solvent

While choosing the optimal solvent for ring-closing metathesis, the following factors must be taken into account: product and catalyst solubility and stability at the reaction temperature as well as solvent price. It should also be noted that the reaction medium may influence the catalyst initiation rate and stability. Studies on RCM of *N*,*N*-diallyl-2-iodoaniline showed better performance of Grubbs first generation catalyst in DCM than other solvents (*e.g.*, toluene, THF or EtOAc).[45] In addition, studies reported by Grubbs and co-workers also demonstrated better activity of Grubbs second generation catalyst in DCM in comparison to benzene, THF, or even chloroform.[46] On the other hand, Fürstner and Nolan showed that in the synthesis of macrocyclic lactones, toluene works well providing the products with high yields.[47] Marcaurelle, in turn, observed a positive effect of methylene chloride on the result of macro-RCM of amide dienes (20% better yield than in toluene),[48] while Grela *et al.* noted a strong activating effect of perfluorinated solvents in the ring-closure reactions of various dienes using first and second generation catalysts.[49] Another interesting study was performed by Skowerski, who in a number of model ring-closing and cross-metathesis reactions tested several green alternatives to DCM and toluene, showing good performance of ethyl acetate. Notably, in this study the solvents were used without distillation and the reactions were carried out in air.[50] A class of green solvents that recently has gained more and more attention are dimethyl (DMC) and diethyl (DEC) carbonates, mostly because their superiority in terms of safety and limited toxicity.[51] While RCM catalysed by ruthenium systems is mostly carried out in non-etheral solvents, THF is commonly used for reactions performed with *Z*-selective [52] and stereoretentive [53] complexes.

2.3.5. Temperature

Another key parameter for the yield of macrocyclisation reactions is temperature. For example, during the study on RCM of dec-9-en-1-yl dec-9-enoate (**30**), the correlation between the process temperature and the yield of the resulting 19-membered macrolactone **31** was evaluated. The studies indicated that increase of temperature from RT to 50 °C simultaneously improves the yield of the expected product (Scheme 7). However, with further increase of temperature, up to 70 °C, decrease of process productivity was observed, which is related to the faster decomposition of complex **Ru5** under reaction conditions.[54]

Scheme 7



Ru5 (2 mol.%), **TFBQ** (4 mol.%),
PhMe, 5 h, C_M = 1.5 mM

T/°C	Yield (%)	*E*/*Z*
rt	47	3.5 : 1
50	77	3.5 : 1
70	73	3.2 : 1

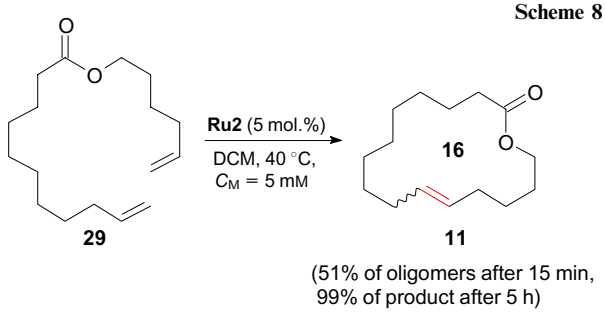
2.3.6. Time

When conducting a macrocyclisation reaction, one has to be aware that time has dual effect on its progress. In the initial phase of the process, rapid decrease of diene concentration occurs, which is connected with formation of macrocyclic product and kinetically stable oligomers. As proven by Fogg in 2007, prolonged reaction time enables not only the transformation of the remaining substrate **29** into product **11**, but also the conversion of oligomeric by-products into the desired macrocycle (Scheme 8).[38] On the other hand, the extension of the reaction time also promotes the catalyst degradation to hydrides,[55] dimers,[56] and nanoparticles,[57] which are known to promote the undesired double bond migration in both substrate and products, resulting in lower yield of macrocycle.

2.3.7. Structure of the catalyst

The choice of the right catalyst is of great importance for the success of RCM macrocyclisation.[58] The result of a macrocyclisation process depends on the activity and durability of the catalyst used. In addition, stability of the catalyst is of high importance, as its decomposition usually leads to the formation of isomerisation-active species, which should be suppressed. Otherwise, formation of a compli-

Scheme 8



cated mixture of bigger and smaller macrocyclic rings is often observed.[47] Furthermore, isomerisation-active species from decomposed catalyst could ruin the desired *E*/*Z* double bond geometry in a newly formed macrocycle. The most common catalysts used in macrocyclisation are Grubbs **Ru1**, **Ru2**, Hoveyda – Grubbs complexes **Ru3** and **Ru4** as well as indenylidene type catalysts **Ru6-9**, as presented in Fig. 9. Highly active catalysts like nitro-Grela **Ru5** also found numerous applications in macrocycles syntheses.[59 – 61] Over time, a number of Ru catalysts optimised for the RCM production of macrocycles have been developed, including structures shown in Fig. 12.

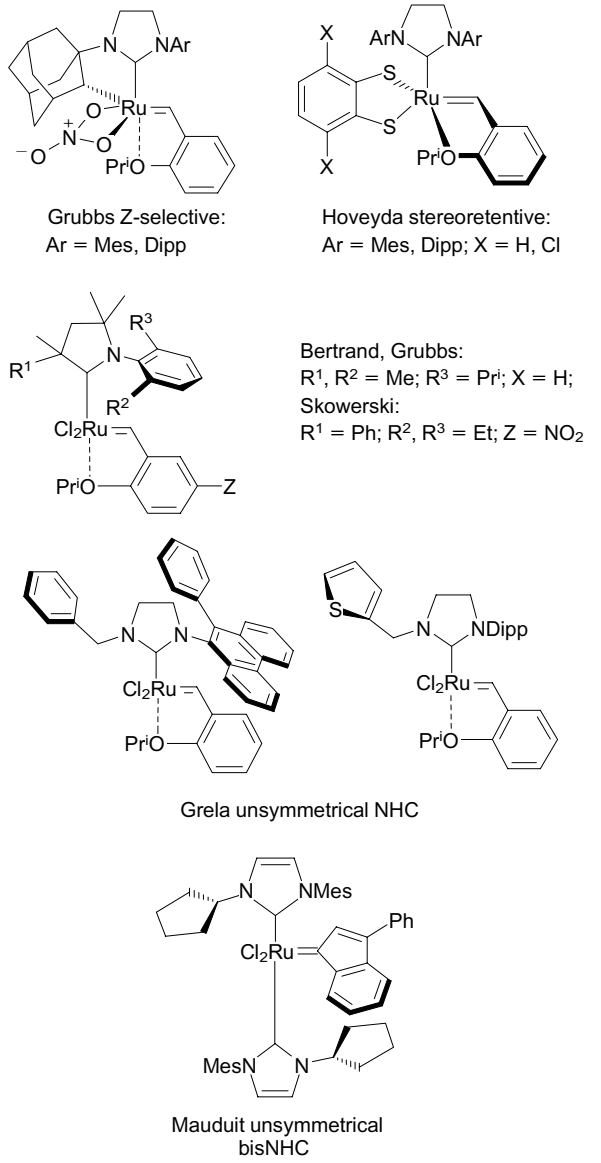


Figure 12. Ruthenium complexes highly effective in macrocyclisation. Dipp is 1,3-diisopropylphenyl.

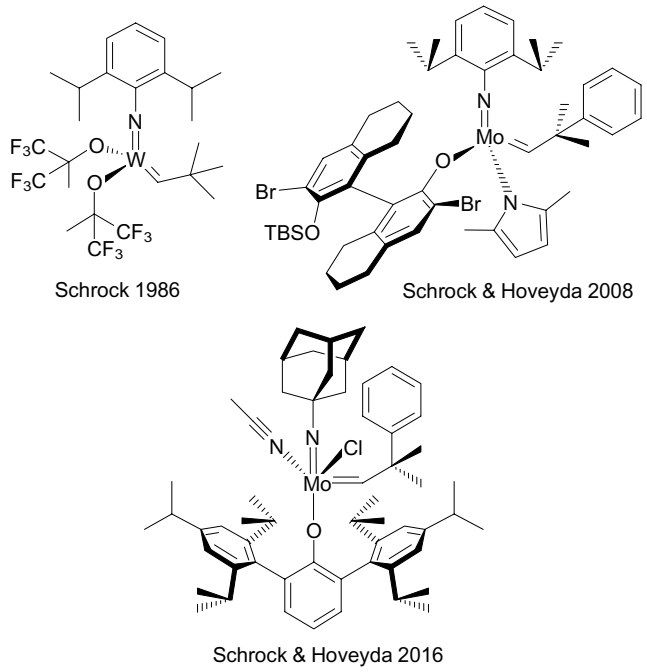


Figure 13. Tungsten and molybdenum catalysts used in RCM macrocyclisation. [See R.R.Schrock. *Acc. Chem. Res.*, **19** (11), 342 (1986); S.J.Malcolmson, S.J.Meek, E.S.Sattely, R.R.Schrock, A.H.Hoveyda. *Nature (London)*, **456** (7224), 933 (2008); J.K.Lam, C.Zhu, K.V.Bukhryakov, P.Müller, A.Hoveyda, R.R.Schrock. *J. Am. Chem. Soc.*, **138** (48), 15774 (2016)]

The second important group of catalysts used in RCM reactions are complexes based on molybdenum and tungsten (Fig. 13).

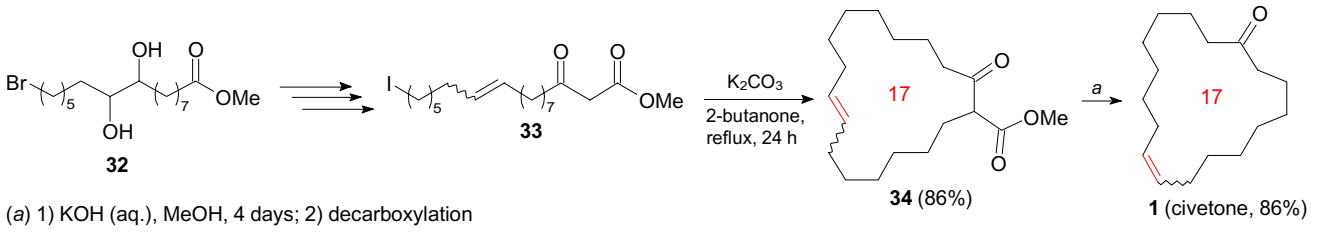
3. Olefin metathesis *vs.* other synthetic methods in preparation of macrocyclic musks

Two of the best-known macrocyclic compounds with an intense musk odour are the aforementioned civetone (**1**) and muscone (**2**) possessing 17- and 15-membered rings, respectively. The important role of these fragrances for the perfume industry is highlighted by the number of publications and diversity of methods used for their production. The biggest challenge in synthesis of civetone was to deliver the product with the desired *Z*-geometry of the double bond, while in case of muscone it was the introduction of the right configuration of substituent at C(3) position.

