Ruthenium-Catalyzed Ring-Closing Metathesis: Recent Advances, Limitations and Opportunities

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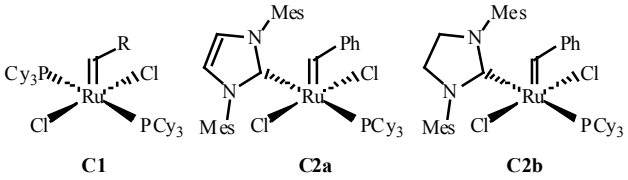
Abstract: Recent advances in ruthenium-catalyzed ring closing metathesis are discussed, in context of both substrate and catalyst parameters. As well as thermodynamic (substrate) constraints on ring-closing, root causes and effects of non-ideal catalytic performance are examined. Key substrate parameters are outlined, with a particular focus on the balance between oligomerization and ring-closing in RCM macrocyclization reactions. Advances in catalyst design are examined from a mechanistic viewpoint, including initiation requirements, catalyst deactivation, and opportunities resulting from incorporation of pseudohalide ligands. An overview of methods for reducing ruthenium residues in organic products to ppm levels is presented.

1. INTRODUCTION

Over the past decade, olefin metathesis has emerged as an exceptionally powerful tool for carbon-carbon bond formation, largely owing to advances in the design of well-defined molecular catalysts [1]. Ring-closing metathesis (RCM) and cross-metathesis (CM) reactions have had major impact in organic synthesis, and feature as key steps in an increasing number of natural product syntheses [2-13]. While the Group 6 catalysts pioneered by Schrock have long set the benchmark in terms of metathesis activity and selectivity [14-16], ruthenium systems (beginning with the Grubbs catalyst **C1**; Fig. (**1**)) have steadily gained ground in terms of activity [17]. The growing dominance of Ru-catalyzed metathesis stems in large part from the ease of handling these late-metal catalysts, which are much less oxophilic than the Group 6 systems, less susceptible to decomposition by air, water, and certain polar functionalities, and which exhibit improved thermal stability [18]. They can thus be deployed in much less stringently controlled reaction conditions, and with a wide range of functional groups. This robustness should not be overstated, however: while many of the precatalysts exhibit reasonable stability toward oxygen, particularly in the solid state, the *active* catalyst is oxygen-sensitive [19-22]. In addition, an increasing number of reports describe sensitivity toward protic functionalities (particularly allylic alcohols [23-25] and alcohol solvents) [26-29]. A susceptibility to poisoning by soft donors such as phosphine or sulfide groups has been suggested [5,15], which may inhibit, if not necessarily arrest [30,31], metathesis.

Advances in design of ruthenium catalysts up to 2001, including development of "second generation" systems containing N-heterocyclic carbene (NHC) ligands such as **C2**, have been amply reviewed [1-3,32-36], and will not be discussed in any detail here. Applications of olefin metathesis in organic synthesis are summarized in a recent Handbook [1]. Cogent overviews of the applications of RCM [2-5] in organic synthesis have appeared: of these, Armstrong's review gives a particularly useful analysis of the scope and limitations of early and late-metal catalyst systems, much of which remains relevant to catalysts subsequently developed [5]. Other recent reviews describe synthesis of specific target classes *via* RCM: these include medium-sized rings [37,38], heterocyclic rings containing phosphorus [6], sulfur [6,39], oxygen [7], or nitrogen [7]; and biologically relevant targets, including the epothilones [9], carbohydrate derivatives [10], several natural products [2,8], and macrocycles containing (*E*)-alkene units [40]. Overviews of domino [11,12] and tandem [41-44] metathesis strategies have also recently appeared (for mechanistically-based definitions of these and related terms, see Ref. [41]). This review will focus on recent developments in Ru-catalyzed RCM. Current limitations and opportunities for advances in terms of lifetime and selectivity will be considered from a mechanistic standpoint, as will related issues of catalyst deactivation and removal. In the following sections, Ru catalysts and complexes will be distinguished from organic species by use of a parallel numbering scheme, in which they are designated with the prefix **C**.



C1 **C2a** **C2b**

Fig. (1). Prototypical Ru metathesis catalysts: the Grubbs catalyst, **C1**, and second-generation catalyts containing an NHC ligand.

2. MECHANISTIC CONSIDERATIONS IN METATHESIS

2.1. RCM and Competing Metathesis Manifolds

The Chauvin mechanism for olefin metathesis [45] involves a sequence of [2+2] cycloadditions and retro-additions, in which the key intermediate is a

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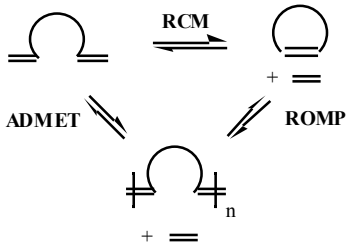
metallacyclobutane species. Each step of the catalytic cycle is in principle reversible (Scheme **1**), resulting in an equilibrium mixture of olefins unless a bias can be exerted to drive the reaction in a chosen direction. Ring-closing metathesis of dienes is entropically favoured by the formation of two olefinic products from a single diene precursor. Where both olefinic groups in the diene are terminal, one equivalent of ethylene is formed for each cycloalkene, and ring-closing is driven by loss of volatile ethylene. Cross-metathesis, or "acyclic diene metathesis" (ADMET) [46] of terminal olefins is also favoured by loss of ethylene: factors that can ultimately bias metathesis in favour of RCM products are described below. Steric parameters favour metathesis of α,ω-olefins over internal olefins, as does the decreased volatility and increased solubility [47] of olefinic coproducts heavier than ethylene. Retention of the released olefin in solution increases the probability that it will participate in ring-opening – ring-closing equilibria.



Scheme 1.

The rate, products, and selectivity of RCM processes are determined by a subtle interplay of substrate and catalyst parameters. Substrate parameters, of course, determine whether a target reaction is thermodynamically feasible (though tandem and domino catalysis offer interesting possibilities for driving thermodynamically disfavoured reactions by coupling them with more favoured processes). Reaction *rates* and product selectivity are determined by the interaction of catalyst and substrate properties: the structure-activity relationships are very complex and remain poorly understood. Non-ideal catalyst behaviour, though frequently overlooked, also plays a key role: discussion of this point will be deferred to Section 3.

2.2. Effects of Ring Size

2.2.1. Model Lactones

The rate of ring closing for uncatalyzed reactions is determined largely by strain in the nascent ring system, and the probability of end-to-end encounter [48]. Both contribute to activation energy, the latter owing to the entropic cost of freezing the disordered open chain into the ring-shaped transition state. Strain results principally from imperfect staggering and transannular strain between atoms forced into proximity from opposite sides of the ring, though early force-field calculations on cycloalkanes suggest that bond angle deformation makes a further, smaller contribution [49]. As a cumulative effect of these factors, the activation enthalpy is high for very small lactones (3 members), drops sharply for 4-7 membered lactones, and increases again for medium-sized rings (8-9 members), in which transannular interactions emerge. Further increases in ring size decrease ring strain, and $\Delta H^{\ddagger}$. While the presence of additional heteroatoms or unsaturation modulates total strain (as will the presence of a transition metal), these general trends apply to a wide range of ring systems [48].

For cyclization of small chains, the high probability of end-to-end encounter offsets the loss of rotational freedom in the molecular backbone. As chain lengths increase, however, the probability of intramolecular chain-end encounter drops, while entropic costs associated with loss of rotational freedom in the disordered chain upon ring-closing increase (particularly in the intermediate size regime). $\Delta S^{\ddagger}$ for ring-closing thus decreases with increasing chain size, although this decline ultimately levels off, probably owing to an increase in out-of-plane bending, which can compensate for constraints on internal rotation. At constant concentration, intermolecular reactions become more favourable with increasing chain length, both because of encounter probabilities, and because the loss in translational entropy associated with polymerization becomes less acute with increasing (monomer) chain length, to the point where it may be outweighed by the positive torsional and vibrational entropy resulting from the conformational mobility of the polymer chain. In synthesis of larger rings, high dilutions are commonly employed in order to promote cyclization, over intermolecular coupling. A kinetic bias is also expected, given the first-order dependence of ring-closing on diene concentration, vs. the second-order dependence of oligomerization reactions (however, for an examination of the validity of this proposition, see Section 2.3). The activation enthalpy and entropy required for uncatalyzed cyclizations to form 3-18-membered macrolactones were quantified by Illuminati and Mandolini, and used to predict relative rates of ring-closing as a function of ring size (Fig. (**2**)) [48].

