REVIEWS

The remarkable metal-catalysed olefin metathesis reaction

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Catalytic olefin metathesis—through which pairs of C=C bonds are reorganized—transforms simple molecules to those that are complex and precious. This class of reactions has noticeably enriched chemical synthesis, which is the art of preparing scarce molecules with highly desirable properties (for example, medicinal agents or polymeric materials). Research in the past two decades has yielded structurally well-defined catalysts for olefin metathesis that are used to synthesize an array of molecules with unprecedented efficiency. Nonetheless, the full potential of olefin metathesis will be realized only when additional catalysts are discovered that are truly practical and afford exceptional selectivity for a significantly broader range of reactions.

To appreciate the importance of catalytic olefin metathesis, we must consider the power of chemical synthesis. The ability to prepare molecules is crucial to advances in medicine, biology and materials science[1]. Chemical synthesis challenges and expands our understanding of the fundamental principles of reactivity and selectivity, and gives us the opportunity to examine special molecules that were previously non-existent or available in such small quantities that a study was not feasible—for example, anticancer epothilones[2,3] and anti-hepatitis C agent **43** (see below). A recent remark by the director of the National Institutes of Health is apropos: "One interesting result of the NIH Roadmap development process came when we surveyed scientists to find out what the stumbling blocks for biological sciences were. The number one stumbling block turned out to be synthetic organic chemistry"[4].

For synthetic chemistry to provide its full impact, certain advances must first be realized. One crucial area is catalyst discovery. Catalytic processes represent a degree of efficiency superior to those that require one or more equivalents of a reagent (ideally, one mole per cent catalyst or less should be used). Of particular significance is the identification of effective catalysts that are readily available, easy to handle, reliable, and promote transformations at high selectivity with a broad range of substrates with minimal waste generation. Catalytic olefin metathesis[5–10] is a ground-breaking advance that has significantly enhanced the power of chemical synthesis, and is likely to continue to do so.

Olefin metathesis and its importance

Olefin metathesis ('metathesis' from the Greek meaning 'change of position, transposition') reorganizes the carbon atoms of two C=C bonds (olefins or alkenes), generating two new ones; it promotes unique skeletal rearrangements, and is significant for several reasons. First, some olefins are easy to prepare and others require more effort to access. Terminal and some disubstituted alkenes are prepared with relative ease; tri- or tetrasubstituted olefins, on the other hand, present a challenge owing to higher levels of steric hindrance and complications associated with controlling *cis* and *trans* (or *E* and *Z*) selectivity. Olefin metathesis allows facile access from the easily prepared olefins to those that are cumbersome to access. Efficient and stereoselective synthesis of the more substituted olefins is an important and largely unsolved problem in synthesis. Second, olefin metathesis reactions either do not generate a by-product or only produce one, such as ethylene, which can be removed by evaporation[11]. Third, chemists routinely use olefins to interconvert molecules. Olefins are useful largely because they present the better of two worlds: stability and reactivity. Olefins are stable—they are typically stored indefinitely without decomposition. And yet, olefins contain a π-bond that is sufficiently reactive to be used in a wide range of transformations.

The repertoire of olefin metathesis catalysts. Olefin metathesis may be classified into three categories: cross, ring-closing and ring-opening metathesis (Fig. 1)[12]. Cross metathesis is the most pedagogically relevant version[13]. As shown in Fig. 1, with an appropriate catalyst, $C_1=C_2$ and $C_3=C_4$ can be transposed into $C_1=C_3$ and $C_2=C_4$. It is perhaps difficult to see, at first glance, why one set of olefins would be favoured; this is a key issue, as all olefin metathesis reactions are in principle reversible. The possibility that products might be re-converted to the starting materials dictates that chemists must design reactions that avoid back-tracking.

Another type, thus far the most widely used, is ring-closing metathesis (Fig. 1)[14]. Here, two terminal alkenes react with the catalyst to generate a cyclic olefin, releasing a smaller olefin ($C_2=C_4$ in Fig. 1). Ring-closing metathesis reactions can proceed to completion partly because volatile by-products are removed, trumping a reverse process.

Finally, there is ring-opening metathesis[15] (Fig. 1), through which a cyclic olefin reacts with a linear (acyclic) olefin, generating an

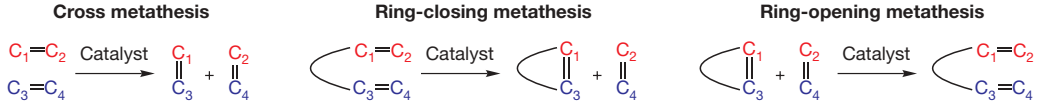

Figure 1 | Different types of olefin metathesis. Cross metathesis, ring-closing metathesis and ring-opening metathesis: each represents a different type of reaction and furnishes a different kind of product.

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acyclic diene. The driving force is the release of strain[16] in ring structures; this also ensures minimal reaction back to the cyclic compound. Reactions that involve cross metathesis are mechanistically more complex, and controlling such transformations can be difficult (versus ring-closing). To promote cross metathesis, the catalyst must fuse together two different cross partners; otherwise, homodimerization predominates. Such complications do not occur in ring-closing metathesis where an intramolecular process is often preferred over an intermolecular one (unless strained and entropically disfavoured rings are sought[17]).

Catalysts that make it possible. Some of the olefin metathesis catalysts that are widely used and have served as the basis for a range of other systems are shown in Fig. 2. Centre-stage is a molybdenum (Mo; ref. 18) or a ruthenium (Ru; ref. 19) atom. The Mo=C or Ru=C double bonds (a Mo alkylidene or a Ru carbene) serve as points of contact between the catalyst and olefins. As we will see, the metal centres are crucial to the properties of these catalysts. Although complexes of other metals (such as tungsten[18,20,21], rhenium[22] and osmium[23]) promote olefin metathesis, these exhibit lower stability and/or reactivity, and have not been as extensively investigated. Development of such catalysts, however, is a compelling future objective, because—similar to Mo and Ru systems—additional metal complexes are likely to provide unique or complementary reactivity and/or selectivity profiles.