3.1. Civetone

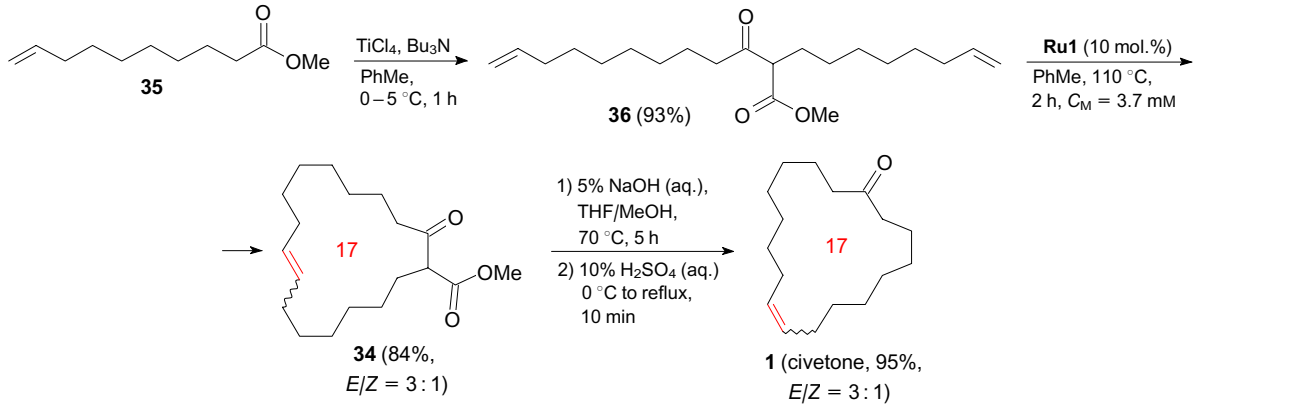
The first literature report on total synthesis of civetone based on internal nucleophilic substitution was published by Hunsdiecker in 1942 (Scheme 9).[62] Six years later similar concept was used by Blomquist *et al.*,[63] whereas Stroll *et. al.* described an alternative methodology involving the acyloin and Dieckmann condensations.[64]

Scheme 9

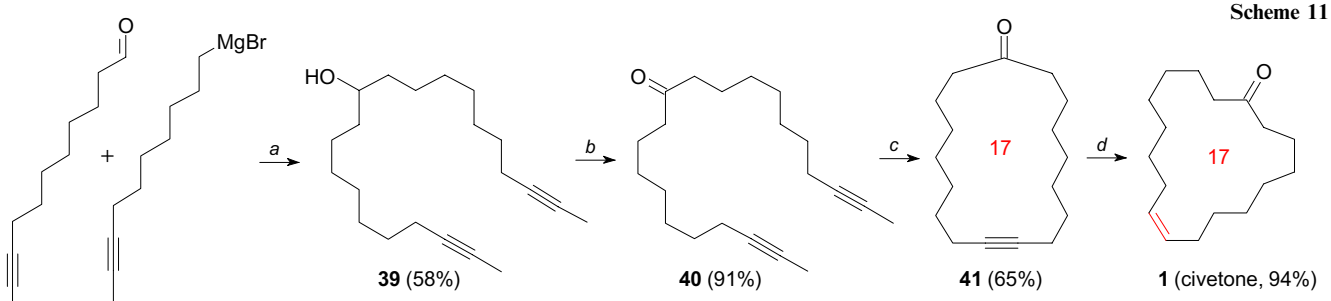


(*a*) 1) KOH (aq.), MeOH, 4 days; 2) decarboxylation

Scheme 10



Scheme 11



(*a*) THF, −30 °C to rt, 11 h; (*b*) PDC, DCM, rt, 16 h;
(*c*) 10 mol.% $(Bu^tO)_3W{\equiv}CCMe_3$, PhMe, 80 °C, 30 min, C_M = 6 mM;
(*d*) Lindlar cat., H_2 (1 atm), quinoline, DCM, rt, 2 h

Tanabe and co-workers[65] used the sequence of Claisen condensation and subsequent olefin metathesis (Scheme 10). The reaction of 9-decenoic acid methyl ester (**35**) with titanium tetrachloride proceeded smoothly providing diene **36** in a very good yield (93%). Next, the macro-RCM in the presence of Grubbs first generation catalyst was performed (84% yield), followed by spontaneous decarboxylation, yielding the desired ketone **1** in 95% yield (total yield of 75% was achieved after 3 steps). When the same sequence was performed as a one-pot procedure, civetone (**1**) was obtained in 48% isolated yield as a mixture of *E*- and *Z*-isomers.

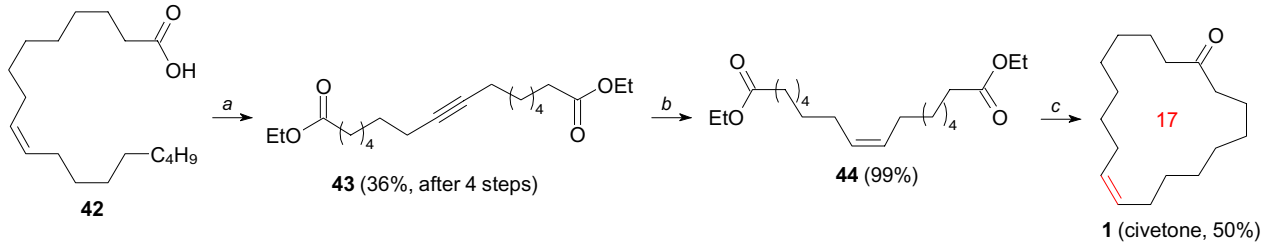
As mentioned, the biggest challenge in synthesis of naturally occurring civetone isomer is to achieve *Z*-geometry of the C−C double bond. The pioneering research in this direction was conducted in the Fürstner's group and included alkyne metathesis and subsequent semihydrogenation as the key steps (Scheme 11).[66] First, the symmetrical secondary alcohol **39** was synthesised, followed by oxidation with pyridinium dichromate. The resulting symmetrical ketone **40** was than subjected to the alkyne metathesis macrocyclisation catalysed by tungsten-based complex, followed by semihydrogenation in the presence of Lindlar's catalyst and quinoline. This four-step synthesis gave an access to the pure *Z*-isomer of macrocyclic ketone **1**.

Another player in the field, Hagiwara, developed the synthesis of civetone (**1**) that relied on natural and easily available oleic acid.[67] Its self-metathesis performed in the presence of 0.1 mol.% of Grubbs second generation catalyst led to unsaturated diacid which was subjected to bromination and elimination sequence to synthesise **43**. The thus obtained acetylene derivative was transformed into ester **44**, reduced with Lindlar's catalyst, cyclised in Dieckmann condensation, and decarboxylated to produce civetone (**1**) (Scheme 12).

3.2. Muscone

Another important and widely used ketone-based macrocycle is muscone. Also numerous attempts have been made to synthesise this 15-membered macrocycle. Given the presence of a chiral centre on C(3) position, the reported

Scheme 12



(*a*) 1) self-metathesis, 2) bromination, 3) elimination, 4) estrification; (*b*) H_2, Lindlar cat., quinoline, AcOEt, rt; (*c*) 1) KH, THF, reflux; 2) 1 M NaOH/EtOH (1 : 1), rt; 3) H_2SO_4, 0 °C

synthetic methods are divided to those providing muscone either as a racemic mixture, or as a single enantiomer.

In 2007, Knopff and co-workers proposed an innovative approach to stereoselective synthesis of muscone starting from readily available 3-methylcyclopentadecane-1,5-dione (**45**).[68, 69] Two key stages of this synthesis, namely intramolecular condensation of diketone **45** and Eschenmoser fragmentation, delivered compound **47**, which was exhaustively reduced to the desired **2**. Interestingly, partial reduction achieved in the presence of Lindlar's catalyst leads to compound **49** possessing even more intense smell (Scheme 13).

The method proposed by Zou *et al.*[70] can be recognised as an oxy-version of the well-described Cope rearrangement. The synthesis begins with the protection of halohydrin **50** with the silyl group and the halogen exchange in Finkelstein's reaction. The resulting iodide **52** in reaction with amide derivative **53** gave **54**, which after deprotection of the hydroxy group and reduction of the amide group of **55** was converted to dialdehyde **56**. The key step of the synthesis is reaction of the unsaturated aldehyde **56** in the presence of boron trifluoride diethyl etherate, acting here as a Lewis acid, leading to the formation of **57**. The subsequent reduction and hydrogenation lead to the desired product **2** in 91% yield in the final step (Scheme 14).

In the literature several methods of muscone synthesis utilising ring-closing metathesis as a key step are described. All are based on three reactions: (*a*) synthesis of an appropriate diene, (*b*) RCM reaction in the presence of Ru-catalyst, and (*c*) reduction of the unsaturated C–C double bond by means of palladium catalyst under hydrogen atmosphere.

Ikariya developed a novel method for selective isomerisation of allylic alcohols leading directly to saturated carbonyl compounds. Because of its wide applications, this method was also implemented in the asymmetric synthesis of muscone (Scheme 15). (±)-*Z*-**59** was prepared by addition of 9-decenyllithium to neral. The subsequent isomerisation of this alcohol with Ru-based complex lead to (*R*)-**24** in good yield and enantiomeric excess. In the next step, the prepared diene was subjected to ring-closing metathesis with Grubbs second generation catalyst, followed by reduction of C=C bond, resulting in 61% of isolated yield over two steps.[71]

In the enantioselective version of the previous reaction, Tanabe utilised cross-Claisen condensation of optically pure acid **60** in the presence of titanium(IV) chloride leading to ketoester **61**. The latter underwent decarboxylation to create diene **24**. Final RCM step, followed by reduction of a C–C double bond provided the optically pure muscone (**2**) in a good isolated yield (Scheme 16).[72]

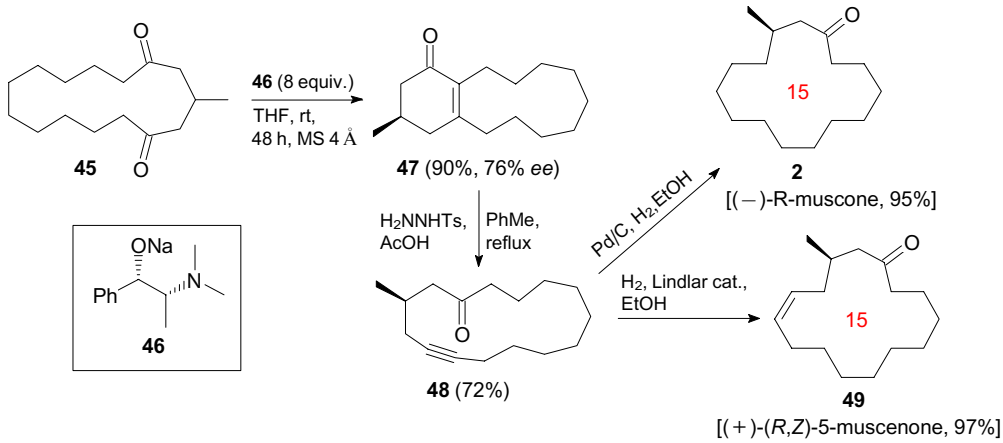
In 2015, Shen proposed a new method of synthesis of optically pure muscone starting from methyl (*R*)-5-bromo-4-methylpentanoate (**62**). In the several simple steps, he was able to obtain analogue of optically pure diene **27** with less crowded double bond. Its ring-closing metathesis and final reduction led to the desired (*R*)-muscone (Scheme 17).[73]