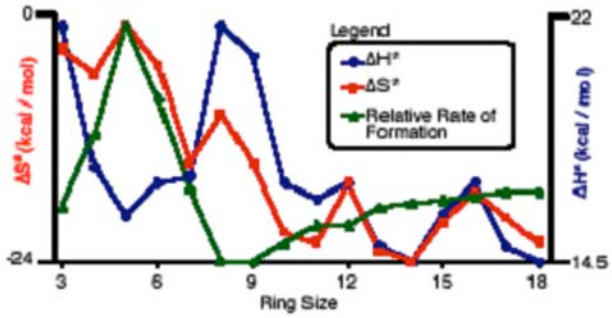


Fig. (2). Activation energy parameters and relative rates of (uncatalyzed) ring closing for saturated macrolactones [48].

2.2.2. Ring Size and RCM Rates

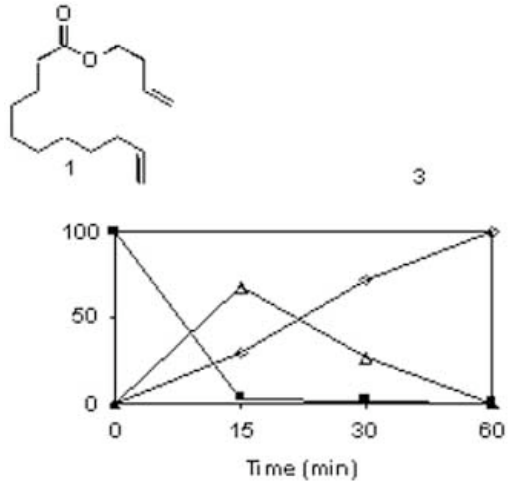
General trends in rates of RCM accord well with the analysis above. RCM is fastest for small rings, for which both enthalpic and entropic factors are favourable. Ring-closing to form conformationally unbiased rings of 8 to ll members is problematic: indeed, ROMP is entropically and enthalpically favoured for cyclooctene [50a]. As the size of a (monocyclic) ring increases to 11 members and more, conformational costs are relaxed, but encounter probabilities also decrease, and RCM rates remain much slower for macrocycles than small (5-6-membered) rings. Slow rates of metathesis can translate into lower yields because of the limited lifetimes of the Ru catalysts (Section 3). The reversibility of the various metathesis manifolds can also

enable re-opening of rings, such that oligomers may be formed by cycloolefin ROMP (ring-opening metathesis polymerization), as well as ADMET of the diene starting material. An equilibrium can thus be established between macrocycles and oligomers (including cyclooligomers formed by backbiting [50,51]; see next section). In the extreme of high concentration (0.7 M and higher), Hodge and Kamau reported entropically-driven ROMP of macrocycles with 21-84 ring atoms [52].

In view of the analysis above, it is unsurprising that RCM and ADMET are often regarded as competing reaction manifolds. Macrocycle synthesis is almost invariably carried out at elevated temperatures, as well as high dilution, in order to maximize thermal weighting of the entropic parameter, and to overcome the unfavourable effect of dilution on reaction rates. Routine protocols minimize oligomerization at the cost of experimental convenience: low diene concentration is achieved by slow, dropwise addition of substrate to the refluxing solvent, and because the lifetime of the Ru catalysts is short at elevated temperatures, dropwise addition of catalyst is also advisable. Despite such efforts, ADMET *dimerization* remains favoured for unsymmetrical dienes in which one partner is rendered less reactive by electronic or steric effects [53]. Recent evidence discussed in the next section, however, suggests that even for symmetrical α,ω-dienes, ADMET oligomerization may be both more common, and potentially less detrimental, than has generally been recognized.

2.3. Experimental Evidence for Macrocycle formation *via* ADMET-Backbiting RCM

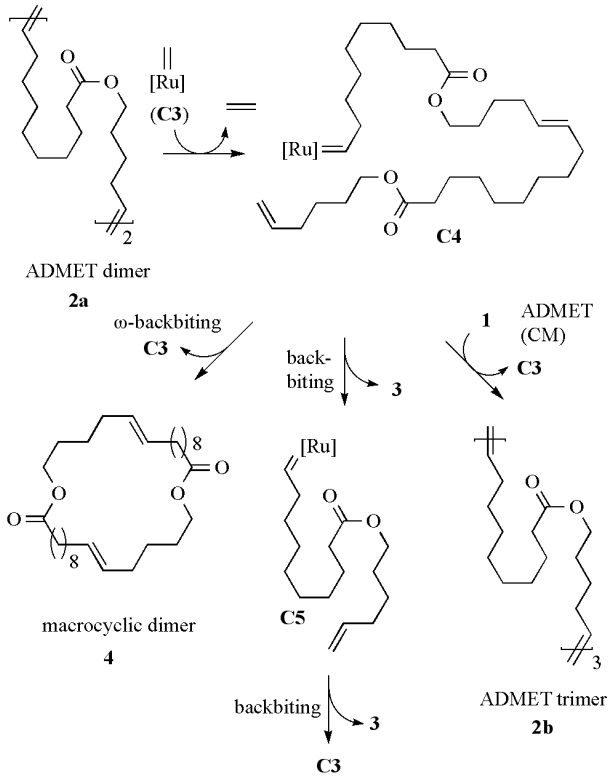
In model studies directed at RCM of diene **1** *via* catalyst **C2a**, we recently reported that ADMET was *kinetically* favoured even on use of high dilutions (5 mM) and elevated temperatures [54]. Importantly, however, this did not interfere with formation of macrocycle **3** (Scheme **2**), even where the efficiency of loss of ethylene was maximized. Quantitative GC analysis, using response factors independently measured for **1** and isolated **3**, revealed up to 70% loss in the total GC integration after 15 minutes, but ultimate yields of **3** approached 100%. MALDI analysis enabled identification of the "missing" material as oligomeric chains containing up to twelve repeat units.



Scheme 2.

The observation that near-quantitative macrocycle formation is *preceded* by significant ADMET suggests that the dominant pathway for macrocycle formation involves reinstallation of a metal endgroup on the oligomer, followed by degradation of the oligomers *via* backbiting. This can be recognized as an example of classic "oligomerization-cyclodepolymerization" behaviour [55], although its predominance even at high dilution is an unexpected feature. Concentration-dependent ring-chain equilibria have been discussed extensively in the ROMP literature [50,56-58]. Of particular interest in the present context, cyclodepolymerization of polybutadienes occurs *via* thermodynamically favoured elimination of the smallest rings, or "cyclotrimers", at high dilution [57,58], as predicted by Jacobson-Stockmayer theory [59,60]. Given these precedents, the relevance of ring-chain equilibria to RCM reactions has been surprisingly little discussed. In a notable exception, Grubbs and coworkers employed alkali metal ions as templates to aid in metathesis decyclopolymerization of linear polyethers [61]. Solely ADMET oligomers were observed at a diene concentration of 1.2 M, but crown ethers were produced at 0.02 M in the presence of the templating ion.