Mo catalyst **1**[24], prepared and handled under inert atmosphere, is generally more active than Ru catalysts **2**[25–28] and **3**[29] (Fig. 2), which are stable to air and moisture. The activity of Mo and Ru catalysts are, to a large degree, complementary[18]. Ru catalysts may be used with substrates that carry an alcohol, a carboxylic acid, or an aldehyde, but can be rendered inactive in the presence of structurally exposed amines[30] and phosphines[31]; the reverse holds for Mo catalysts[18]. Metal complexes **1**–**3**, as well as a number of Ru-based derivatives[32–34], are commercially available.

Mo and Ru catalysts **4**–**6**[35–37] (Fig. 2) are chiral. Handedness, or chirality, is an attribute of many molecules of life; polypeptides, nucleic acids, carbohydrates, and numerous naturally occurring molecules that exhibit biological activity exist as a single enantiomer and consist of enantiomerically pure smaller units. A critical objective of modern chemistry is the development of catalysts[38] that promote the formation of chiral molecules of high enantiomeric purity (ideally >98% purity) from readily available and inexpensive achiral ones[39]. Catalysts **4**–**6** initiate reactions that favour formation of one enantiomer. Thus far, Mo-based chiral catalysts, one of which is commercially available[35], promote ring-closing metathesis with higher enantioselectivities for a wider range of substrates[18,36,40]; both classes are effective in enantioselective ring-opening/cross metathesis, affording carbo-[37,41] and heterocyclic products[42,43] (see below). The development of chiral olefin metathesis catalysts is less advanced than that of the achiral variants, and many important discoveries remain to be made. For instance, there are no effective chiral catalysts for enantioselective cross metathesis[41].

Catalytic ring-closing metathesis

A general pathway[44] illustrating how such transformations proceed is shown in Fig. 3A. All olefin metathesis reactions involve association of the metal with an olefin substrate[45–47]. It is in this crucial interaction that one significant difference between Mo- and Ru-based catalysts presents itself. A high-oxidation-state Mo centre (+6) is a Lewis acid that chelates with a Lewis basic olefin; in contrast, in Ru catalysts, it is the alkene substrate that serves primarily as a π Lewis acid[48,49].

Overall, the catalytic cycle (Fig. 3A) consists of an initiation phase (generation of the active complex) and a propagation phase (the active complex promotes additional cycles). Catalysis commences by a cross metathesis between an active carbene or alkylidene (M=C) and one of the two olefins of the substrate (**i**) to generate a metallacyclobutane (**ii**)[50,51]. The metallacyclobutane might revert to **i** and M=C (pathway a) or the other two bonds of the ring might be ruptured, furnishing **iii**, where the metal (M) is within the substrate (pathway b). Formation of another metallacyclobutane (**iv**) and its disintegration furnishes cyclic product **v** and $M=C_3$ (**vi**), which is the metal-bearing agent serving as the catalyst. What typically drives reactions is that the cyclic product (**v**) does not easily react with the active catalyst ($M=C_3$) to cause ring-opening metathesis.

The identity of the intermediates in the catalytic cycle is well understood[52]; it is, however, often unclear whether it is catalyst–substrate association (**i** and **vii** first chelate with the metal centre of M=C before conversion to **ii** or **viii**), formation of the metallacyclobutane[50,53] or its cleavage that is the irreversible, product- or

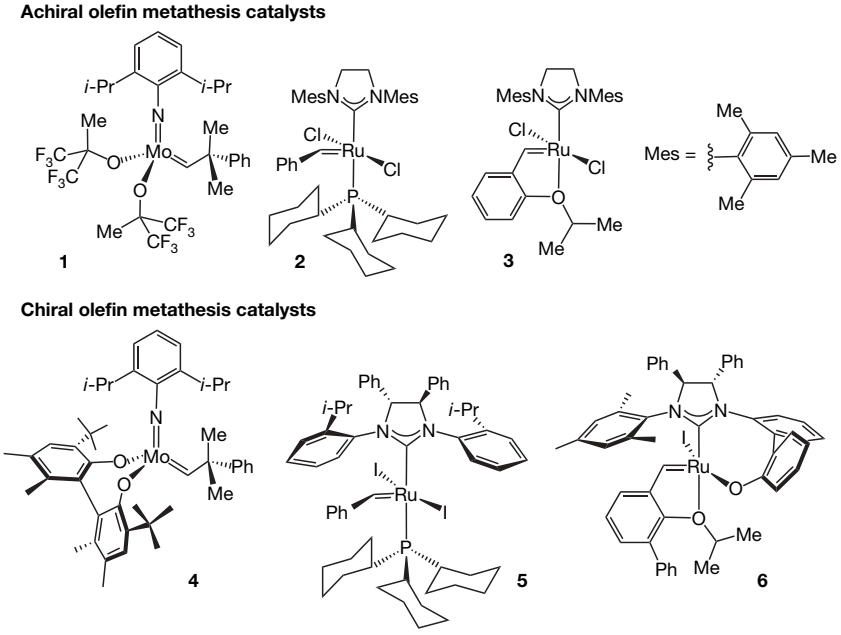

Figure 2 | Representative olefin metathesis catalysts. Catalysts **1**–**3** (top) are among the most commonly used achiral catalysts. Catalysts **4**–**6** (bottom) are chiral, and can react at different rates with two enantiomers of a substrate (kinetic resolution) or can convert an achiral molecule to a chiral one with preference for one of the two enantiomers (asymmetric synthesis). Mo-based catalysts **1** and **4** are air sensitive but generally more active than air-stable Ru-based catalysts **2**, **3** and **5**, **6**, respectively.

rate-determining step (Fig. 3A). It is a daunting task to predict a 'most effective catalyst' or to design—in the true definition of the word—one: what differentiates a selective process from one that is non-selective is a mere 2–2.5 kcal mol^{-1} difference in activation barriers (for example, rotation around the C–C bond of ethane requires only ~3 kcal mol^{-1}), and seemingly insignificant alterations in the substrate structure or conditions can change the energetics of the catalytic cycle (which step is rate-determining)[54]. These considerations indicate that seeking a truly 'general catalyst' is likely to be futile—different classes of substrates may require a different 'optimal' catalyst. Chemists address such challenges through invention of a class of catalysts (as opposed to one compound) that are easily modified to achieve maximum reactivity and/or selectivity. The more readily modifiable a catalyst class, the larger the number of available catalysts, and the better the odds of obtaining more desirable results[18].