3.3. Exaltolide, ambrettolide and isoambrettolide

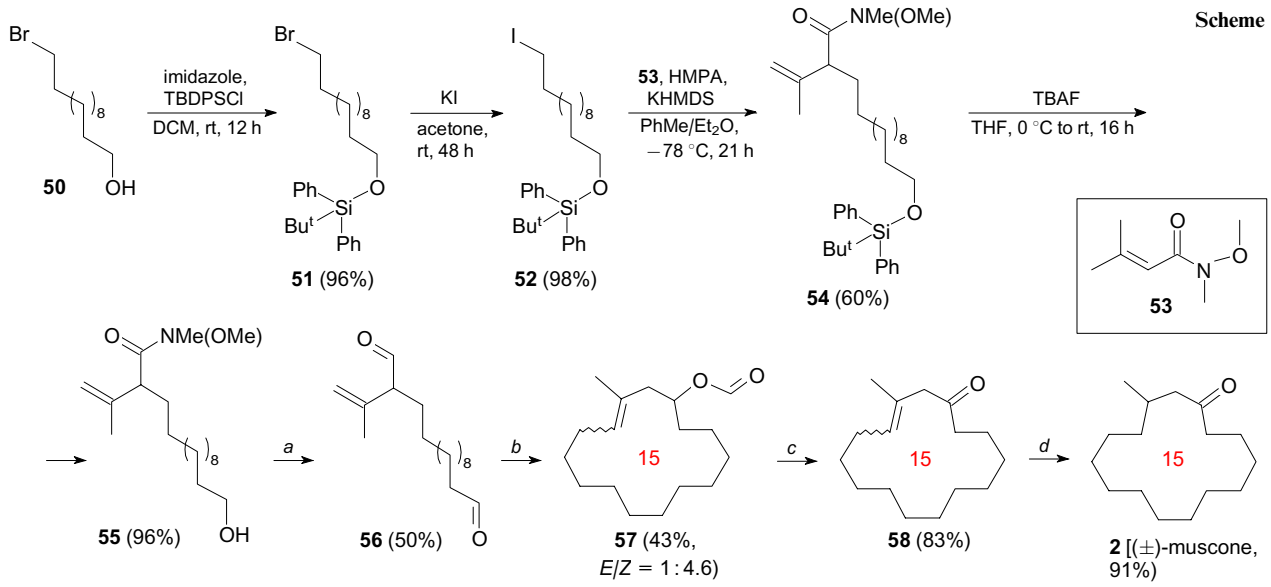
Historically, the first example of RCM leading to a macrocyclic musk (an unsaturated exaltolide derivative **11**) was given by Villemin in 1980.[74] As a catalyst, he used the poorly defined systems, composed of WCl_6 and Me_4Sn at rather high loadings (*ca.* 20 mol.%).

As compared with macrocyclic ketones described above, syntheses of macrocyclic lactones are generally much simpler. While in the case of civetone (**1**) or muscone (**2**) it was necessary to use multistage syntheses, in the case of lactones

Scheme 13

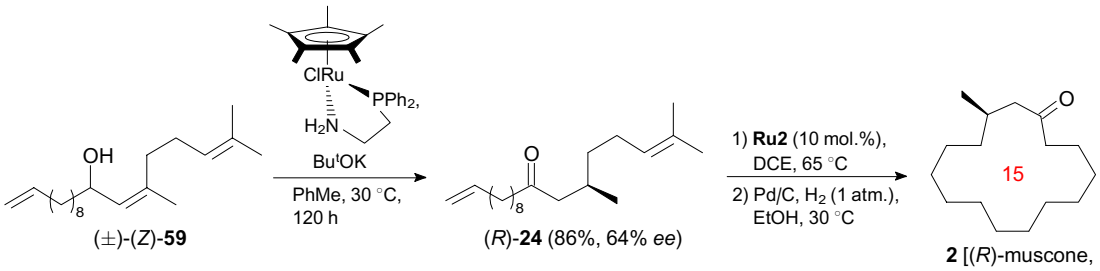


Scheme 14

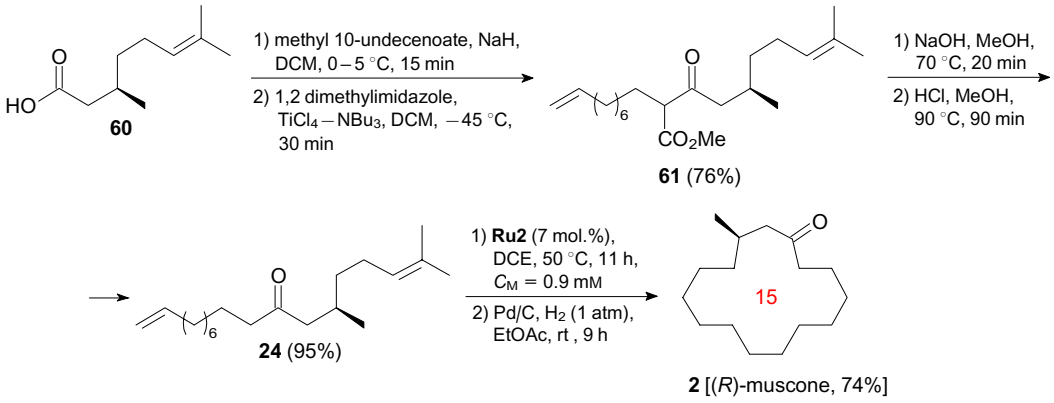


(*a*) 1) $LiAlH_4$, THF, 0 °C, 3 h; 2) PCC, DCM, rt, 2 h; (*b*) BF_3OEt_2, DCM, rt, 101 h, C_M = 1.0 mM; (*c*) 1) $LiAlH_4$, Et_2O, 0 °C, 15 min; 2) PCC, DCM, rt, 3 h; (*d*) Pd/C, H_2 (1 atm.), c-hex, rt, 3 h

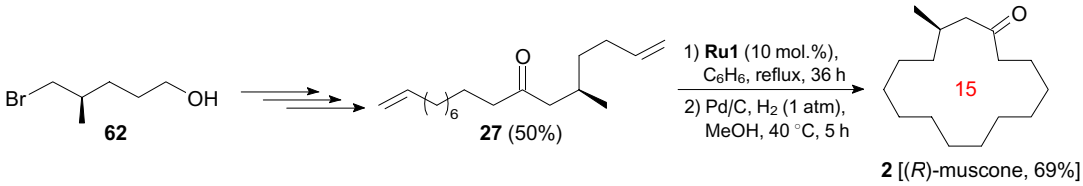
Scheme 15



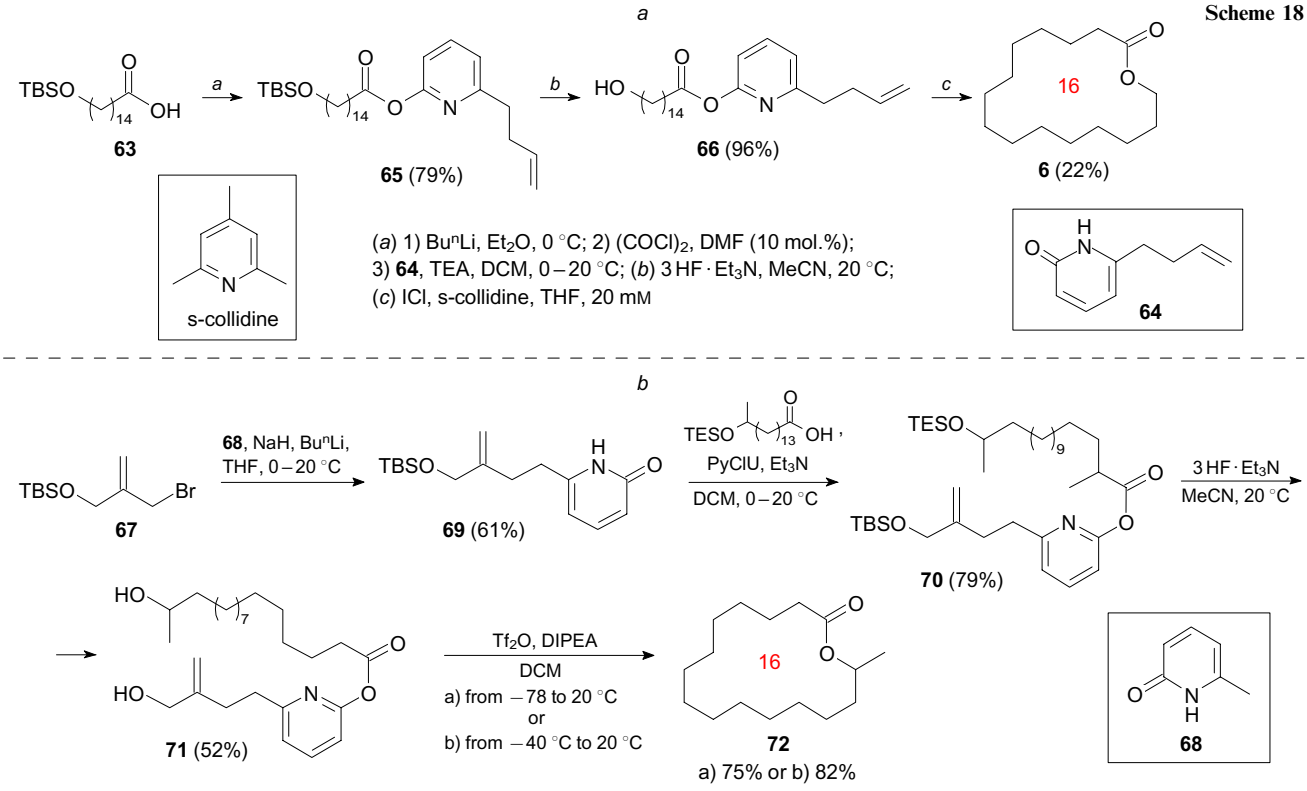
Scheme 16



Scheme 17



Scheme 18



like exaltolide (**6**), relatively straightforward methods such as esterification can be used.