Cyclization of the oligomers of **1** to afford macrolactone **3** does not require a template, but occurs at rates that are highly catalyst-dependent (see later) [54]. High yields of macrocycle can be obtained, providing that the catalyst lifetime is sufficient. The proposed CM-backbiting RCM sequence is shown in Scheme **3**: for simplicity, we illustrate the major reactions beginning with the ADMET dimer **2a**,



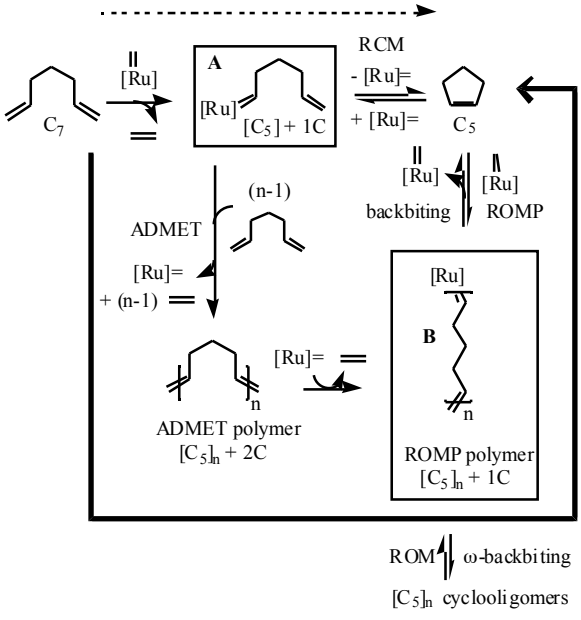
Scheme 3. Pathways for reaction of ADMET dimer (regiochemistry arbitrarily represented). **C3** = $RuCl_2(L)(PCy_3)(=CH_2)$ (**C3a**: L = PCy_3; **C3b**, L = NHC).

and omit reverse reactions. The key intermediates are Ru-alkylidenes of type **C4**, formed by reaction of methylidene **C3** with dimers, trimers, etc. Intramolecular (backbiting) attack on the internal olefin within **C4** eliminates one equivalent of macrocycle product, and forms Ru-alkylidene **C5**, shorter by one repeat unit than **C4**. The ADMET oligomers are thus not side-products, but intermediates formed en route to cycloolefin products. A similar mechanism is implicit in both the crown ether example above,[61] and in reports of ADMET dimerization using one, comparatively unreactive catalyst, but subsequent production of macrocycle by treating the isolated dimer with a more reactive catalyst [53a,62,63].

Intermediate **C4** can also, of course, undergo ADMET oligomerization *via* intermolecular condensation with further diene. That such processes are kinetically favoured, even at high dilution and elevated temperatures, is evident from the complete consumption of diene prior to any significant buildup of macrocycle product (Scheme **2**). This presumably reflects the reorganization energy required to place the internal olefin in proximity to the alkylidene, and the steric barrier to reaction with internal olefin [64], vs. a sterically unencumbered α,ω-diene.

Extrusion of macrocycle in the cyclodepolymerization reaction requires intramolecular cross-metathesis of the metal alkylidene with the proximal olefinic site. Larger ring sizes were not observed at dilutions of 5 mM. Consistent with Jacobson-Stockmayer theory, however (vide supra), cyclooligomeric byproducts were observed at higher concentrations (10 mM), as also reported in other work [62]. Interestingly, new pseudohalide catalysts (Section 4.2) show complete conversion to the macrocycle within 15 minutes [65]. Whether this represents improved selectivity for RCM over ADMET, or simply faster backbiting, is as yet unclear.

A simplified schematic summarizing the relationships between the various metathesis manifolds is shown in Scheme **4**. Reactions evolving ethylene are represented as irreversible. The relevant pathways are illustrated for reaction of a Ru methylidene species (the resting state in RCM of α,ω-dienes) with 1,6-heptadiene as an idealized substrate, chosen as a convenient "stand-in" model to facilitate explicit atom tracking. Evident from this picture is the convergence on Ru-alkylidene intermediates that can undergo ADMET, backbiting RCM, or (depending on concentration) [51,52] ROMP. The findings above indicate that the ADMET pathway indicated with a bold arrow is kinetically dominant, irrespective of reaction temperature, even at high dilution. Importantly, however, this is not a detriment to macrocycle formation. Indeed, it may be advantageous, given the longer lifetime of Ru-alkylidene, vs. methylidene, species [66,67] (Section 3.2): following reinstallation of the Ru endgroup on the ADMET chains, macrocycle yields will be determined *only* by the lifetime of alkylidene **B**, with the rate of macrocycle formation being controlled by the rate of intramolecular backbiting. While exploration of a broader range of ring sizes and architectures is clearly warranted, this mechanistic picture leads to the intriguing inference that the cumbersome synthetic protocols currently employed to minimize ADMET during macrocycle synthesis may be unnecessary.



Scheme 4. Integrated schematic showing relationship between different metathesis manifolds. Bold arrow indicates favoured path for diene **1**; dashed arrow indicates direct RCM.

2.4. Conformationally Directed RCM

In a recent study describing the synthesis of bicyclic lactones by RCM, Rodriguez et al. noted a steady decrease in yield as ring sizes increased from six to 14 members (Fig. (**3**)), with competing formation of polymeric "byproducts" [68]. The results outlined in the previous section suggest that the reaction time may be a key parameter determining the ultimate yield of cyclic products from oligomeric intermediates. Nevertheless, the high yields found for the typically challenging eight- and nine-membered rings, vs. the 14-membered ring, illustrate the value of conformational constraints in the synthesis of medium-sized rings. Maier has summarized a number of other cases in which cyclic conformational constraints help to promote RCM [37]. Examples include the synthesis of benzo-fused eight-membered heterodicycles [69,70] and, notably, construction of the nine-membered core of ciguatoxin, a marine natural product [71]. The precursor in the latter chemistry (**10**, Scheme **5**) contains an ether linkage flanked by rigid fused rings: this functions as a molecular hinge to align the dienes, enabling selective, albeit slow, RCM.

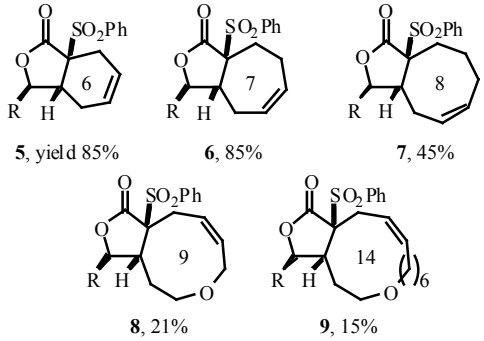
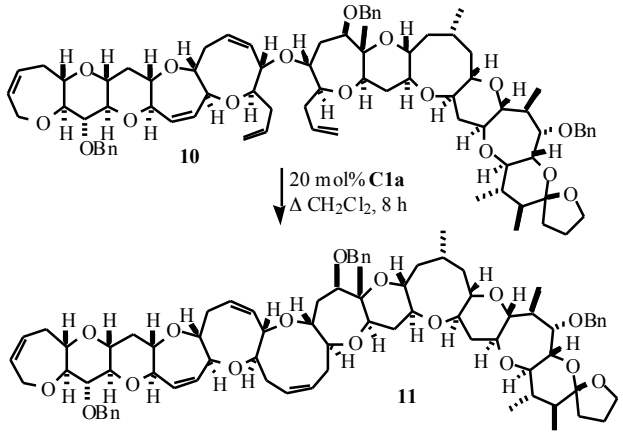


Fig. (3). Ring size and RCM yields for α,β-fused γ-lactones.



Scheme 5.

Conformationally *flexible* RCM targets can be challenging. A common strategy directed at introduction of acyclic conformational constraints involves incorporation of geminally-disubstituted substrate, in order to exploit the gem-dialkyl [72] and Thorpe-Ingold effects (Fig. (**4**)) [73]. Both increase the probability of encounter between the metal alkylidene and the subtended olefin, increasing the rate and selectivity for RCM. Forbes et al. showed that these effects can be used to select for RCM of favoured (five- and seven-membered) ring sizes over ADMET even in neat substrate, though exceptions were also noted, even for five-membered rings [74].