There is little doubt that ring-closing metathesis has elevated the art and science of chemical synthesis[55,56]. Two ring-closing metathesis reactions that have been carried out for the synthesis of the large rings of two natural products are shown in Fig. 3B. The linear chain of **7**, with Lewis-basic and potentially catalyst-deactivating oxygen- and nitrogen-containing groups, is converted to the 14-membered ring lactam **8** by catalyst **1**[57]. In two additional steps, the product of ring-closing metathesis (**8**) is transformed to antifungal and anti-influenza agent fluvirucin B_1[58]. The volatile ethylene ($H_2C{=}CH_2$) is the by-product.

It is easy to appreciate the power of catalysis when one considers the alternative pathways—exits on a reaction highway either avoided or traversed reversibly. The challenge in any ring-closing is that a cross metathesis, such as generation of **9** (Fig. 1), represents a competitive route; the catalyst must be sufficiently active to reverse this 'wrong turn'. The two C=C bonds in **7** are not identical: one is the more accessible and reactive monosubstituted alkene. Formation of **9** is therefore of particular concern, since it arises from coupling of two molecules of **7** by a reaction of the less hindered olefins. How is it, then, that **8** can be prepared in 92% yield? The key lies in the reversibility of olefin metathesis. Substantial amounts of **9** are indeed formed, but catalyst **1** reverts **9** to **7**. Macrocyclic **8**, on the other hand, does not undergo further reaction (ring-opening); the central olefin of **9** is less hindered than the olefin in **8** (trisubstituted). The success of the seemingly straightforward closure of **7** to afford **8** involves several nuances. Efficient synthesis of the large ring depends on striking a balance among cross metathesis, a process that delivers the undesired coupling of two substrate molecules, ring-closing

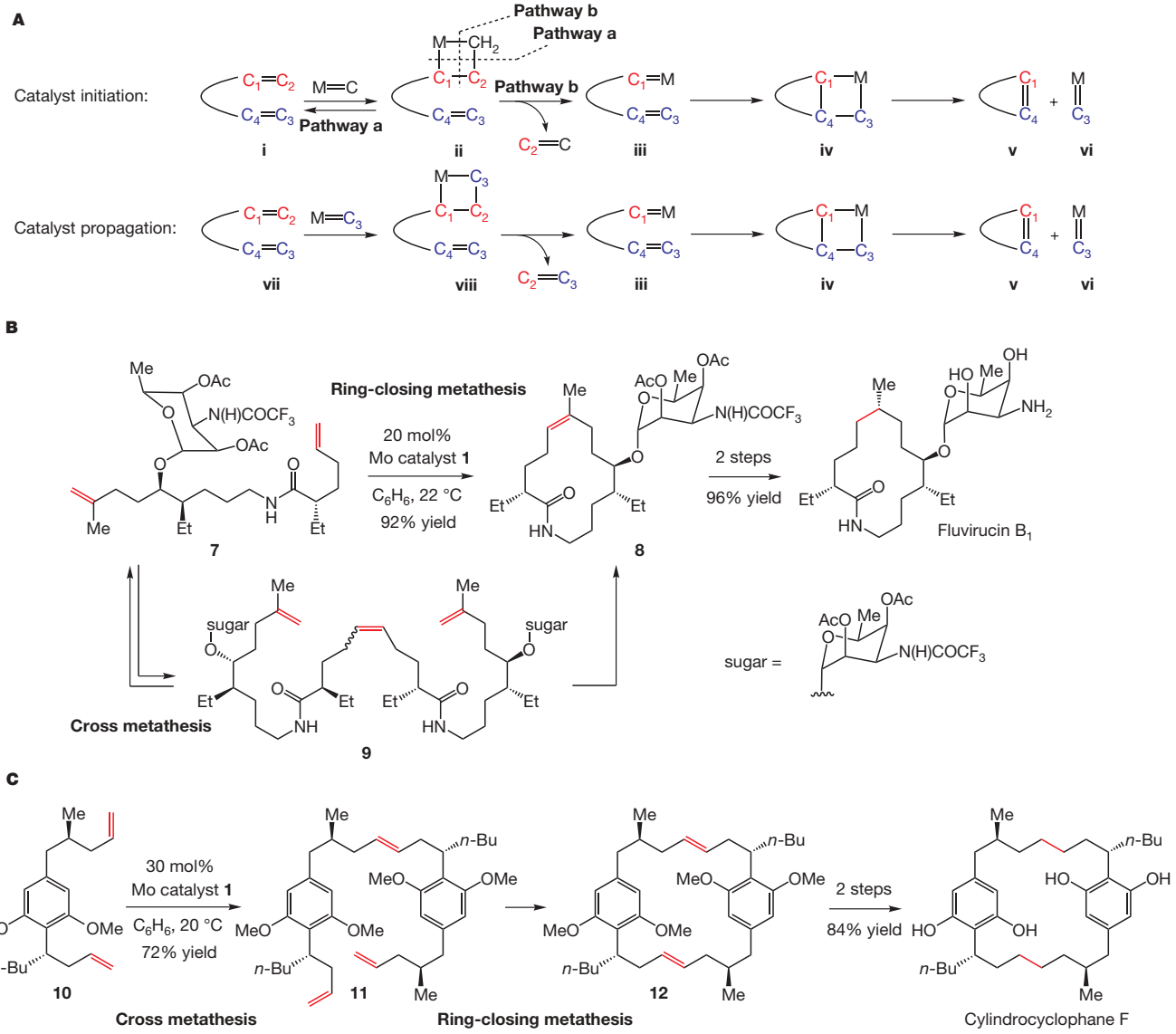

Figure 3 | The general mechanism for ring-closing olefin metathesis. This mechanism involves the intermediacy of metallacyclobutanes (**A**); also shown are two examples (**B** and **C**) that illustrate the power of catalytic ring-closing metathesis in the total synthesis of biologically active natural products (M = Mo or Ru). In both cases, the reversible nature of cross metathesis is critical to efficient synthesis of the desired macrocycles.

metathesis, a reaction that affords the desired product, and a ring-opening metathesis pathway that would dismantle the desired cyclic compound.