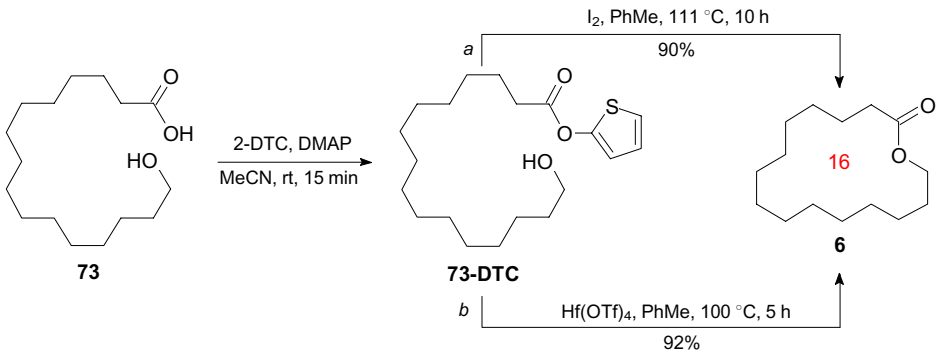
Barrett and Frederiksen [75] described esterification using Mukaiyama pyridinium esters (Scheme 18).[76] Intermediate **65** was synthesised from TBS protected hydroxyacid **63** by deprotonation with n-butyllithium, followed by reaction with oxalyl chloride and **64**, and final desilylation as the third step of the sequence (Scheme 18 *a*). 2-Pyridyl ester **66** prepared in such a way underwent intramolecular *N*-alkylation leading to the desired macrocycle **6**. However, synthesis of exaltolide resulted in low yield (22%). To increase the yield of desired macrocycle, the authors decided to improve the structure of the lactone precursor. They synthesised 2-pyridyl ester **70** (Scheme 18 *b*), followed by deprotection of silyl ether groups, resulting in **71** in 52% isolated yield. Subsequent macrolactonisation gave 75%–82% yield, depending on the temperature (Scheme 18 *b*).

In 2004, Mukayiama and co-workers focused on development of intermolecular esterification method utilising 2-DTC (di-2-thienyl carbonate) in the presence of DMAP,[77] which can be accelerated by addition of an equimolar amount of iodine.[78] These conditions were then adopted in macrolactonisation reactions providing the desired products with different ring size (12 to 17 atoms, Scheme 19 *a*) in moderate to very good yields.[79] Alternatively, the improvement of yield can be achieved by addition of Lewis acids as activators.[80] Detailed studies revealed that hafnium(IV) triflate is the most efficient (Scheme 19 *b*); however, good results were also achieved with zirconium, titanium, or scandium triflates. In the case of exaltolide (**6**), both methods provided the desired product in high yields; however, in the presence of Hf(OTf)$_4$ (0.1 equiv.), the reaction time was reduced by half (see Scheme 19).

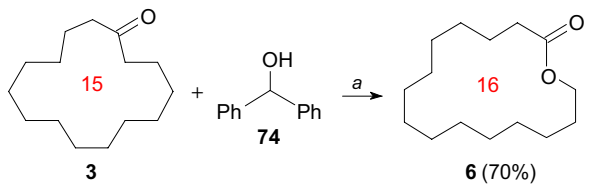
Another pathway for synthesis of exaltolide was described by Kamae's group.[81] The authors obtained exaltolide (**6**) by Bayer–Villiger oxidation of **3** with H_2O_2 generated *in situ* from diphenylmethanol (**74**)/O_2 system on treatment with NHPI and AIBN as a radical initiator in good yield and with excellent selectivity (Scheme 20).

In 2016 Matsubara and co-workers,[82] adapted the strategy used by Mukuyiama [77] to obtain exaltolide. He implemented 2,4,6-trichlorobenzoyl chloride (**75**) to activate

Scheme 19



Scheme 20

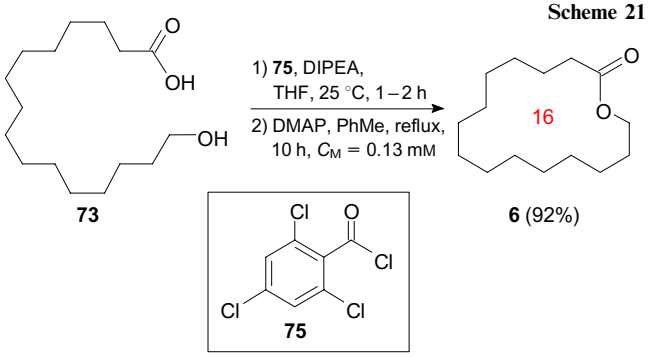


(*a*) 1) cat. NHPI, AIBN, MeCN, 75 °C, 22 h; 2) HFIP, 60 °C, 24 h; 3) PPh_3, 25 °C, 3 h

hydroxyacid **73**, and obtained **6** in DMAP-catalysed macrocyclisation (Scheme 21).

In turn, Spinella and co-workers[83] decided to investigate the use of enzyme-promoted macrocyclisation leading to musks. In the synthetic sequence, hydroxy function in **76** was first protected with TBS group, the resulting ester **77** was reduced to aldehyde **78**, and then converted into internal olefin **81** in Wittig reaction with independently prepared phosphonium salt **80**. Finally, the hydroxyl group in **81** was deprotected. The last stage was the enzymatic macrocyclisation of **82** at high dilution with the use of the lipase *Candida antarctica* from the fungi kingdom, giving ambrettolide (**5**) in 83% yield (Scheme 22).

Scheme 21



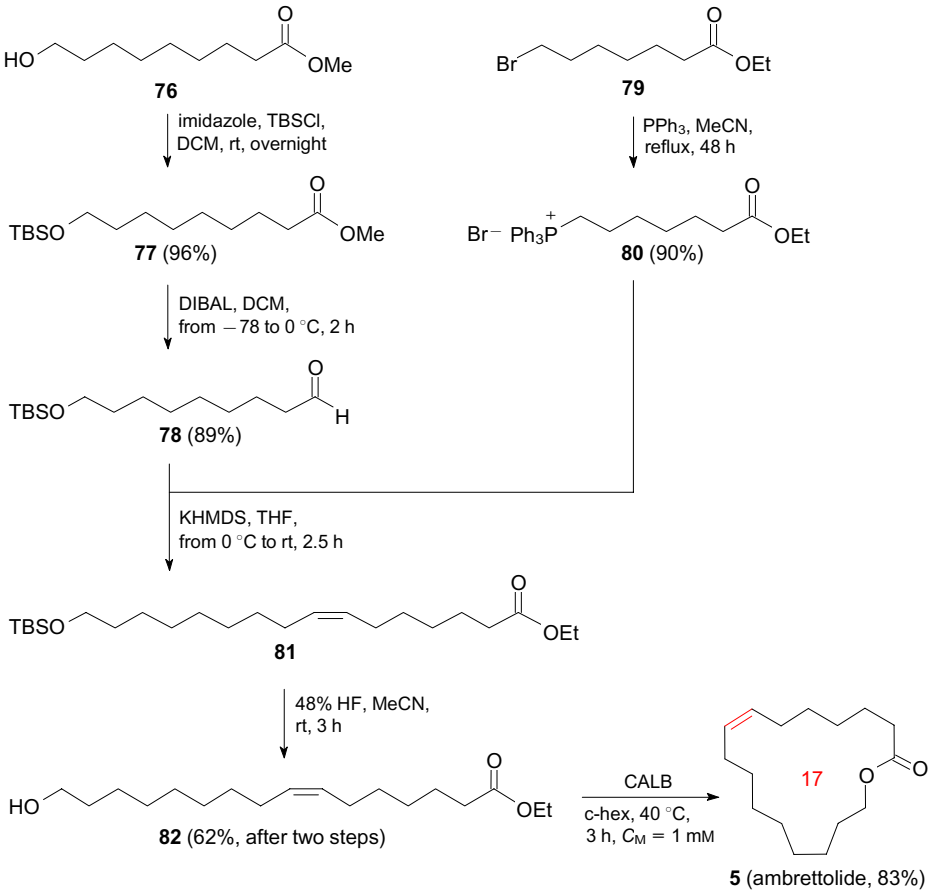
Fürstner frequently used alkyne RCM to obtain various lactones and lactams. Following the protocol used previously for the civetone (**1**) synthesis (*cf.* Scheme 11), he executed the synthesis of ambrettolide. In this case, the three-step sequence, starting from 9-undecyn-1-ol (**83**) led to the geometrically pure (*Z*)-ambrettolide (**5**) in 63% yield (Scheme 23).[84]

4. Recent advances in synthesis of macrocyclic musks *via* olefin metathesis

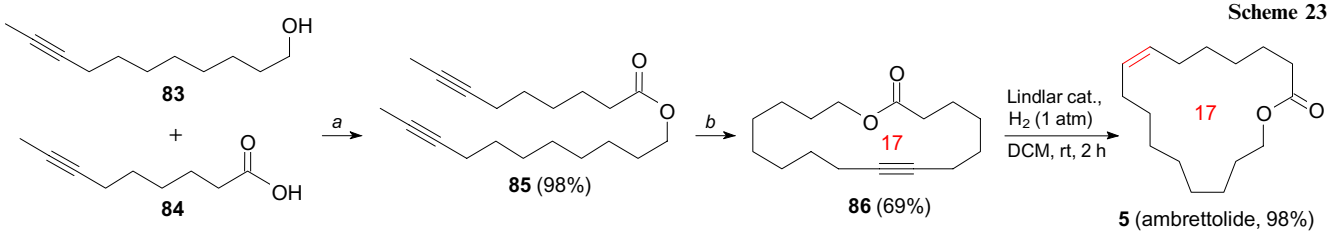
4.1. Improvements in RCM macrocyclisation

Since the 1980s, the synthesis of unsaturated macrocyclic musks has been of constant interest to the scientific community. Olefin metathesis has become a very important tool in the synthesis of these compounds and has many applications. However, during these decades many problems, including high catalyst loading and very low dilutions necessary to obtain acceptable yields, have not been sufficiently resolved. Therefore, there is still a need to find more effective and economical solutions to prepare these valuable macrocyclic products.