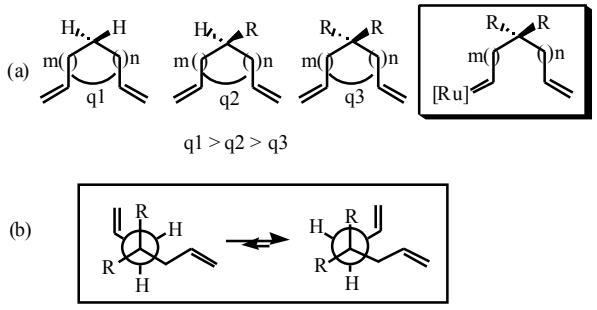
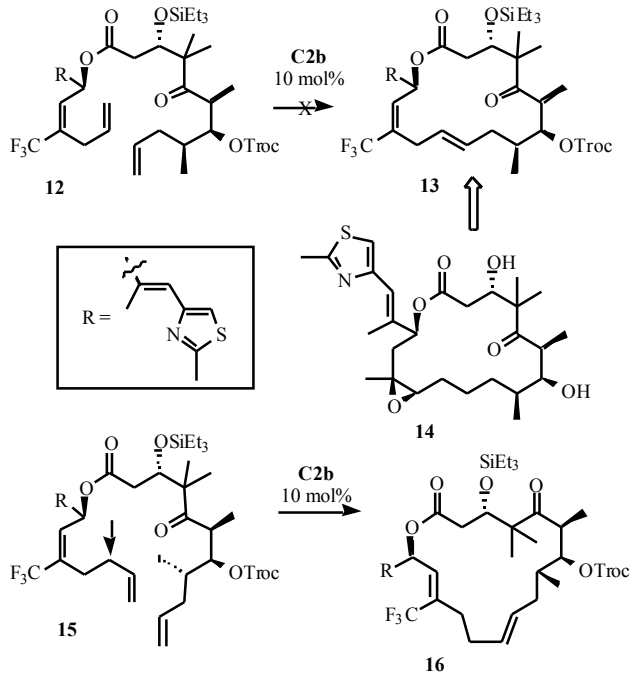


Fig. (4). Conformational constraints in acyclic substrates: (a) the Thorpe-Ingold effect; (b) the gem-dialkyl effect.

Limitations to this strategy, suggested by the trend shown in Fig. (**3**), are further illustrated by data for lactone formation, which indicate that the effects of geminal substitution are negligible for flexible rings larger than nine members [48]. In general, the high number of possible conformations present in larger rings, even where flexibility is attenuated by functionalization, means that conformational control is not intuitively obvious, and RCM of complex substrates remains unpredictable. The position of the double bonds, relative to auxiliary functional groups, plays an important role in determining the outcome of macrocyclizations, though these effects remain poorly understood [75,76]. In RCM to form an epothilone framework, for example, the macrocycle could be formed only after inserting one methylene into the other side of the diene (Scheme **6**): this outcome was attributed to the "gearing effect" of the dienes, but could not be predicted a priori [9].



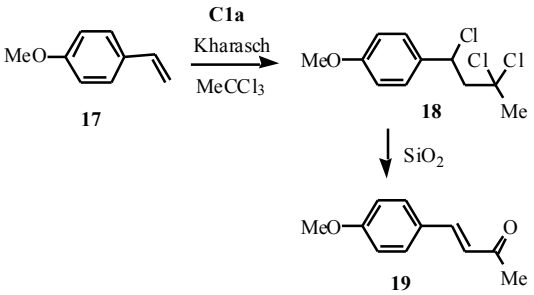
Scheme 6.

3. EFFECTS OF NON-IDEAL CATALYST BEHAVIOUR

3.1. Alternative (Non-Metathesis) Reaction Manifolds

Where RCM is slow, unwanted reaction pathways can dominate. In addition to the competing metathesis processes described in Section 2.1, the exceptional catalytic versatility [77] of ruthenium can enable alternative reaction pathways, altering both products and product distributions. Well documented in a recent review is the impressive range of non-metathetical processes promoted by the Grubbs catalyst **C1a** [43]. These include olefin isomerization, dehydrogenative coupling of silanes, carbonyl hydrosilylation, Kharasch addition, and vinylation of acetylenes with carboxylic acids, as well as deprotection of amines [43,78,79]. Particularly relevant from the perspective of product contamination are catalytic side-reactions accessible under the conditions of the desired metathesis chemistry. Key among these undesirable side reactions are olefin isomerization [69,70,80-83] (vide infra), and Kharasch functionalization *via* addition of chloroform across olefinic bonds [84,85] Such "unexpected" chemistry has in some cases been exploited to good effect: Snapper's group, for example, has developed an efficient one-pot route to vinyl ketones *via* hydrolysis of Kharasch products [84] (Scheme **7**). An instructive review of the problems and potential inherent in the isomerization chemistry has recently appeared [42]. Such "auto-tandem" catalyses [41], in which two mechanistically distinct transformations are concurrently triggered by the same precatalyst, can offer powerful, efficient opportunities for selective synthesis. However, they are more difficult to control than "assisted tandem" processes, in which a change in mechanism is deliberately

triggered once an initial transformation is complete. Examples of the latter are particularly well-documented in metathesis-hydrogenation chemistry [86-91]. Typically, **C1** is converted into well-defined ruthenium hydride species (vide infra) [92] by addition of hydrogen following metathesis. An elegant illustration of the potential of assisted tandem catalysis comes from recent reports describing controlled metathesis-isomerization sequences, effected by addition of hydrogen, inorganic hydrides, or alcohol and base following metathesis [93-96]. These methodologies enable synthesis of (e.g.) cyclic enol ethers from easily prepared acyclic allyl or homoallyl ethers, without isolation of the primary metathesis products.



Scheme 7.

The breadth of reaction chemistry noted above is not unique to **C1**. The "second generation" catalysts **C2** display much of the same behaviour, in some cases with significantly higher activity [42,43]. Because the majority of highly active Ru precatalysts for olefin metathesis converge on $RuCl_2(NHC)(=CH_2)$ (**C17b**; R = H) as the catalytically active intermediate (Section 4.1.2), they can be expected to share a common set of opportunities and limitations. More generally, any ruthenium catalyst that exhibits amplified metathesis activity will exhibit a parallel increase in activity for any other catalytic process that likewise requires an electron-rich metal center, and a vacant basal site for substrate binding [41,43].

As an important example of this principle, we recently pointed out the common structural elements required for maximum activity in Ru-catalyzed olefin metathesis and isomerization (as well as olefin hydrogenation) [97]. Olefin isomerization is a particularly problematic side-reaction in RCM, as it transforms a terminal olefin into a less reactive internal olefin, successful RCM of which affords a ring-contracted product. Isomerization activity is exacerbated for catalysts of type **C2**, containing an N-heterocyclic carbene (NHC) ligand [80-83,98,99], and appears to be worse in aromatic solvents [80,89], While it remains unclear whether the Ru-alkylidene itself can induce isomerization, a ruthenium hydride contaminant [98] or decomposition product [100,101] is widely regarded as the culprit. (Most disconcerting, however, is the recent finding that substrate itself can mediate deactivation and formation of hydride species: Section 3.2) [100]. A study involving well-defined hydride complexes demonstrates that maximum activity for isomerization *and* metathesis (as well as hydrogenation) results from the presence of a strongly electron-donating NHC ligand in conjunction with a coordinatively labile donor that is readily displaced by substrate [97]. This trend is exemplified in Fig. (**5**): complex **C6**, containing a labile PPh_3 ligand, is significantly more active than PCy_3 complexes **C7** or **C8**. The isomerization activity of **C8** is damped by the low lability of the phosphine trans to the NHC ligand.

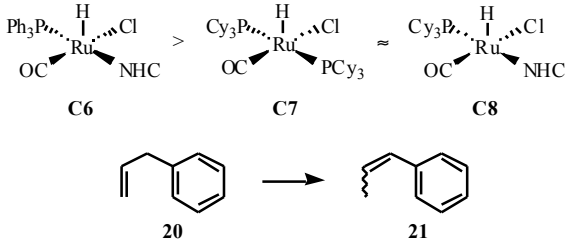
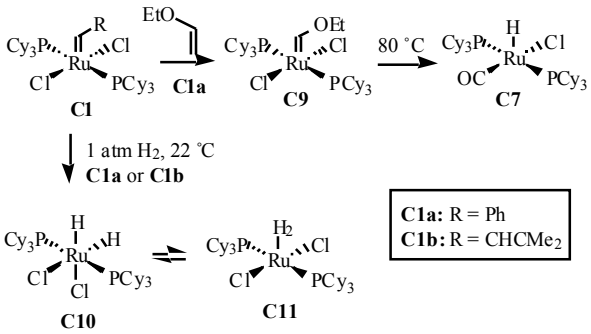


Fig. (5). Order of isomerization efficiency of well-defined, electron-rich Ru hydrides.