Another revealing example is the 'stitching' of two molecules of **10** to access 22-membered ring **12** en route to the cytotoxic agent cylindrocyclophane F (Fig. 3C)[59]. The homodimerization of **10** must transpire in the desired fashion, as the two olefins within each molecule of **10** are different. The coupling can occur in two ways: head-to-head or head-to-tail, and the head-to-tail is needed for the subsequent ring-closing metathesis that affords **12**. The successful synthesis of **12** is not due to preferable formation of **11** over the alternative head-to-head product—it is because ring-closing metathesis of **11** is more favoured. Detailed investigations reveal that the head-to-head product is generated but is converted back to **10**, which undergoes coupling to generate **11**. The reversible nature of olefin metathesis proves crucial again.

In the case of **8**, the olefin, generated through olefin metathesis, is erased by palladium-catalysed hydrogenation to establish the distal methyl-bearing stereogenic centre. To untrained eyes, fluvirucin B_1 or cylindrocyclophane F are structures that do not contain an olefin within their macrocycle, and the idea of using olefin metathesis to access these molecules may not be evoked. When a synthetic chemist contemplates a target from the perspective of olefin metathesis, she must choose, among various possibilities, where to place an olefin in the precursor substrate, all signs of which may subsequently be erased. In designing a route, she commits to a strategy that predicates the identity of the bonds that realize their union. The chemist makes a move, one that affects the others that will follow[1,60].

The total synthesis presented in Fig. 4 is based on the insight that the architecture of longithorone A can be born through coupling of two (nearly identical) smaller building blocks **16** and **19**[61]. Cyclizations of **13** and **17**, providing the 15-membered rings of **15** and **18** (Fig. 4) are catalysed by Ru complex **14**[62], an earlier version of **2** (Fig. 1). These ring-closing reactions involve an alkyne in processes referred to as enyne metathesis[63–65]. Products **15** and **18** are transformed to **16** and **19** such that these unsaturated macrocycles can be directed to participate in two separate Diels-Alder additions, courtesy of enyne metathesis products. The protagonists in the first act are identified in red: the 1,3-diene of **19** (red) reacts with the olefin of **16** (red) to join the two pieces while generating a cyclohexene (red). This is followed by another cycloaddition between the 1,3-diene (blue) and an olefin (blue) that resides within **16**.

Catalytic ring-opening and cross metathesis reactions

A general scheme illustrating the mechanism of ring-opening metathesis is depicted in Fig. 5. A cyclic olefin (**ix**) joins with a catalyst (M=C) to generate a metallacyclobutane (**x**), which may collapse to furnish a metal-containing intermediate **xi**. Acyclic **xi** can react with another acyclic olefin (C_3=C_4 versus cyclic olefin **x**) to yield another metallacyclobutane (**xii**). Rupture of **xii** furnishes the final product (**xiii**) and affords the active catalyst (**xiv**), which propagates additional cycles. The second olefin metathesis sequence, involving conversion of **xi** to **xiii**, constitutes a cross metathesis, and hence the concatenation of events that converts **ix** to **xiii** is referred to as ring-opening/cross metathesis. If the cyclic olefin proves more reactive than the cross partner, or if a cross partner (for example, C_3=C_4) is absent, **xi** can react with another molecule of **ix**. The resulting M=C transforms another **ix** and soon the active species romps through the substrate molecules, generating polymeric products. Such a process is referred to, appropriately, as ROMP (ring-opening metathesis polymerization). Alternatively, if the cross partner is more reactive (versus cyclic olefin), the major product arises from homo-coupling

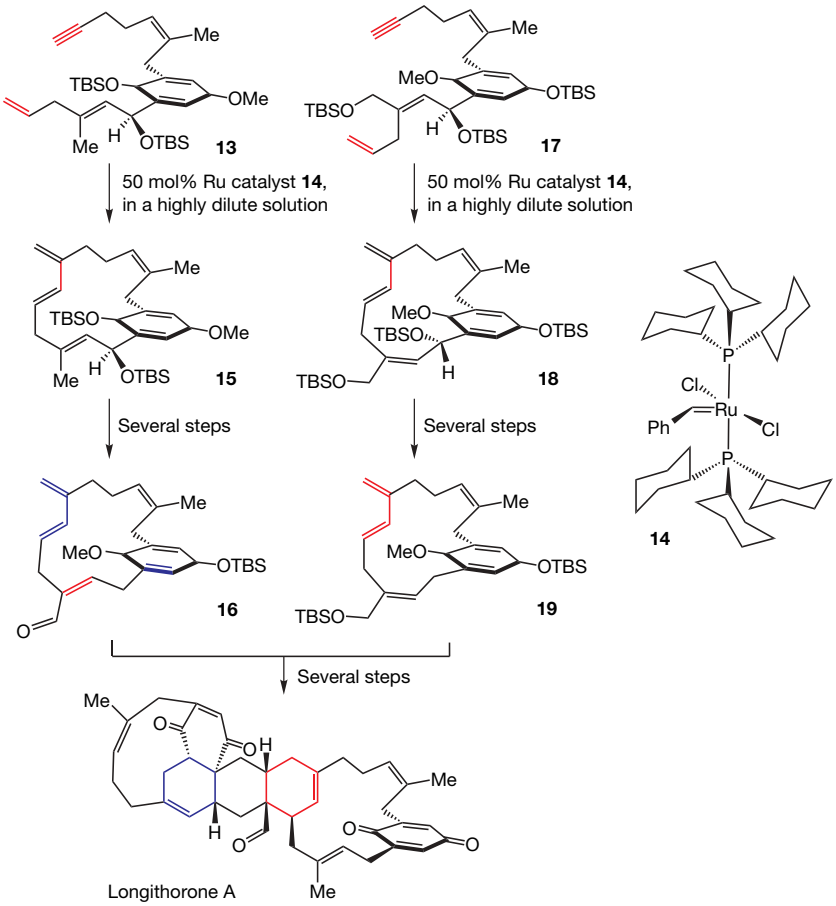

Figure 4 | A concise synthesis of longithorone A. This synthesis involves coupling of segments **16** and **19**, both of which were prepared by ring-closing ene-yne metathesis reactions of **13** and **17**, respectively. TBS (*t*-butyldimethylsilyl) is a common protecting group that masks alcohols.