Scheme 22



Scheme 23



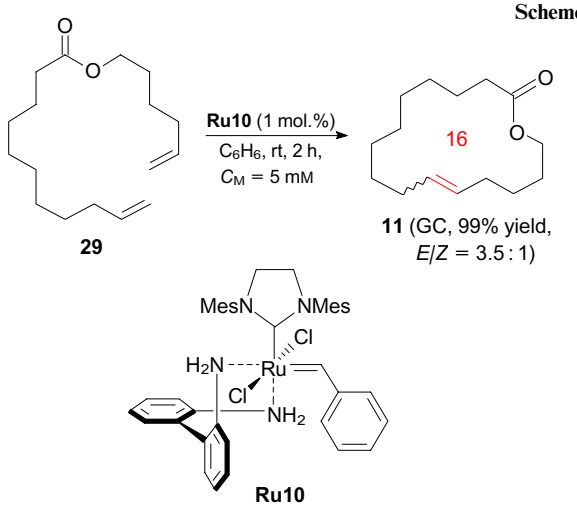
(*a*) DCC, DMAP, DCM, rt, overnight; (*b*) $Mo(CO)_6$ (5 mol.%), *p*-chlorophenol, chlorobenzene, reflux, overnight

4.1.1. New non-stereoselective catalysts

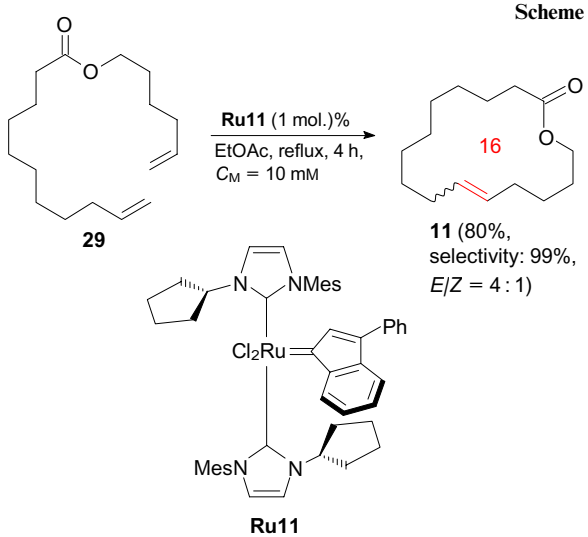
One of possibility to improve the macro-RCM step is the use of better catalysts. Fogg opted for the introduction of hemilabile *o*-dianiline moiety into a standard ruthenium catalyst. The resulting **Ru10** is highly effective in macrocyclisation of terminal dienes (*i.e.*, **29**, Scheme 24), outperforming even the nitro-catalyst **Ru5**.[85]

Mauduit developed an indenylidene complex **Ru11** containing two unsymmetrical NHC ligands (Scheme 25). This complex effectively catalyses the macrocyclisation of dienes in refluxing ethyl acetate, leading to corresponding macrocyclic lactones in high yields, even at relatively high concentration of 10 mM.[86]

Scheme 24

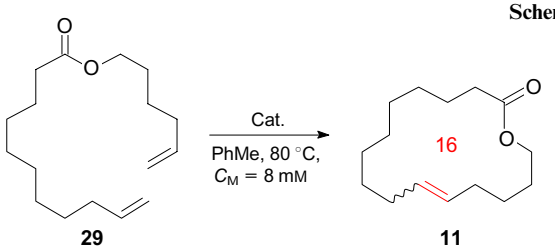


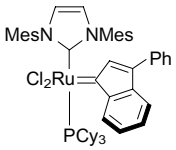
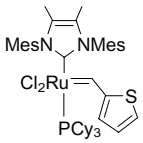
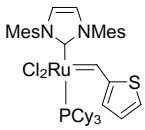
Scheme 25



The amount of catalyst used in macrocyclisation reaction is very important from the point of view of cost-effectiveness, as the amount of the catalyst is definitely one of the determinants of the final product price. The loadings of ruthenium complexes as high as 5 mol.% – 10 mol.% (typical of research papers of mid-2000) are unacceptable today. Kadyrov tested three popular ruthenium complexes, **Ru8**, **Ru12**, and **Ru13** in the model macrocyclisation RCM reaction of **29** using 50 – 75 ppm catalyst loading (Scheme 26).[87] He found that thorough purification of the substrate as well as instantaneous removal of ethylene produced during the reaction were crucial for achieving good results. It was explained that ethylene not only is responsible for unproductive metathesis cycles, but also triggers the catalyst fast decomposition during the reaction.

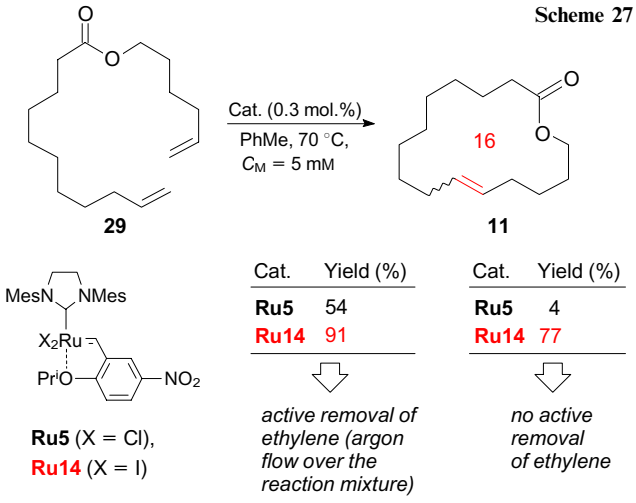
Scheme 26



Cat.			
	Ru8	**Ru12**	**Ru13**
loading	75 ppm	75 ppm	50 ppm
11, yield	83%	80%	88%
E/*Z*	3.2 : 1	3.2 : 1	3.0 : 1

The new iodide-containing nitro catalyst **Ru14** has been developed and commercialised[88] by Apeiron Synthesis company and applied in RCM macrocyclisation, also in green solvents (Scheme 27).[89] It was noted that the augmented steric hindrance in the vicinity of Ru centre (due to higher ion radius of iodide ligands as compared with chlorides) ensures the catalyst higher stability and robustness. This benefit was best manifested under highly challenging conditions, such as in reactions with very low catalyst loading, in protic (MeOH, Pr^iOH) or Lewis-basic solvents (2-MeTHF), or in the presence of various impurities or ethylene. The presence of ethylene (the continuous removal of which is sometimes difficult to be achieved under industrial large-scale conditions) has sometimes a dramatic

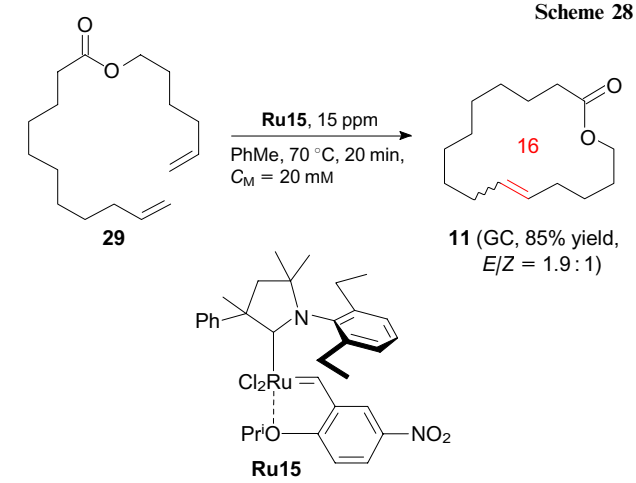
Scheme 27



effect on the reaction yield and selectivity, as illustrated in Scheme 27. Increased stability of the ruthenium methylidenes generated from **Ru14** makes this catalyst especially suitable for macrocyclisation of dienes, like **29**, also in the presence of ethylene.[89]

Apeiron Synthesis company developed also an innovative CAAC ligand-containing complex **Ru15** and tested it in musk macrocyclisation under industrially relevant conditions, namely, in loading as low as 15 ppm and in relatively high concentration of 20 mM, obtaining very promising results (Scheme 28).[90]

Scheme 28

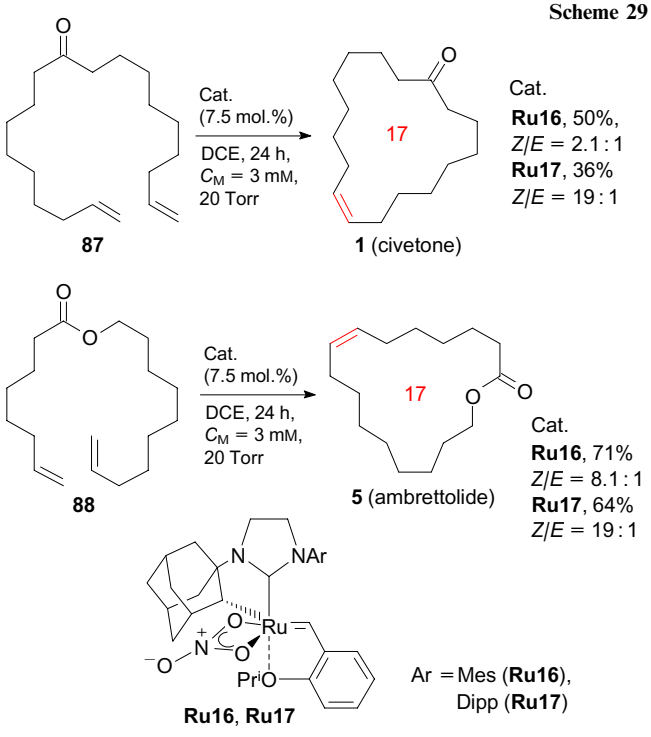


The ruthenium complexes with CAAC ligands are becoming more and more important in catalytic transformations. With the modifications introduced by Skowerski,[90] challenging CM of acrylates and acrylonitrile, dimerisation of α-olefins, as well as highly efficient synthesis of macrolactones *via* RCM became possible. However, there is still a plenty room for improvements, which can be clearly observed from recent publications. New important representatives of CAAC catalysts are bis(CAAC) complexes, which can be easily obtained from cheap and accessible indenylidene complexes **Ru6** (see Figure 9) and show high catalytic activity. In recent work, Fogg examined the stability and productivity of selected Ru-NHC and Ru-CAAC complexes under atmosphere containing 8% of oxygen. Interestingly, for Ru-complexes containing NHC ligands, such as **Ru1**, **Ru3**, or **Ru5**, a significant drop of RCM yield was observed. On the other hand surprising robustness of the CAAC decorated systems in RCM macrocyclisation under oxygen contaminated atmosphere was observed.[91]

4.1.2. New stereoselective and stereoretentive metathesis catalysts

In production of unsaturated macrocyclic musks, it is important not only to find a way to conduct the key RCM reaction in the most effective way, but also to assure control over the geometry of the newly formed C – C double bond. To make this control possible, numerous *Z*- or *E*-selective ruthenium and molybdenum catalysts have been developed. When in 2011 Grubbs synthesised first Ru-based *Z*-selective catalyst,[92] new chapter in metathesis methodology was opened. The first report on *Z*-selective RCM using ruthenium metathesis catalysts was described for complexes **Ru16** and **Ru17**.[52,93] Excellent *Z*-selectivity offered by these catalysts was utilised in the syntheses of civetone and ambrettolide (Scheme 29).[93]

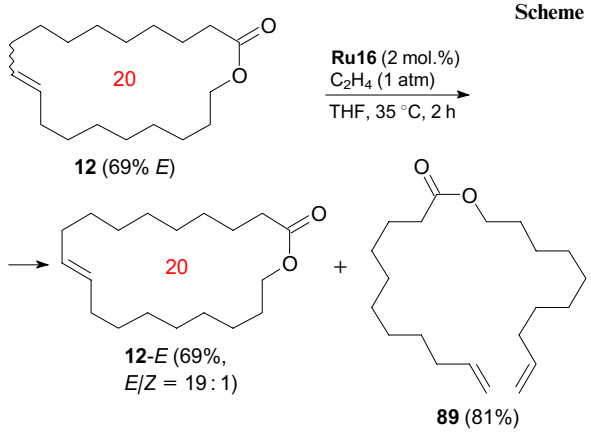
Scheme 29



In the same year, using *Z*-selective ruthenium catalyst **Ru16**, Grubbs *et al.* showed that in ethylene atmosphere it is possible to convert an *E*/*Z* mixture of a macrocycle to a pure *E* isomer in a kind of *Z*-selective ethenolysis-based kinetic resolution reaction. This was possible because the *Z*-configured macrocycle undergoes ethenolysis much faster than the *E*-isomer, thus allowing for resolution of the mixture (Scheme 30).[52]