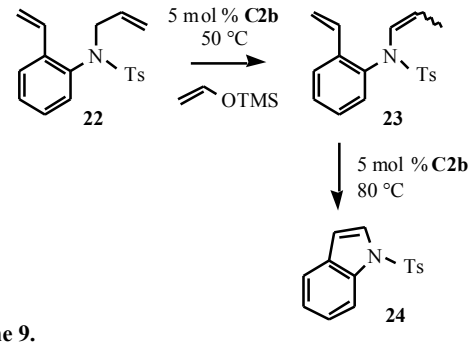
In some cases, isomerization-active species are generated by side-reactions of the ruthenium catalyst. As noted in the Introduction, catalysts **C1** [26], **C2** [27], and related NHC catalysts [28] are readily decomposed by primary alcohols (particularly in the presence of base), undergoing conversion into hydridocarbonyl species such as **C7** or **C8**, and other, unidentified inorganic products. Importantly, the vinyl ethers often used to terminate Ru-catalyzed metathesis reactions can also trigger formation of hydride products. Louie and Grubbs have described the thermal decomposition of **C9**, the product formed from reaction of **C1a** with ethyl vinyl ether, to **C7** (Scheme **8**) [102]. As an alternative means of quenching metathesis, the reaction solution can be exposed to 1 atm H_2 [90,92]. However, hydrogenolysis of the Ru-alkylidene again affords hydride complexes, in this case the Ru(IV) dihydride **C10** and its dihydrogen tautomer **C11** (Scheme **8**). Isomerization *via* these species should be limited in chlorocarbon solvent, in which the tautomeric equilibrium lies completely in favour of coordinatively saturated, comparatively unreactive **C10** [92]. Nonetheless, effective termination of Ru-catalyzed olefin metathesis *without* generation of hydride species remains an underexplored area.



Scheme 8.

Nishida's group recently exploited the isomerization activity of Ru-NHC complexes to develop a route to indoles from N-allylstyrenes, by sequential processes of isomerization and RCM (Scheme **9**) [103]. The isomerization chemistry is mediated by a ruthenium species formed by reaction of **C2b** with various silyl enol ethers:

subsequent RCM chemistry requires addition of a new charge of catalyst.

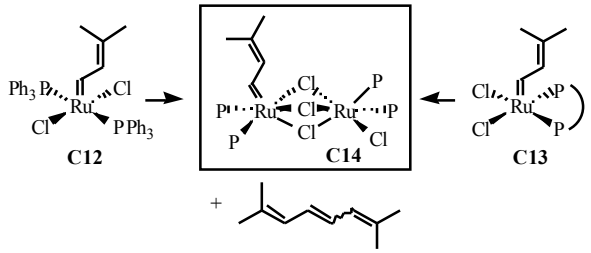


Scheme 9.

3.2. Catalyst Deactivation

Despite the robustness that has led to their widespread use, many of the Ru metathesis catalysts, including the important Grubbs systems, decompose over the timescale of challenging (hence slow) RCM processes. (Indeed, experiments with derivatives of **C1** suggest that the key methylidene species **C3** is particularly susceptible to deactivation, decomposing ca. ten-fold faster than the corresponding alkylidene complex) [66,67]. In consequence, slow RCM (or CM) reactions promoted by these catalysts may not proceed to completion because they are ultimately catalyst-starved. The requirement for high catalyst loadings imposed by facile deactivation is becoming increasingly important as Ru-catalyzed RCM and CM processes enter the industrial arena: high turnover numbers are essential in order to amortize catalyst costs, and to minimize heavy-metal contamination of the products.

Several years ago, our group identified a chloride-mediated decomposition pathway as a key factor in the short lifetimes of model Ru-alkylidene complexes containing two PPh_3 ligands, or bidentate phosphines (Scheme **10**) [104,105]. Rapid evolution of the vinylalkylidene ligand as triene was observed, in a presumably bimolecular deactivation process analogous to that long inferred for catalysts of type **C1**. In addition, however, these studies permitted the first insight into the fate of the *inorganic* fragments: coordinatively saturated, face-bridged dimer **C14** was identified from NMR evidence in both cases, and crystallographically characterized for the chelate complex **C14b** [104]. These dimers are characterized by very low metathesis activity: rates of ROMP are negligible even with the highly reactive monomer norbornene (**25**), and zero activity was found in RCM catalysis. The dimeric structure evidently functions as a catalyst sink in this chemistry,



Scheme 10. Bimolecular deactivation of ruthenium alkylidenes. **C14a**: P = PPh_3; **C14b**; PP = $Cy_2P(CH_2)_4PCy_2$.

reflecting the high thermodynamic stability of the triply-chloride bridged Ru_2 unit.

Consistent with operation of such a dimerization pathway for catalysts of type **C1** is the evolution of stilbene from **C1a** in solution, as well as kinetic evidence for a bimolecular pathway in decomposition of alkylidene derivatives [67,87]. (It should be noted that while the five-coordinate methylidene complex $RuCl_2(PCy_3)_2(CH_2)$ was found to decompose *via* a predominantly unimolecular pathway, the methylidene species formed by loss of one PCy_3 ligand also underwent bimolecular deactivation, albeit more slowly) [67]. Kinetics data were consistent with a mechanism involving dissociation of one bulky PCy_3 prior to dimerization [67,87]. In related work, a tetraruthenium product (Fig. (**6**) [106] was isolated following decomposition of **C10**/**C11** in CH_2Cl_2. X-ray analysis revealed that this species was an N_2-bridged dimer of face-sharing dimers, in which each metal center bears a single PCy_3 ligand. Again, the $Ru_2(\mu\text{-}Cl)_3$ entity emerges as a thermodynamically favoured structural motif in the decomposition process.

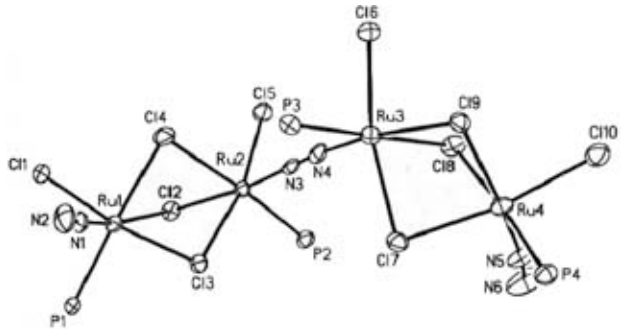
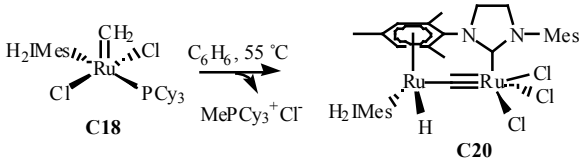


Fig. (6). Molecular structure of decomposition product **C15**, an N_2-bridged dimer of $Ru_2(\mu\text{-}Cl)_3$-bridged dimers. PCy_3 ligands abbreviated to P for clarity.

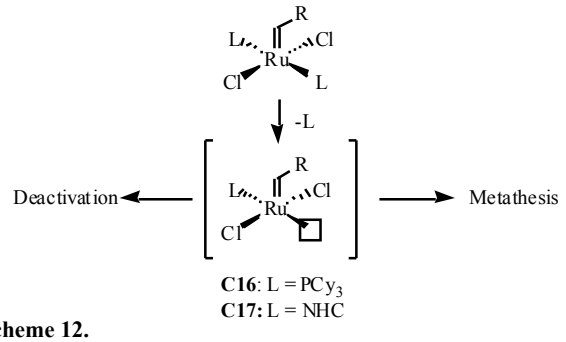
Finally, the Grubbs group recently reported a deactivation pathway for "second-generation" methylidene species **C18**, which was apparently mediated by chloride-bridged intermediates. Loss of phosphine and dimerization culminates in formation of carbide-bridged dimers, in which one Ru center is a piano-stool complex formed by η^6-coordination of a mesityl ring of H_2IMes (Scheme **11**) [101].