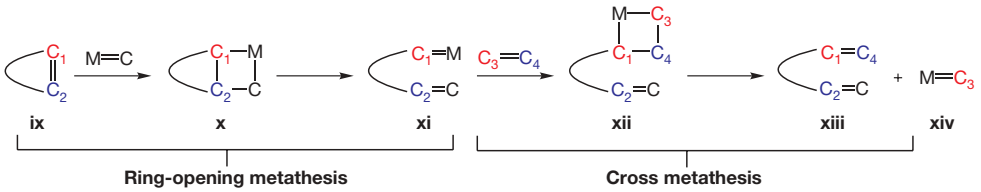

Figure 5 | General mechanism for catalytic ring-opening/cross metathesis. Ring-opening metathesis is initiated by the rupture of a cyclic C–C double bond (olefin) by a catalyst (M=C). This affords a new alkylidene (**xi**), which undergoes cross metathesis with another olefin to furnish the final product (**xiii**).

(cross metathesis). To achieve high yields of ring-opening/cross metathesis, the catalyst must react with the two substrates in the proper sequence with high precision. Such considerations pose demanding challenges in catalyst development. One recent approach involves catalysts that bear a stereogenic metal centre (for example, **6** in Fig. 2 and **49** below), leading to the intermediacy of two diastereomeric metal-carbene intermediates (M=C), each reacting preferably with the cyclic olefin or the acyclic cross partner[42,66].

Small cyclic alkenes are strained[16]—they contain a substantial amount of energy that can be released on rupture (up to ~55 kcal mol^{-1}; ~2 kcal mol^{-1} difference between two pathways means ~97% selectivity). Strain energies have been exploited to promote ring-opening/cross metathesis reactions[15,42]. Two examples are presented in Fig. 6. In a total synthesis of cytotoxic agent bistramide A[67], cyclopropene **20** participates in a catalytic ring-opening/cross metathesis with acyclic olefin **21** to yield **22**. In a subsequent cross transformation, the more accessible alkene of **22** (blue) is set up to react with another acyclic olefin (**23**) to furnish **24** (and gaseous ethylene as by-product). Two olefin metathesis reactions are therefore used to stitch three molecules—**20**, **21** and **23**—together, and, in short order, a complex molecule that constitutes a significant portion of bistramide A is fabricated.

In an enantioselective total synthesis of baconipyrone C[68], a siphonariid (isolated from false limpets, *Siphonaria baconi*) metabolite (Fig. 6), the plane of symmetry within achiral **25** is removed through a ring-opening/cross metathesis with styrene promoted by chiral catalyst **6** (Fig. 2), yielding heterocycle **26** with ~95% selectivity (89% enantiomeric excess). After conversion of **26** to **27**, another sequence involves conversion of **27** to **30** via **28** and **29**. A ring-closing olefin metathesis, this time promoted by achiral catalyst **3** (Fig. 2), furnishes allylic alcohol **30** en route to the target.