High stereoselectivity is also exhibited by complexes based on molybdenum, mainly containing a structural monoaryloxide pyrrolide (MAP) motif. In 2013, Dixon *et al.* published examples of using **Mo1** in *Z*-stereoselective synthesis of numerous macrocycles, including ambrettolide (**5**) and yuzu lactone (**4**), in moderate to good yields and with high *Z*/*E* ratio (Scheme 31 *a*).[94] To keep the momentum, one year later Schrock and Hoveyda reported the first **Mo2** catalyst allowing the synthesis of *Z*-enoates *via* RCM

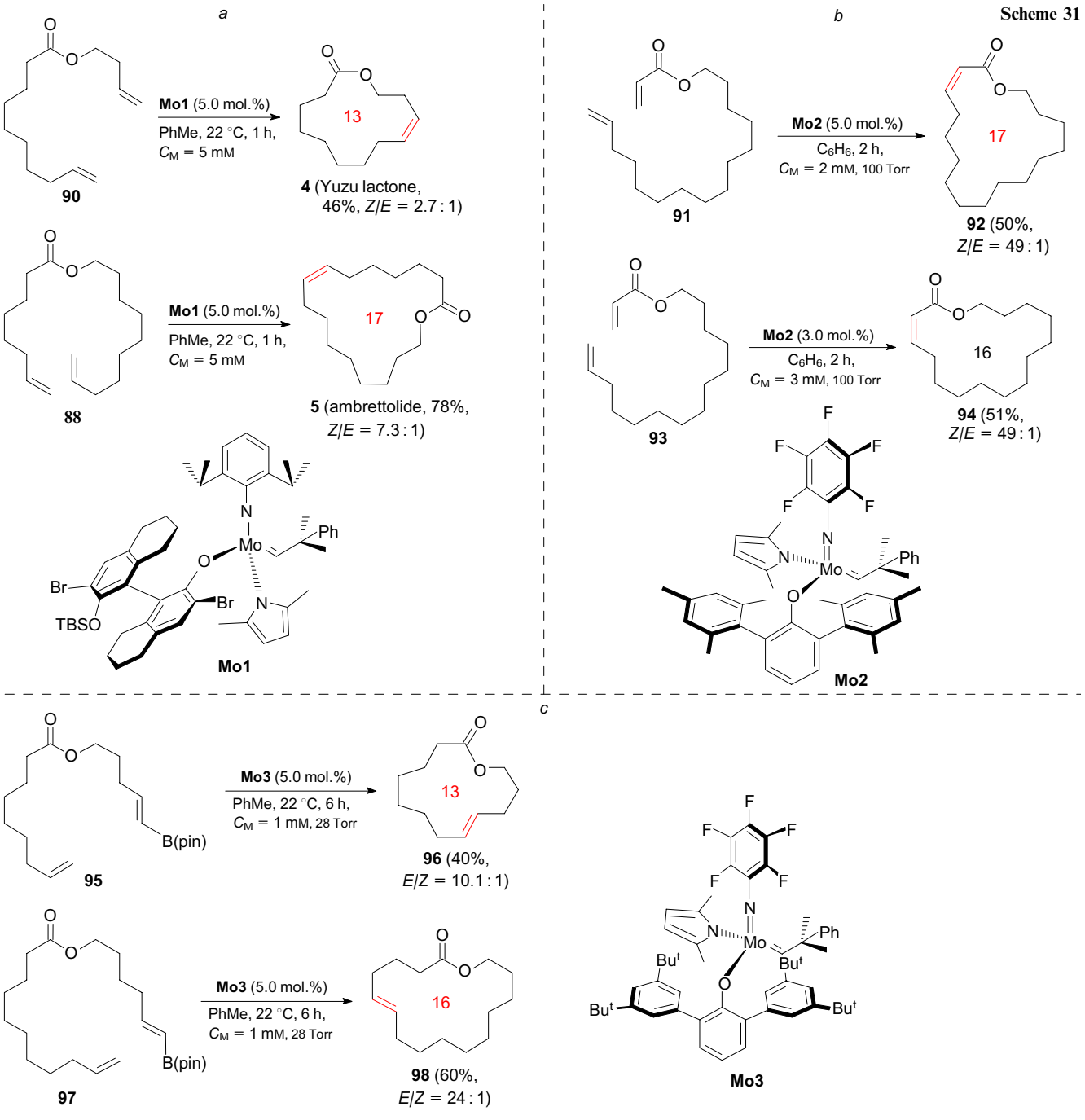
Scheme 30

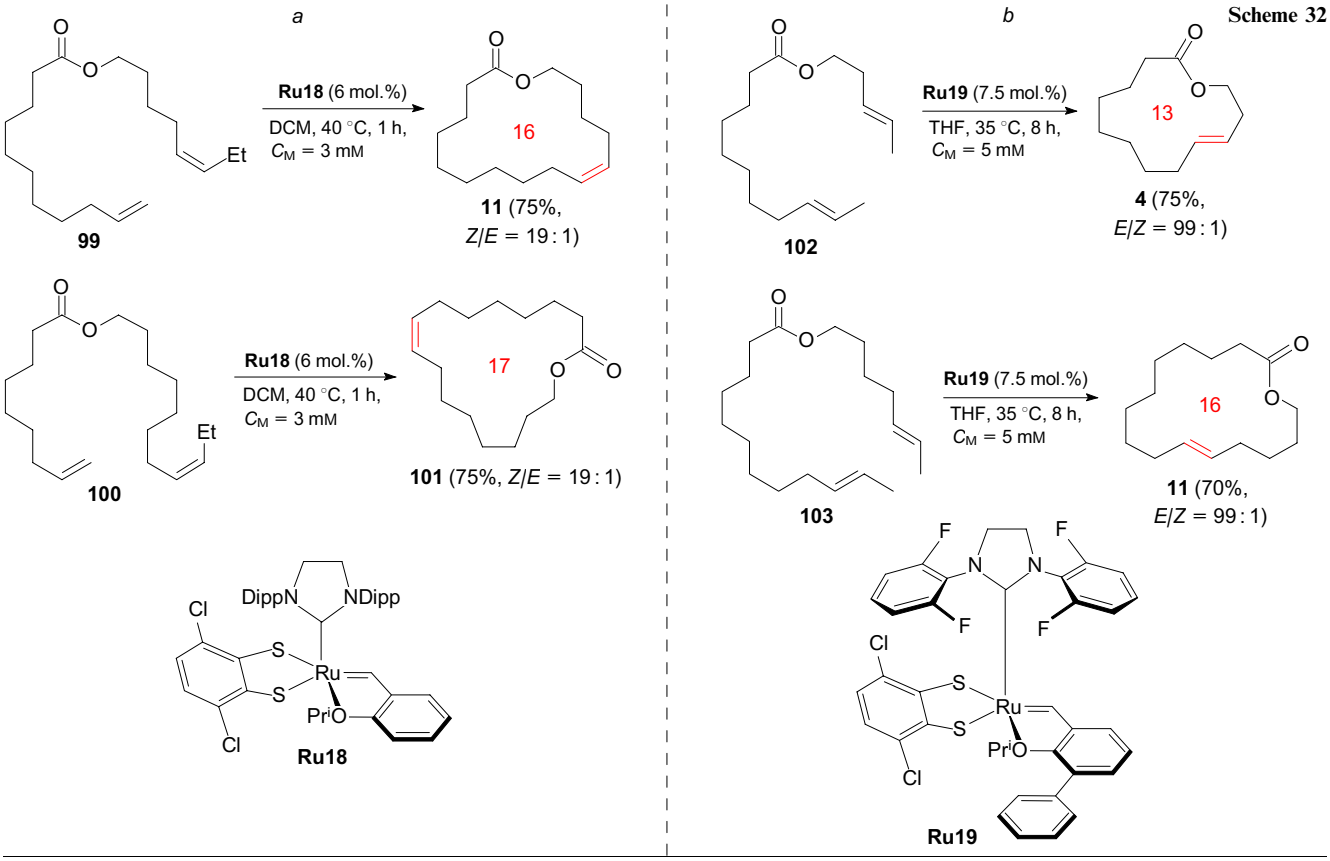


(Scheme 31 *b*).[95] Moreover, the same authors developed a complementary method based on molybdenum complexes in *E*-selective RCM. The key to the success was the introduction of a sacrificial boro(pinacolato) group [B(pin)] into the diene molecules with the appropriate electronic and steric features. The desired macrocycles were synthesised with very good *E*-selectivity and in moderate to good yields (Scheme 31 *c*).[96]

The so-called stereoretentive catalysts, developed by Hoveyda, Grubbs, Mauduit, and others, belong to a new family of ruthenium-based complexes (**Ru18** and **Ru19**, Scheme 32)[97] allowing for the synthesis of *E*- and *Z*-macrocycles. For example Grubbs *et al*. managed to obtain almost pure *Z* (Ref. 98) (Scheme 32 *a*) and *E* (Ref. 53) (Scheme 32 *b*) isomers of macrocyclic lactones in high yields. However, high catalyst loading (up to 7.5 mol.%)

Scheme 31





Scheme 32

and low concentration of dienes (3 to 5 mM) in a carefully degassed solvent were required to perform the macrocyclisation effectively (see Scheme 32).

4.2. Utilisation of renewable substrates

An important factor that must be taken for consideration during industrial validation of a production method is the availability of substrates. Sytniczuk *et al.* focused on the use of biomass-derived reactants in the synthesis of macrocyclic lactones possessing a musky smell.[54] He concentrated on oleic acid (**42**), present in many plant oils, as well as product of its metathesis with ethylene, 9-decenoic acid (**105**), as interesting, renewable building blocks in the synthesis of fragrance compounds (Scheme 33).

Esterification of these acids with alcohols of natural origin, for example: (*Z*)-6-nonen-1-ol,[99] nerol, or citronellol opens the way for synthesis of a variety of bio-sourced dienes that, after ring-closure, can give numerous cyclic musks (Scheme 34). In the same work it was shown, that although terminal dienes seem to be the best substrates from the atom-economy point of view, they do not necessarily have to be the cheapest. For example, the use of oleic acid (**42**), instead of decenoic acid (**105**), allows the synthesis of macrocycles with comparable efficiency. In addition, the use of internal olefin, instead of terminal one, extends the life time of the catalyst, due to elimination of poisoning ethylene by-product formation.[87]

Another idea was to combine the metathesis reaction with a C–C double bond shift reaction (sometimes called 'isomerisation') to shorten the aliphatic chain of the substrate (*i.e.*, **30**) and thus obtain macrocycles of stronger smell (Scheme 35).[100] Additional advantage of such substrate modification is that ethylene by-product is not present in the reaction medium, thus extending the longevity of the catalyst.