Scheme 11.

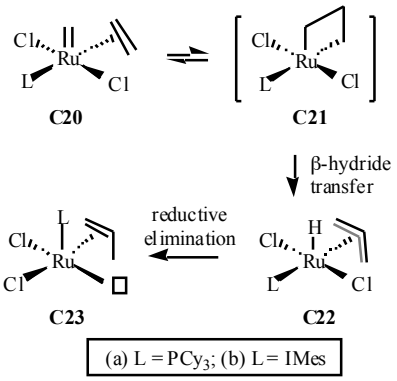
The cumulative weight of this evidence strongly suggests that productive metathesis and catalyst deactivation are mediated by a common intermediate formed by loss of one basal "sacrificial" ligand from the Grubbs-class catalysts **C1**/**C2** (Scheme **12**). By implication, modification of the catalyst precursor by incorporating a more labile ligand will increase not only catalytic activity, but also the rate of decomposition. This suggestion is borne out by experiment: within the $RuCl_2LL'(CHR)$ family of catalysts, including the

NHC derivatives, a general correlation exists between high catalyst activity, and decreased catalyst lifetime [67]. Catalyst design strategies directed at circumventing chloride-mediated deactivation are described in Section 4.



Scheme 12.

The ligands play a key role in enabling the deactivation pathways summarized above, pointing toward a limitation inherent in the convergence of many of the highly reactive Ru metathesis (pre)catalysts on $RuCl_2$(NHC)(=CHR) as the active species. These issues underline the need for greater diversity in catalyst design, as discussed in greater detail in the following section. More troubling, however, is a recent study pointing toward a *substrate-mediated* deactivation pathway (Scheme **13**). Sasol workers described theoretical and experimental evidence for β-hydride transfer within metallacyclobutane **C21** to form allyl hydride **C22**, in a pathway potentially competitive with metathesis [100]. The computational analysis highlighted the accessibility of a reductive elimination pathway that would afford π-propene species **C23**. (The calculated barrier between **C22** and **C23** was lower for the IMes species than its PCy_3 analogue, potentially accounting for the isomerization activity of the NHC systems). Consistent with the β-hydride transfer mechanism, propene was identified as the dominant product in metathesis of ethylene *via* **C20**. Similar transformations have been reported for closely related systems [107]. Alternative decomposition pathways are suggested by the isolation of IMes•HCl as a byproduct in these reactions. It remains unclear, however, whether substrate-mediated deactivation is an *inherent* property of ruthenium methylidene species, again emphasizing the importance of expanding the structural diversity of Ru metathesis catalysts.



Scheme 13.

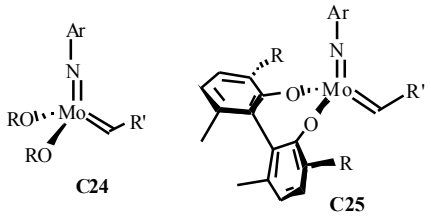


Fig. (7). Examples of tunable metathesis catalysts containing alkoxide and biphenolate ligands.

4. ADVANCES IN CATALYST DESIGN

A breakthrough in the activity of the Ru catalysts came with the development of N-heterocyclic carbene complexes of type **C2** [17], and much subsequent effort has focused on modification of the alkylidene, the NHC ligand itself, and/or the remaining neutral, "L-donor", ligand in such complexes. Fine-tuning of activity and selectivity has remained elusive, however. In contrast, the Schrock-Hoveyda catalysts e.g. **C25**, (Fig. (**7**)) afford exceptional control of these parameters, with particularly impressive performance in asymmetric and desymmetrization metathesis reactions [14-16]. A key advantage of the Schrock systems is the presence of modular, tunable aryloxide or alkoxide ligands, in place of the simple chloride ligands typically used in the Ru chemistry. Our purpose in this section is to trace some of the major current themes in design of new ruthenium catalysts, rather than to undertake a comprehensive review. Overviews of recent developments in the design of individual catalyst classes have appeared elsewhere [32-36,108-110].

4.1. Catalyst Architecture and Mechanism

Experimental [66,111,112] and computational [113-117] studies support identification of the active catalyst in Ru-catalyzed olefin metathesis as the 14-electron species (e.g. **C16**, **C17;** Scheme **11**), formed by reversible dissociation of one neutral ligand. The dissociative mechanism is imposed by the architecture of these five-coordinate complexes. In the absence of distortions imposed by, for example, a large rigid chelate ring [118], their preferred geometry is square pyramidal, and the high trans-influence alkylidene ligand is constrained to occupy the apical site [105]. This situation is not unique to metathesis chemistry: a similar effect is found in five-coordinate ruthenium complexes containing a high trans-influence hydride ligand (Fig. (**5**)) [97]. Productive reaction in either case requires placement of incoming substrate cis to the active site (that is, in the basal plane), and high catalytic activity therefore requires that such species either isomerize easily, or readily dissociate a basal ligand. As a corollary, complexes containing four non-labile ligands in the basal sites (Fig. (**8**)) can be expected to exhibit low metathesis activity.

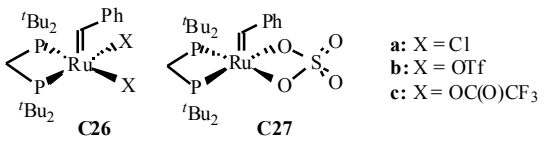
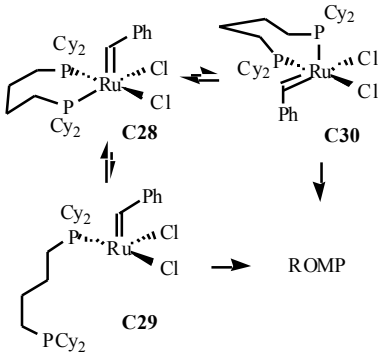


Fig. (8). Examples of Ru metathesis catalysts containing four non-labile basal ligands [119,120].

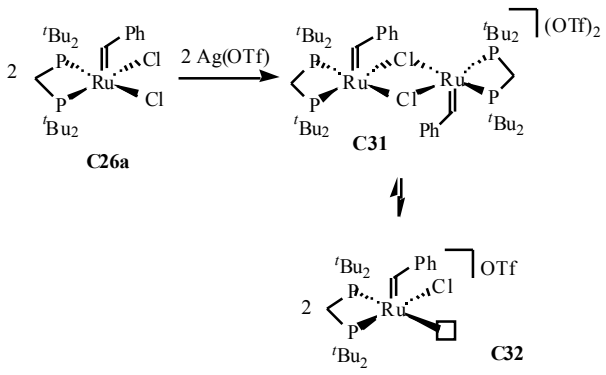
We described a possible, rare case of geometric isomerization several years ago, in a study involving a diphosphine complex with a flexible, seven-membered chelate ring (**C28**, Scheme **14**) [121]. This catalyst exhibited high activity in ROMP of norbornene (**25**); while RCM activity was not investigated, the mechanistic issues relating to catalyst initiation are identical. The absence of free phosphine (NMR evidence), the deleterious effect of the phosphine scavenger CuCl, and the exceptionally narrow polydispersity of the polymer (signifying faster initation than propagation), tend to argue against catalysis *via* **C29**, formed by equilibrium decoordination of one phosphine "arm". Computational studies confirmed that the "normal", apical alkylidene geometry (see **C28**) was most thermodynamically stable, but pointed toward the energetic accessibility of isomer **C30**, in which placement of alkylidene in the basal site precludes the need for ligand loss [121]. Interestingly, smaller chelate ring sizes show no such tendency [119,120], and complexes of type **C26a** are essentially inactive until a chloride ligand is abstracted (vide infra). Because **C28** was prepared in situ, however, some uncertainly about the mechanism remains. A more stable analogue was recently isolated [122] which may give further insight. This behaviour remains, however, an exception to the rule: in general, the dissociative mechanism can be expected to prevail in Ru-catalyzed olefin metathesis.