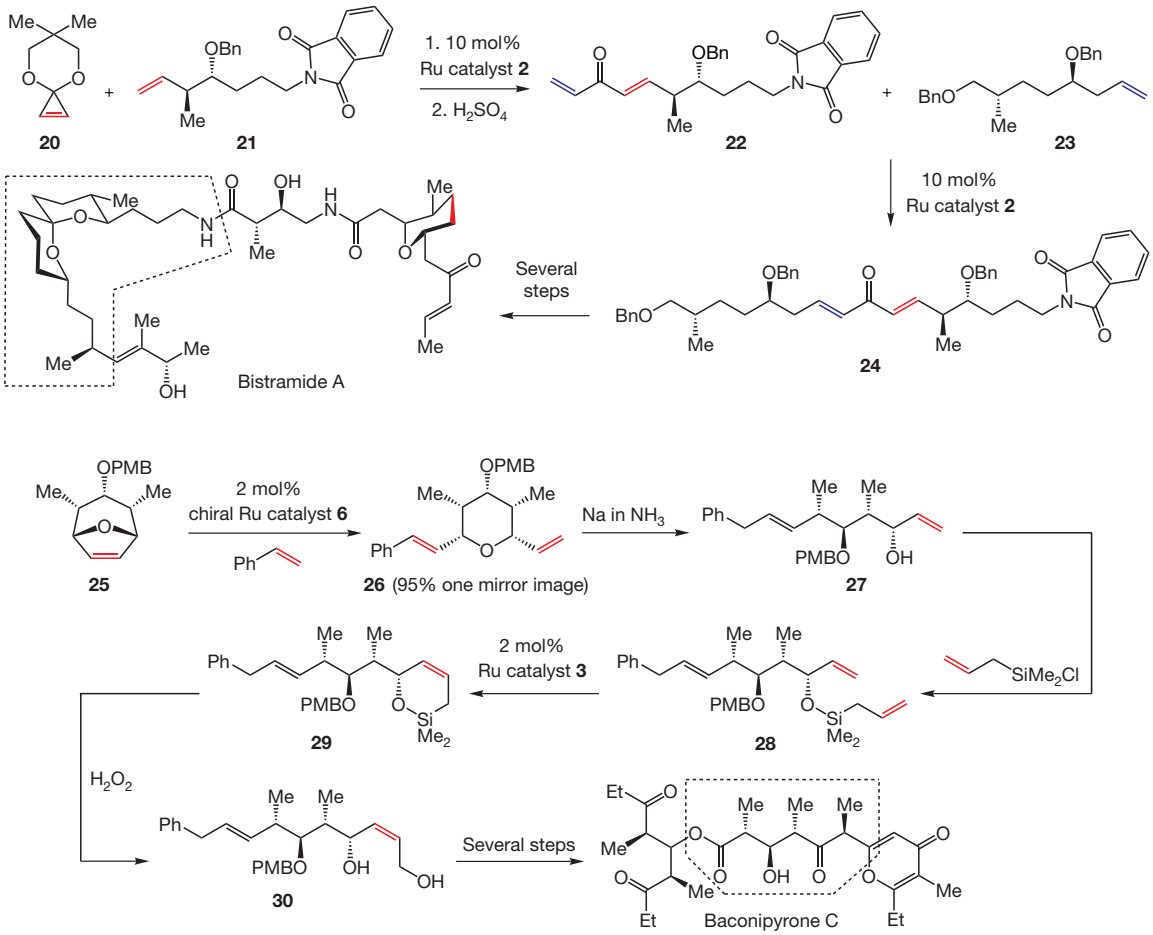

Figure 6 | Catalytic ring-opening/cross metathesis provides uniquely efficient pathways for synthesis of biologically active natural products. In the total synthesis of bistramide A, a Ru-catalysed ring-opening cross metathesis is followed by another cross metathesis to furnish **24**. In the total synthesis of baconipyrone C, a chiral Ru catalyst converts achiral **25** to pyran **26** with strong preference (95%) for one enantiomer. Bn (benzyl) and PMB (*p*-methoxybenzyl) are protecting groups that prevent alcohols from undergoing reaction. Dashed boxes represent segments of the target molecules prepared through catalytic olefin metathesis.

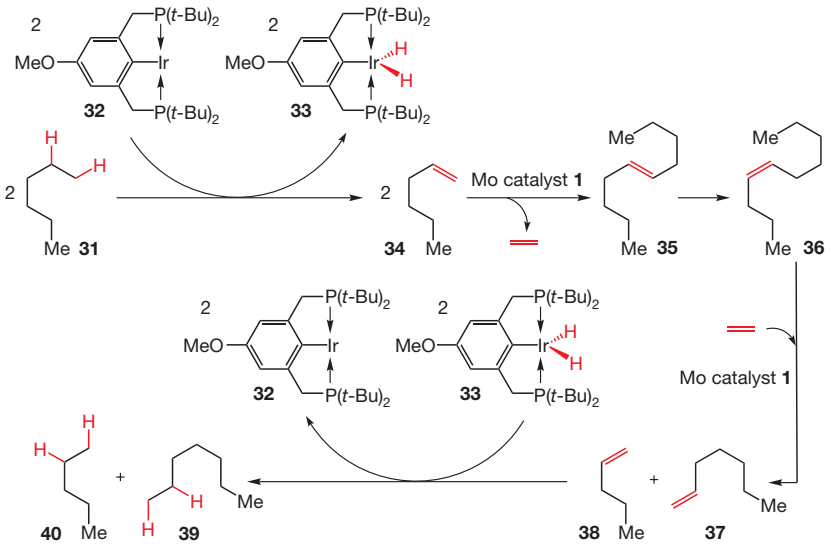

Figure 7 | Catalytic C–H activation is coupled with catalytic olefin metathesis for a net 'alkane metathesis' process.

Thus far, we have considered how, after ring-closing, ring-opening/cross or cross metathesis, olefins within the product might be masked by a subsequent reaction. The sequence in Fig. 7 illustrates a transformation that takes this 'vanishing act' to another level: although catalytic olefin metathesis is involved, neither the products nor the starting materials contain an olefin[69]. The alkenes needed are obtained in the course of the transformation by iridium-based catalyst **32**, which converts two equivalents of the saturated hydrocarbon (alkane) **31** to two of alkene **34** by C–H activation[70]; this process transforms **32** to iridium-dihydride **33**. Mo catalyst **1** (Fig. 1), present in the mixture, waiting for olefins to become available, connects with two molecules of **34** and transforms them to **35** and ethylene (cross metathesis). Alkene **35** can revert back to **34** after cross metathesis with ethylene, or, alternatively, its alkene may undergo isomerization to generate **36**, in a reaction that is also catalysed by iridium complex **32**. Alkene **36** participates in a Mo-catalysed cross metathesis with ethylene to produce two new terminal alkenes **37** and **38**, which can be converted to alkanes **39** and **40** by iridium-dihydride **33**, delivering back the hydrogens it borrowed from **31** to the olefins of **37** and **38**. The last reaction leads to re-formation of **32** from **33**, which moves on to afford alkene **34** and initiate additional cycles. One feature of this molecular choreography is that the sizeable iridium dihydride **33** deposits its two hydrogens on the terminal alkenes of **37** and **38** but not on the more hindered internal olefins of **35** or **36**. On the other hand, if **33** adds its hydrogen atoms to the olefin in **34**, substrate **30** is generated again and the catalytic cycle begins anew.

With a two-catalyst approach for alkane cross metathesis, will it be feasible to design a catalytic alkane ring-closing metathesis? In cases where a cycloalkane is desired, such a direct process could be more efficient than a two-step, alkene ring-closing metathesis/hydrogenation sequence. An inherent advantage of catalytic olefin metathesis is, however, the range of useful possibilities that the rich chemistry of olefins offers. Nevertheless, such considerations have led to the development of tandem catalytic reactions carried out in a single vessel, promoted by one catalyst and involving olefin metathesis reactions; Ru-catalysed olefin metathesis/hydrogenation and olefin metathesis/olefin isomerization are representative examples[71].

Catalytic olefin metathesis and a better quality of life

Through a select few examples (there are many more[55,72–76]), we have seen how catalytic olefin metathesis has allowed chemists to synthesize medicinally relevant agents in entirely new ways. The utility of this class of reactions extends beyond small-scale laboratory preparation. A catalytic ring-closing metathesis promoted by catalyst **42**[77], a precursor to **3** (Fig. 2), has been used by scientists at Boehringer-Ingelheim to prepare multi-kilogram quantities of **43** (Fig. 8), a complex molecule that is precursor to a potent anti-hepatitis C agent[78–80].