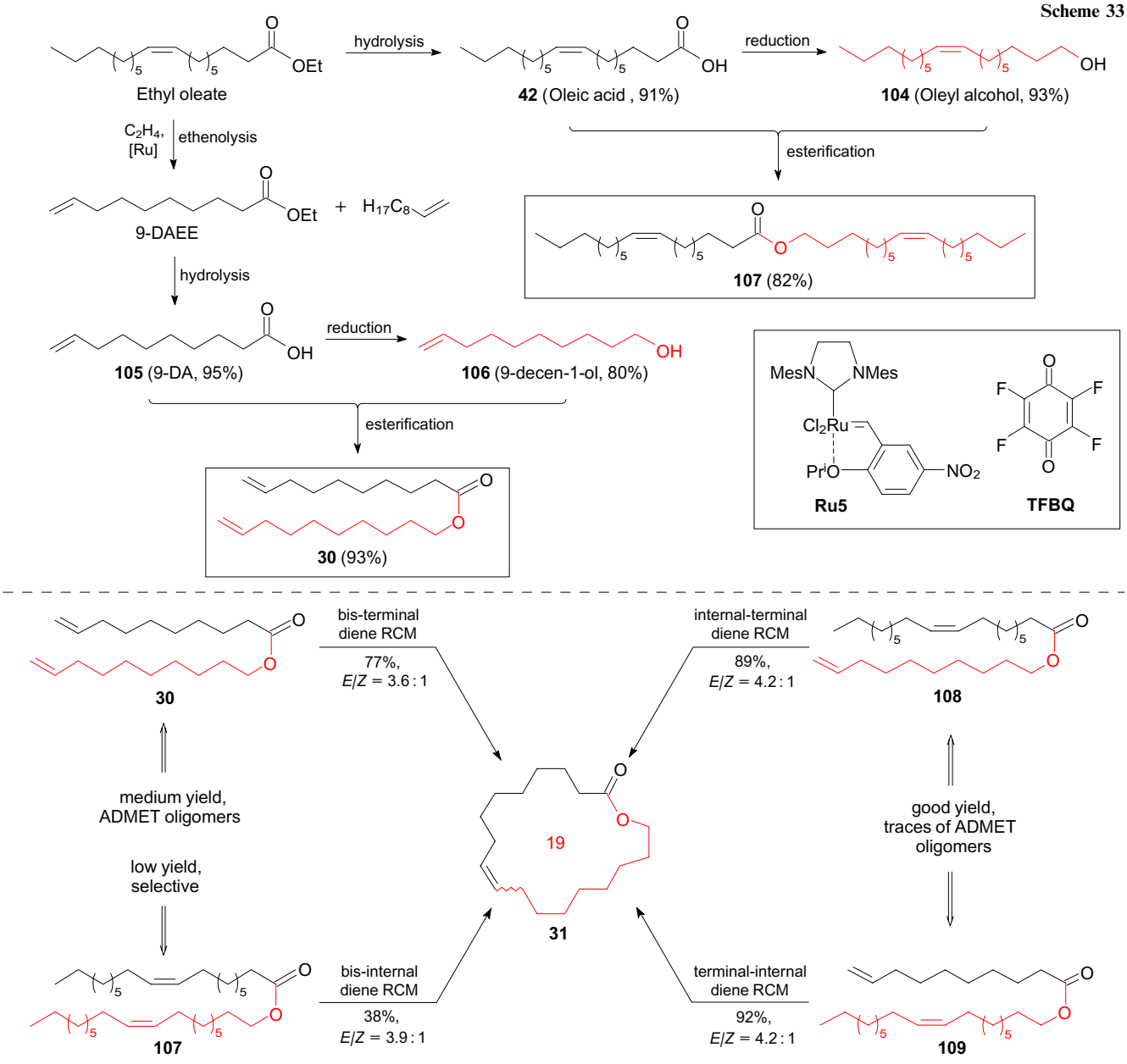
4.3. RCM macrocyclisation in continuous flow and at higher concentration

Collins and colleagues compared the synthesis of macrocyclic dienes in batch (C_M = 5 mM), microwave, and flow reactors (C_M = 10 mM). In-batch macrocyclisation takes up to 5 days, while in a flow reactor, the time can be reduced to about 5 hours, but with a drop of the yield from 57% to 32%. Nevertheless, flow reactors prove to be more efficient in the final results, which illustrates the dormant potential of flow technology.[101]

Jee *et al.* developed an interesting heterogeneous catalyst where the Hoveyda-type complex was covalently attached to a mesocellular siliceous foam (MCF), which enabled the authors to synthesise a number of macrocycles of ring size from 14 to 27 in concentration of 20 mM, so visibly higher than the one recommended for homogeneous RCM (Scheme 36).[102] The authors explained that the yields and conversion rates of the MCF-supported catalyst can be controlled by adjusting the support pore size and the catalyst loading density.

Recently, Buchmeiser and co-workers[103] developed a novel method for synthesis of macrocycles using heterogeneous catalyst based on SBA-15. To do so, he designed a Ru-based complex with modified NHC ligand and immobilised it inside specially engineered spaces of mesoporous silica materials, which caused increased selectivity in macro-

Scheme 33

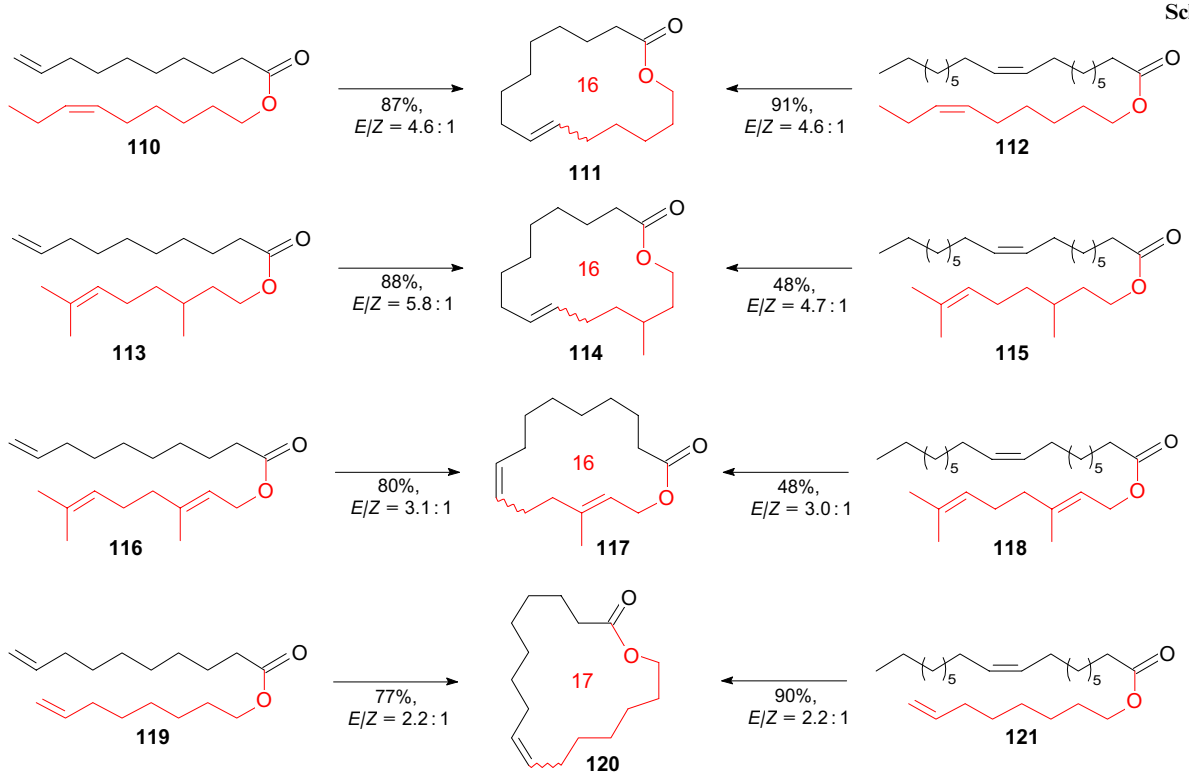


cyclisation reactions of numerous dienes at concentration up to 25 mM. Careful tuning of the pore size, the structure of substrate, as well as modification of the inner surface of the pores with dimethoxydimethylsilane increased the macrocycle/oligomer ratio (Fig. 14).[103]

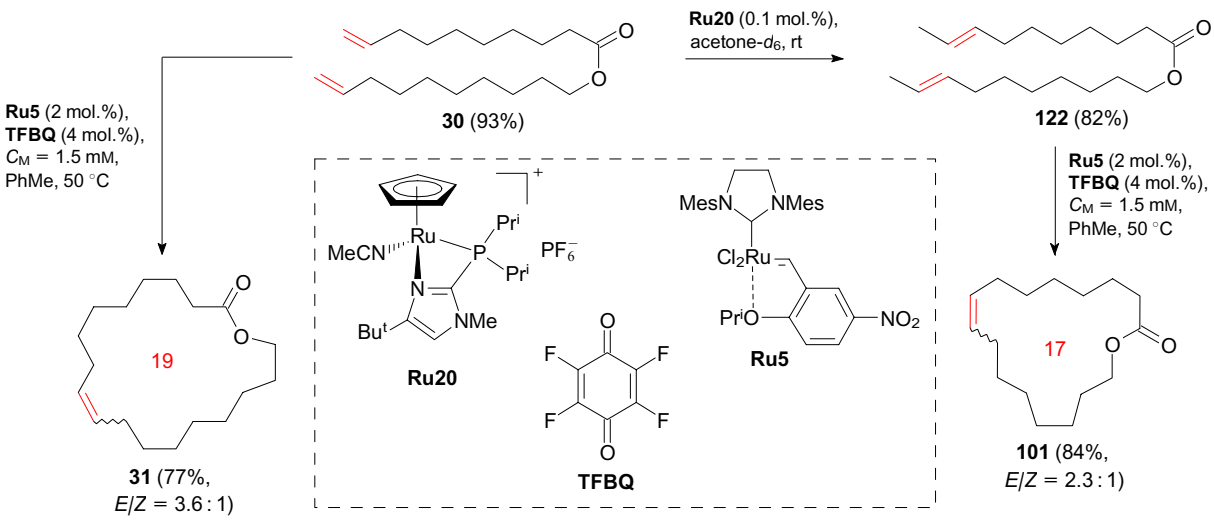
In patent literature, the use of metal-organic framework (MOF) supported FixCat™ ruthenium complex[104] as a hybrid catalytic system for synthesis of macrocyclic lactones was disclosed.[105] The RCM was possible at concentrations up to 20 mM in EtOAc, leading to a 15-membered macrocyclic lactone in 35% yield. Although results were not as good as for Buchmeiser highly engineered system,[103] the preparation of MOF-supported catalyst is effortless and the catalyst exhibits stability up to 110 °C.[105]

Inspired by the famous Carothers' polymerisation – depolymerisation process, Sytniczuk and co-workers developed an alternative way of synthesising macrocyclic musks by first polymerising a diene and then distilling a macrocycle off the reaction mixture at 110 °C under vacuum.[106] This process utilises equilibrium of the olefin metathesis polymerisation – depolymerisation processes[24] and was made possible only by a careful selection of thermally stable catalysts that did not decompose under harsh distillation conditions (such as **Ru24**, or the hybrid catalyst shown in Fig. 15). The reaction basically can be run neat; however, to achieve proper heat transfer and stirring, paraffin oil or PAO polyolefins were used, making RCM possible at concentration of 200 – 700 mM and higher. This methodology works well with terminal as well as with internal dienes, such as oleic acid derivatives, and led to a number of macrocyclic musks (*e.g.*, **1**, **110**, Scheme 37).