Scheme 14.

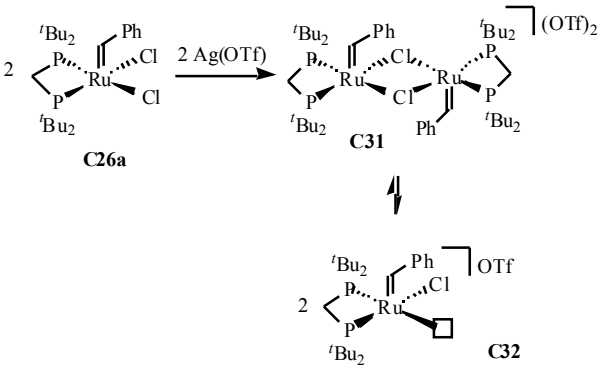
The required vacancy in the basal plane can be generated by loss of either a neutral donor or abstraction of a chloride ligand. In a rare example of the latter approach, Hofmann's group demonstrated that impressive increases in ROMP activity can be effected by chloride abstraction from **C26a** to generate dicationic dimer **C31** (Scheme **15**) [120,123,124]. The dative chloride bonds in such edge-bridged catalysts are labile, in contrast to the thermodynamic stability of face-bridged dimers $Ru_2(\mu\text{-}Cl)_3$ (e.g. **C14**, **C15**). Highly reactive **C32** is thus accessible in solution. Particularly intriguing in this strategy is the potential for improved selectivity associated with loss of chloride, rather than a bulky phosphine donor. Despite their potential, these catalysts have not yet been applied to RCM, and surprisingly little effort has focused on design of new cationic catalysts, though *in situ* abstraction of chloride is sometimes employed as a useful means of amplifying catalyst activity [22].

More commonly, Ru metathesis catalysts are activated by loss of a neutral ligand. In consequence, synthetic convenience (which benefits from strong ligand binding) and



Scheme 15.

catalyst performance are typically at odds. The superior performance of the "second generation" NHC catalysts, for example, is impeded by the sluggish loss of phosphine from precatalyst **C2**. Loss of PCy_3 is reportedly accelerated by addition of CuCl [112], but as this treatment can also diminish catalyst productivity, this protocol has not been broadly adopted. The low lability of PCy_3 trans to an NHC ligand was noted above: in fact, **C2b** undergoes loss of phosphine nearly *two orders of magnitude* more slowly than **C1a** [66,125]. The higher metathesis activity of **C2** is due to the preferential reaction of intermediate **C17a** with olefin, vs. free PCy_3 (Scheme **16**). A major recent theme in the literature has thus focused on incorporating a sacrificial ligand more labile than PCy_3, as discussed in the following section.



Scheme 16.

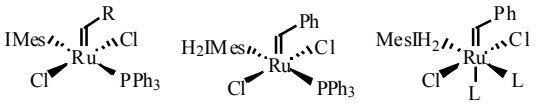
4.2. Recent Strategies in Design of Highly Active RCM Catalysts

In the discussion below, we draw inferences about catalyst activity on the basis of product formation at various (perhaps arbitrary) time intervals, as reaction rates are not generally reported. Comparison of different metathesis catalysts is further complicated by the fact that the concentration of the *active* catalyst varies widely, even where (pre)catalyst loading is held constant. High activity can be masked by slow initiation, for example (as the foregoing discussion illustrates), while moderate activity may be exaggerated by fast initiation. The homogeneity of catalyst initiation is not easily assayed by RCM chemistry. ROMP studies, though underutilized, can provide powerful insight into this important issue, *via* measurement of

absolute chain lengths and polymer polydispersities by (e.g.) light-scattering gel permeation chromatography.

4.2.1. Catalysts that Converge on $RuCl_2(NHC)(CH_2)$

Arylphosphines such as PPh_3 have long been recognized as weaker, and hence more labile, donors than basic trialkylphosphines [17e]. Fast-initiating triphenylphosphine derivatives **C35** (Fig. (**9**)) have been prepared from PPh_3-containing precursors such as $RuHCl(PPh_3)_3$ (**C36**) [126] and $RuCl_2(PPh_3)_2(CHPh)$ (**C37**) [127], and from pyridine complex **C38a** following reaction with PPh_3 [66]. In a study of complexes of type **C35** containing *para*-substituted triphenylphosphine ligands, a linear free energy relationship was established between the rate constant for phosphine dissociation, and the donor ability deduced from phosphine pK_a values [125]. More electron-poor phosphines, unsurprisingly, dissociated at faster rates than electron-rich phosphines. The pyridine complexes are themselves rather labile, despite their coordinative saturation; particularly reactive is **C38b**, in which the donor ability of the 3-bromopyridine ligand is attenuated by inductive effects [128,129]. All of these catalysts show higher activity than the corresponding complex of type **C2** in RCM of diethyldiallyl malonate (DEDAM, **26)** [125,127]. The latter diene, though a conformationally biased and comparatively undemanding RCM substrate (see Section 3.2), is widely used as a benchmark for preliminary screening of RCM activity: with the advent of steadily more active catalysts, however, a need is emerging for a more challenging "standard" substrate, or adoption of a more demanding set of screening conditions.



C35a: R = Ph
C35b: R = $CHCMe_2$

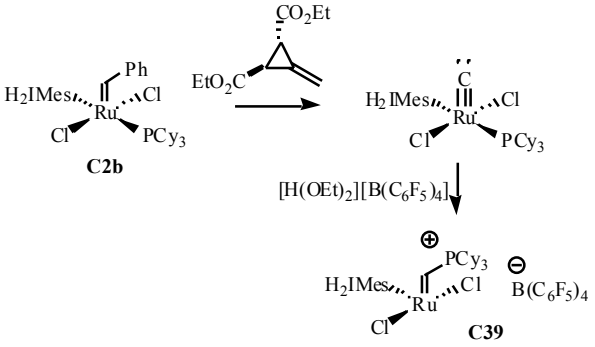
C35c

C38a: L = py
C38b: L = 3-bromo-pyridine

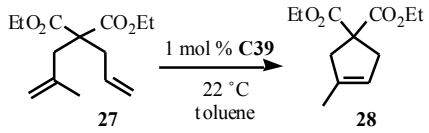
Fig. (9). "Second-generation" catalysts activated by the presence of a labile donor ligand.

Despite their significant increase in activity, catalysts **C35** and **C38** have been comparatively little used for RCM of more demanding substrates, relative to commercially available **C1a** and **C2**, or the Hoveyda catalyst [130] **C40**. High activity has been reported for **C38** in the cross-metathesis of acrylonitrile with allylbenzene, though **C40** (vide infra) also performed well [129]. As pointed out in Section 3.2, however, increased activity generally exacts a price in terms of decreased lifetime, and catalyst loadings thus remain high (typically 1-5 mol %), although it remains unclear to what extent this reflects standard practice, as opposed to the minimum requirement. Mol has reported turnover numbers (TON) approaching 200,000 for RCM and CM *via* **C2** in the absence of solvent, at DEDAM:**C2b** ratios of 1,160,000:1 [131]. (Successful RCM even in neat DEDAM illustrates the thermodynamic driving force for cyclization associated with gem-disubstitution, as noted in Section 2.4). These high turnover numbers are particularly impressive given that catalyst poisoning by trace impurities can severely reduce TON values at very low catalyst loadings.

A further recent development signals a new area of advance. The Piers group reported highly active, four-coordinate phosphonium alkylidene **C39**, formed by attack of $[H(OEt_2)_2][B(C_6F_5)_4]$ on a carbide species derived from **C2b** (Scheme **17**) [132]. The activity of **C39**, though as yet explored with a small number of substrates, appears remarkably high. It is approximately twice as active as **C38a** in RCM of DEDAM at 0 °C, and effects quantitative RCM of trisubstituted diene **27** within 10 minutes at 22 °C (Scheme **18**). A key question still to be explored in this chemistry is whether the superior performance of **C39** is due to efficient initiation, or whether it reflects the absence of an agent (such as phosphine or pyridine) capable of recapturing the active species. (The lack of a trapping agent, however, is likely to reduce the lifetime of the active species, as discussed in Section 3.2).