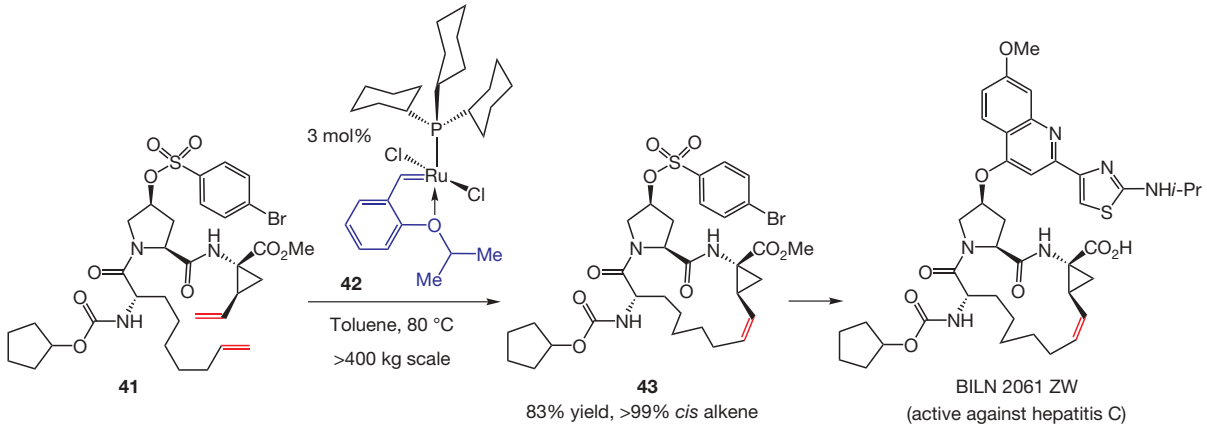

Figure 8 | Catalytic olefin metathesis has been used in the large-scale preparation of pharmaceutical candidates. An example is the potent hepatitis C protease inhibitor BILN 2061 ZW developed by Boehringer-Ingelheim. Macrocyclic intermediate **43** has been prepared in multi-kilogram quantities as a single C=C (olefin) isomer with high efficiency.

The influence of olefin metathesis has spread beyond biological chemistry[81]. Large-scale preparation of common organic feedstock chemicals and polymers is one area that has been affected. Polymers can be produced under mild conditions with commercial catalysts through ROMP processes. Commercially produced ROMP polymers include polyoctenamer (Vestenamer), polynorbornene (Norsorex) and polydicyclopentadiene[82] (polyDCPD, Metathene, Metton, Pentam, Prometa, Telene). Fully hydrogenated analogues of some of these polymers are available as well; Zeonex is a saturated ROMP polymer of substituted polynorbornene.

Perhaps the most widely commercialized ROMP polymer is polydicyclopentadiene, which is prepared from *endo*-dicyclopentadiene—a by-product in naphtha crackers[83]. Various 'ill-defined' olefin metathesis catalysts are used to manufacture polydicyclopentadiene. For example, in a process that affords Telene, tetrakis(tridodecylammonium)octa-molybdate serves as a precatalyst along with the activating mixture that consists of $EtAlCl_2$, $SiCl_4$ and propanol. A crucial advantage of well-defined Ru-based catalysts is their high degree of polymerization, an attribute that allows for removal of the odour that emanates from the un-reacted dicyclopentadiene monomer in polydicyclopentadiene[82]. Polydicyclopentadiene is easily castable and mouldable by reaction injection moulding technology; moreover, owing to its durability and resistance to corrosion, polydicyclopentadiene has found a wide range of applications in heavy machinery manufacturing (for example, agricultural equipment).

Although numerous polymers are used in the manufacturing of high-end sporting and recreational goods, day-to-day items, medical instruments and electronics, and have applications in optics, access to other ROMP polymers requires development of more efficient and 'smarter' catalysts. Within this context, Chen has devised an approach to the synthesis of alternating copolymers that is based on differential reactivity of diastereomeric carbene intermediates in ROMP processes[66]. These transformations are promoted by complex **49**, which bears a stereogenic Ru centre (hence the involvement of stereisomeric carbenes). Cyclooctene is thus co-polymerized with norbornene to afford an alternating copolymer, whereas copolymerization of these monomers under standard protocols delivers only a random copolymer. Chen's method is proof-of-principle; future research is required to address the need for active catalysts that yield a variety of alternating ROMP copolymers.

Block copolymers are poised to have a significant impact on nanotechnology. One approach to effective synthesis of these macromolecules involves ROMP processes promoted by rapidly initiating olefin metathesis catalysts. A new application for block copolymers, disclosed by General Electric, involves an inorganic-organic block copolymer of polynorbornene-decaborane as a single-source ceramic precursor, which was prepared by co-polymerization of norbornene with 6-(norbornenyl)decaborane[84,85]. This copolymer was subsequently converted to nanostructured boron carbonitride and mesoporous boron nitride. In another development, Nuckolls has shown that a functionalized Ru-metal surface may catalyse olefin metathesis[86]. Thus, ROMP on such a surface could furnish conducting polyene nanowires.

The robustness of the ROMP polymers, and of the catalytic processes used to prepare them, has allowed the ROMP reaction to be incorporated into manufacturing methods. For example, olefin metathesis has been used in the design of self-healing materials[87]. Cracks, resulting from wear and tear, that appear in structural polymers can be made 'self-healing' by incorporation of small vesicles of dicyclopentadiene monomer, a highly effective ROMP substrate, within the material in question, together with small amounts of an olefin metathesis catalyst. If microcracking occurs, vesicles of monomer interact with the catalyst to elicit fast polymerization, resulting in formation of a robust polydicyclopentadiene plug in the place of the crack.