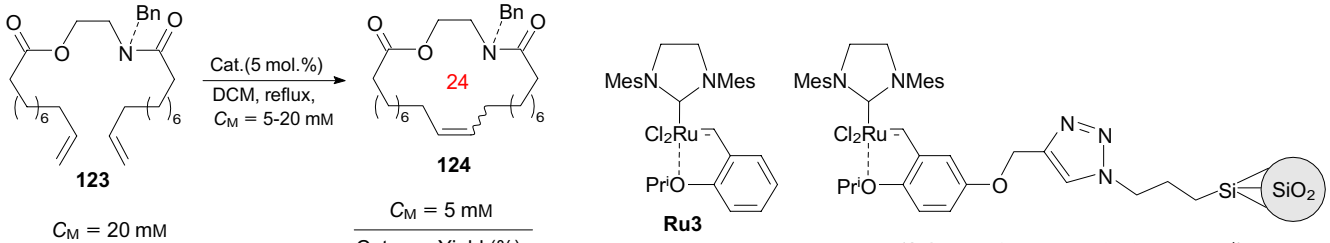
Scheme 34



Scheme 35



Scheme 36



C_M = 20 mM

Cat.	Yield (%)
Ru3	5
Ru21	50
Ru22	43

C_M = 5 mM

Cat.	Yield (%)
Ru3	6
Ru21	75
Ru22	71
Ru23	28

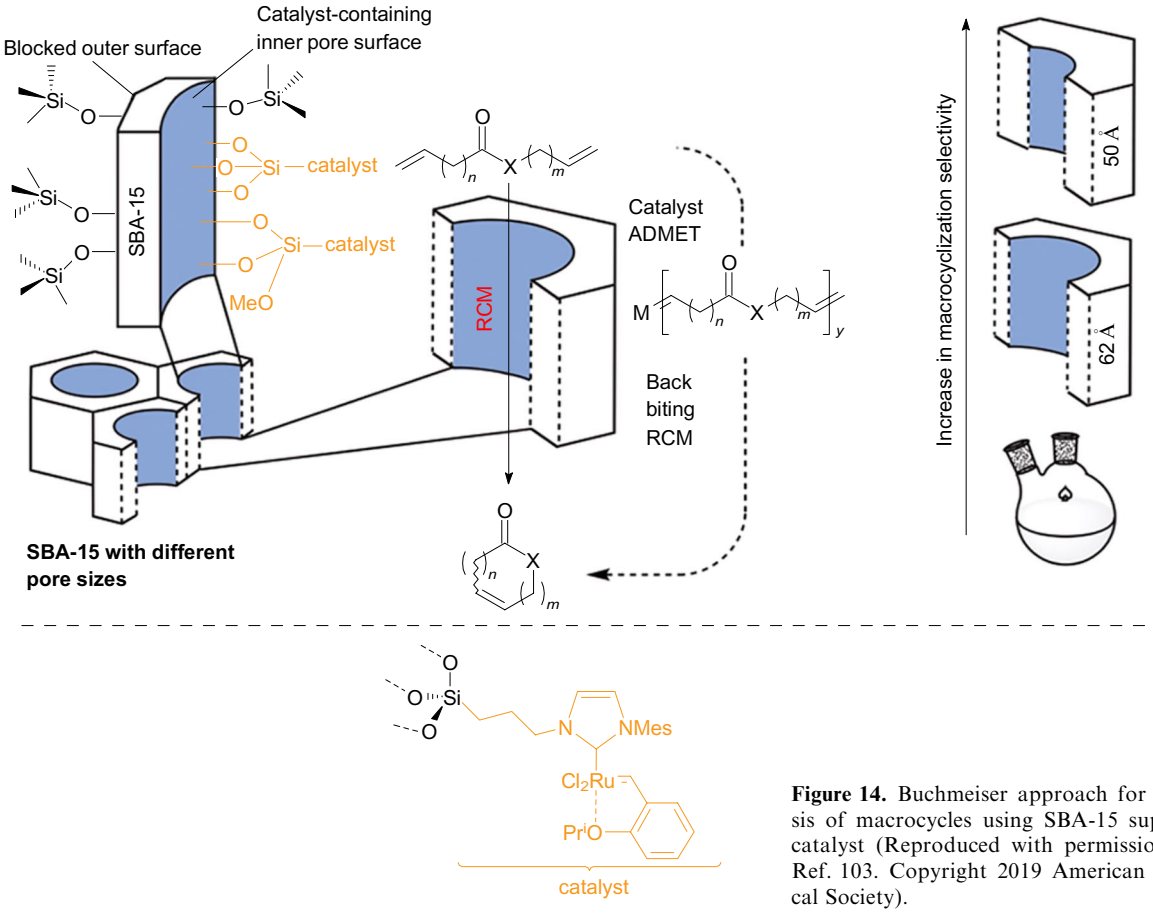


Figure 14. Buchmeiser approach for synthesis of macrocycles using SBA-15 supported catalyst (Reproduced with permission from Ref. 103. Copyright 2019 American Chemical Society).

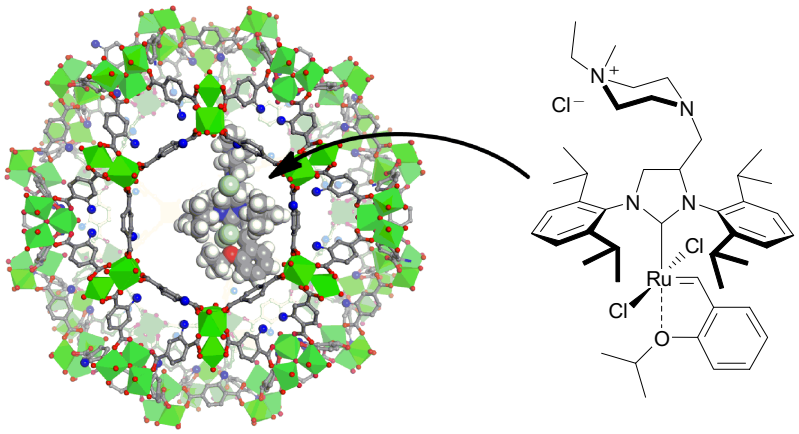


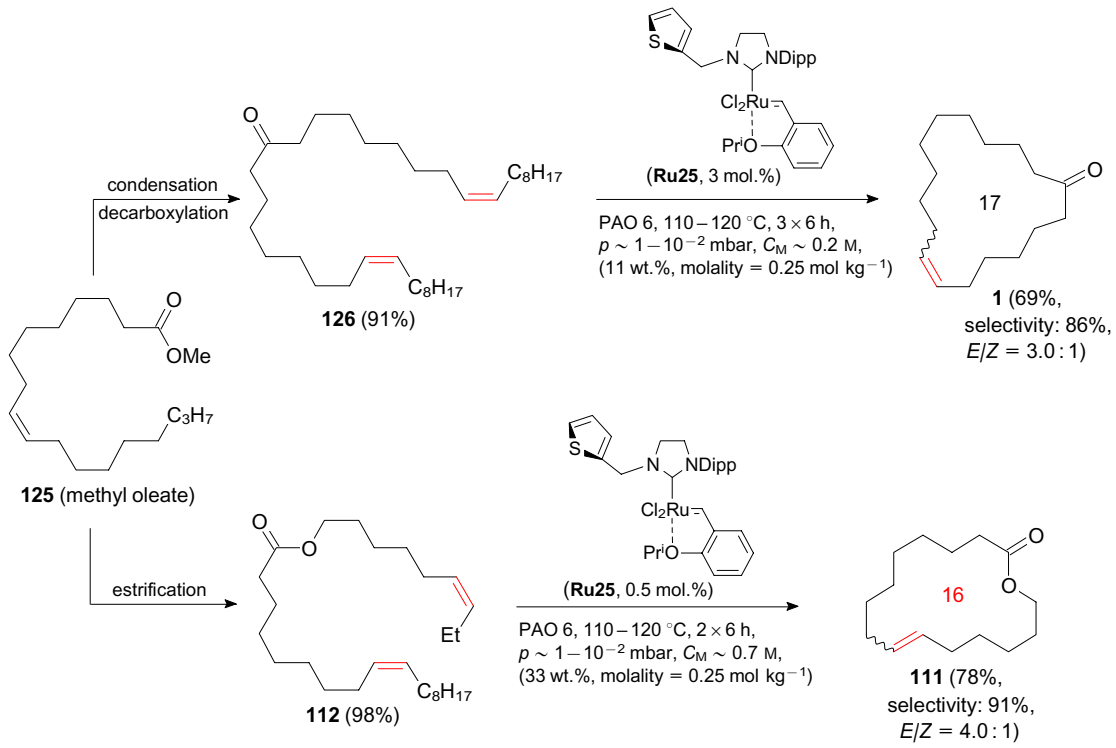
Figure 15. A visual representation of ruthenium supported catalyst (right) in MOF [(Al)MIL-101-NH_2; left].

5. Summary and outlook

The examples briefly described in this review demonstrate potential of olefin metathesis in synthesis of macrocyclic musks. This statement is confirmed by significant amount of scientific reports, from which we selected only the most illustrative examples. We admire classical synthesis of musk macrocycles achieved in past years for they are utilising very elegant and well planned chemistry. It is important, however, to enumerate the potential advantages of olefin metathesis in synthesis of macrocycles, such as high atom economy, option for use of readily available, renewable or at least inexpensive substrates, possibility of precise control over the position and configuration of a C–C double bond, mild reaction conditions, and well-established database of commercially available catalysts. Of course at the same time, the reaction has a number of achy limitations, such as not perfect stability of the popular catalysts, need to operate at high dilution (partially solved only recently).

At the same time, we would like to note enormous progress made only very recently. Definitely, a lot of research is being invested to this field now, and we should expect even more spectacular results to be reported in close future.

Scheme 37



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