Challenges that lie ahead

Many critical discoveries in catalytic olefin metathesis remain to be made. One area relates to the development of more robust yet active catalysts that are easily prepared and provide exceptional control of stereochemistry. Discovery of catalysts that allow for control of olefin stereoselectivity to obtain the thermodynamically less favoured *cis* disubstituted olefins, or those that promote formation of *E* or *Z* trisubstituted alkenes, is a significant challenge, and would constitute a major contribution to olefin metathesis. Identification of chiral catalysts that furnish high enantioselectivity for a range of substrates

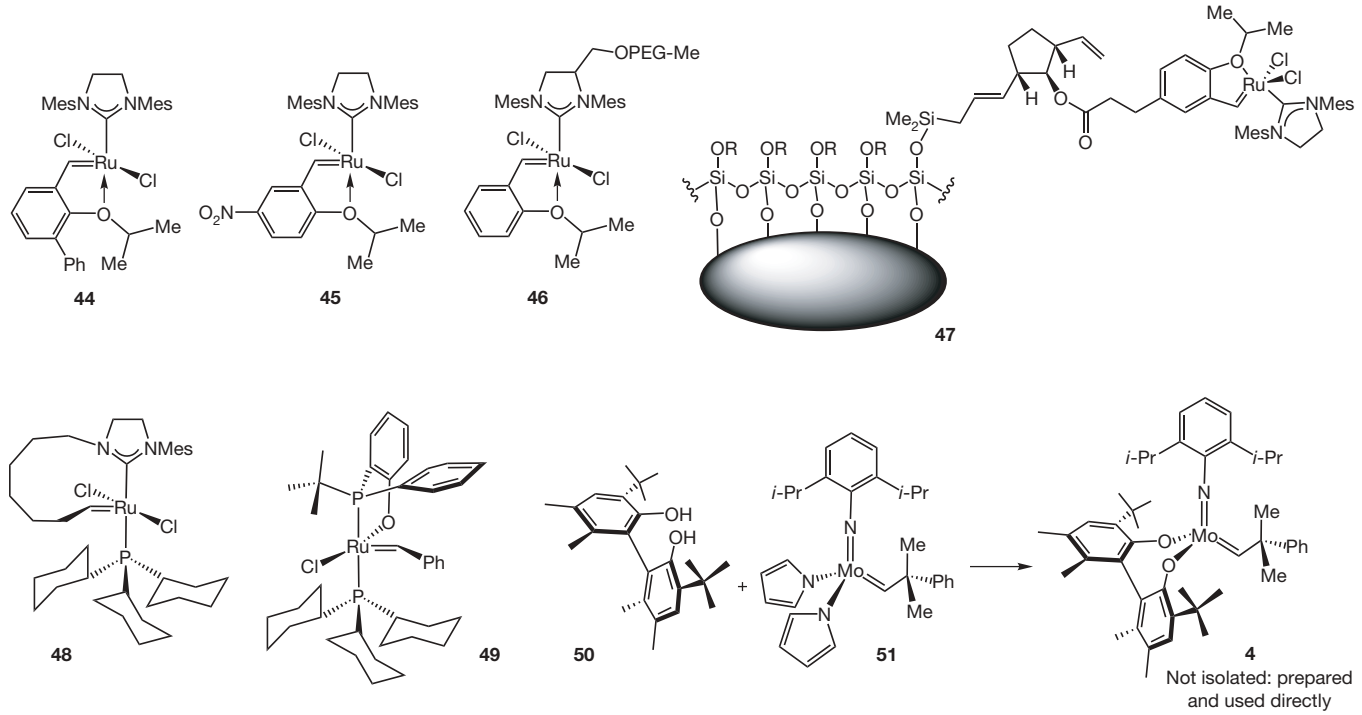

Figure 9 | More recent and modified variants of Ru-based olefin metathesis catalysts 44–49 and an easier way to access a range of chiral Mo catalysts. PEG, poly(ethyleneglycol).

and reaction classes, such as enantioselective cross metathesis or enyne metathesis, are exciting problems that are yet to be addressed.

Although many of the transformations presented above furnish desirable products, the amount of catalyst required for an efficient, cost-effective process is too high. In certain cases, as much as 50 mol% (half the amount of the substrate) of a catalyst is needed (for example, Fig. 4): but even a 3% loading is considered excessive for a 'real-world' industrial process (for example, Fig. 8). High loadings are often the result of less than optimal catalyst lifetimes. Catalyst efficiency is, therefore, about more than simply faster rates, or high turnover frequency—it is crucial that high turnover numbers are achieved. Discovery of active and selective catalysts that are more robust will require a detailed understanding of often unexpected and abstruse deactivation pathways[88].

Removal of trace metal impurities from olefin metathesis products is another complication of note, particularly in cases where compounds will be used in clinical trials. This brings us to the need for catalysts that can be easily recovered and re-used; effective catalysts bound to polymeric surfaces can minimize impurity levels and are economically attractive[89,90]. In many olefin metathesis reactions that involve formation of large rings, high-dilution conditions are required, rendering the use of such processes difficult and prohibitively expensive in larger industrial-scale conditions. Catalysts designed to discourage competitive homodimerization of two substrate molecules (versus cyclization of one substrate molecule) are therefore needed.

With better catalysts, the currently untapped power of olefin metathesis will give rise to increasingly exciting applications. New-generation catalysts with improved properties are beginning to emerge. Notable examples are modified Ru catalysts **44**[91] and **45**[92] (Fig. 9), which can in some cases furnish faster reactions than the parent complex **3** (but, at times, this comes at the cost of lower catalyst stability), or those that can be used to catalyse reactions in water (**46**)[93]. Ru catalysts have been attached to sol-gel glass surfaces to give 'tablets' (**47**); when the tablets are placed in solution, reaction with substrates causes catalyst release, leading to efficient reactions[94]. The tablets can be removed simply with a pair of tweezers (no filtration and washing) and re-used up to 20 times. Catalyst **48** has been used to synthesize cyclic polymers by procedures that do not require linear precursors[95]. The unique features of complex **49**, which, similar to **6**, contains a Ru stereogenic centre, have already been discussed[66]. An important area of research involves development of highly reactive, but sensitive, catalysts by user-friendly *in situ* preparation methods that begin with relatively easy-to-handle precursors (**50** and **51** to give chiral Mo catalyst **4**)[96].

Nature presents us with a range of architectures that are diverse in size, complexity and function. Chemical synthesis—accessing molecules revealed to us by our imagination—is crucial to our ability to produce compounds that are not found in nature, but are perhaps equally as enriching. Catalytic olefin metathesis is a component of making such dreams come true. There is, however, far more that we cannot do. The little that we can do is in need of substantial improvement. To consider catalytic olefin metathesis, or chemical synthesis, a consummated field would be akin to suggesting to Henry Ford that his model T was the be-all and end-all as far as automobiles are concerned.

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