Scheme 17.



Scheme 18.

Parallel work, primarily by the groups of Blechert and Grela, has focused on increasing the lability of the ether donor on the Hoveyda catalyst [130] **C40** (Fig. (**10**)). Because the alkylidene ligand forms part of a chelate ring in these catalysts, initiation requires intramolecular decoordination of the pendant ether donor, which is then eliminated altogether in the first cycle of metathesis. Initiation of **C40** itself is slow, despite the low oxophilicity of Ru(II), owing to the high thermodynamic stability of the five-membered chelate ring. Improved turnon efficiency was achieved by steric (**C41** [133,134]) or electronic (**C42** [109,110,135]) destabilization of the chelate.

Both sterically- and electronically-activated catalysts proved significantly more active than **C2b** or **C40** for RCM of α,ω–dienes, though activity for formation of tetrasubstituted olefins remained poor. Substrates bearing terminal olefins were rapidly cyclized to five- to seven-membered rings under mild conditions (0-23 °C, 1 mol % Ru) [109,110,133-135]; slightly greater activity was generally manifested by **C41b** [110]. The substrates shown in Scheme **19** proved more challenging. Acrylate substrates are not generally problematic in metathesis by second-generation catalysts [136, 137] (though exceptions have been noted) [137, 138] but the trisubstituted olefin present in **29**

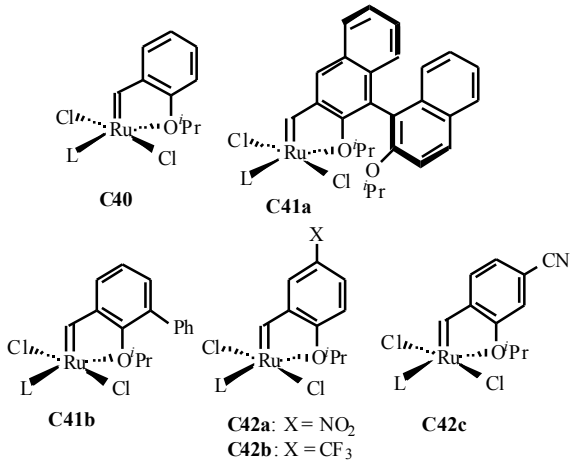
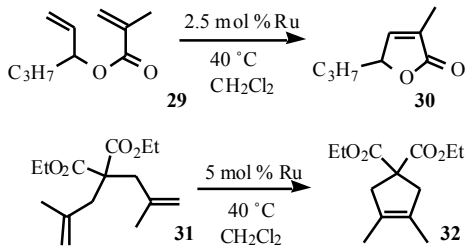


Fig. (10). The Hoveyda catalyst **C40** and representative, sterically- or electronically-activated derivatives.

presents an additional challenge. Catalyst **C42a** achieved up to 76% yield in RCM of **29** within 2 h at 40 ˚C (2.5 mol %) [110]. Tetrasubstituted olefins are more difficult targets: under similar conditions, but double the catalyst loading, yields of **32** were <10% for **C40**, **C41b** and **C42a** after 24 h, vs. 14% for **C2b**. Direct comparison of the merits of these catalysts versus **C35**, **C38**, and **C39** is hampered by differences in substrate and reaction conditions. Highly suggestive, however, is the finding that RCM of **27** (Scheme **18**) *via* **C41b** or **C42a** requires 40 minutes or one hour, respectively, to proceed to 95-99% completion, under conditions comparable to those noted for **C39** above [110]. The activity of **C39** thus appears greater than any other Ru metathesis catalyst developed to date, within the range of substrates explored.

Recapture of the active Ru species by styrene ethers is often regarded as a means of prolonging lifetimes and enabling catalyst recovery in the Hoveyda catalyst systems [130]. Again, however, a tradeoff exists between the high lability required for catalyst activity, and the low lability required for catalyst recovery and sequestration. Labelling



Scheme 19.

studies suggest that bulky and electron-deficient styrene ethers are relatively inefficient recapture agents [139]. Faster deactivation is almost certainly responsible for the poorer performance of these "phosphine-free" catalysts, relative to **C2**, in some challenging metathesis reactions [140].

4.2.2. Pseudohalide Catalysts

Limitations associated with the lack of structural diversity in highly active ruthenium metathesis catalysts, and in particular the convergence of many of the "second generation" (pre)catalysts on the active species $RuCl_2(NHC)(=CHR)$, were alluded to in Section 3. Examination of anionic donors other than chloride is of interest for the potential to improve catalyst lifetime, and to make better use of this site to modulate selectivity and other properties of interest. Comparatively little synthetic effort has been directed at incorporation of alternative anionic donors, despite these opportunities, and the major impact of such ligand systems on the capacity to tune activity and selectivity within the Schrock systems. Discouraging the deployment of effort in this area were early findings of attenuated activity. The reasons for this are now obvious, and fall into three categories: (1) excessive steric crowding; (2) the presence of four non-labile ligands in the basal plane of the square pyramid (see Section 4.1); (3) use of neutral donor ligands with donor abilities inferior to those conferred by PCy_3 or NHC ligands. Improvements have now been achieved, however, as shown in Table **1** (complexes shown in Fig. (**11**)).

Table 1. Relative catalyst activity in RCM of DEDAM

Catalyst	Cat. loading (mol %)	Temp (˚C)	Total TON (time)	Ref.
C1a	5	~22 ˚C	19 (30 min) 20 (1 h)	[141 112,127]
C43a	20	60 ˚C	<0.25 (96 h)	[142]
C43b	20	60 ˚C	3.5 (96 h)	[142]
C43c	20	60 ˚C	2 (12 h)	[142]
C44	5	~22 ˚C	6 (30 min)	[141]
C45a	0.05	45 ˚C	500 (2 h)	[143]
C45b	0.05	45 ˚C	1,400 (2 h)	[143]
C48c	3	70 ˚C	32 (1 h)	[144]
C48b	5	55 ˚C	20 (4 h)	[145]
C49b	5	70 ˚C	20 (4 h)	[145]
C50	0.05	60 °C	1,820 (1.5 h)	[65]
C51b	0.05	60 °C	900 (2 h) 1840 (20 h)	[65]

The most striking example of sterically restricted activity is undoubtedly presented by the four-coordinate alkylidene complexes **C43** [142,146]. Despite their nominal coordinative unsaturation, these exhibit essentially zero RCM activity, even for the conformationally favoured ring-closing of DEDAM, at elevated temperatures (Table **1**) [142]. (It may be noted, however, that protonolyis of the tert-butoxide ligands with HCl can be used to reinstall a chloride ligand, providing a "back-door" route to highly active **C16**). Higher activity is found for acetate [141,143,147] and sulfonate [143] derivatives. Both catalysts **C44** and **C45** have been employed at reduced catalyst loadings, offering welcome insight into their "true" activity. Complex **C44** proved only slightly less active than **C1a** in CM of methyl oleate and trans-4-decene, though significantly less so for RCM of DEDAM; catalyst activity was curbed in donor solvents such as THF [141,147]. Carboxylate **C45b** reached TON values of 1400 for DEDAM: importantly, both **C2b** and **C40** showed very similar activity under these conditions (TON values of 1300 and 1500, respectively).

The activity of iminopyrrole (**C46**) [22], tris(pyrazolyl)borate (**C47**) [148], and Schiff base (**C48**, [144,145] **C49** [145]) chelate complexes (as well as the diphosphine complexes in Fig. (**8**)) is limited by Principles (2) and (3) above. In contrast to **C1a**, these catalysts are essentially inactive at room temperature, and catalysis was carried out in the range 55-70˚C. PCy_3 complex **C46a** shows significantly greater RCM activity in air [19]; the rate of RCM of the 14-electron intermediate presumably exceeds the rate of oxidation by some margin. Interesting work by the Verpoort group has established a correlation between metathesis activity and electron-deficiency of the O-aryl group in the Schiff base catalysts **C48**, pointing toward activation by decoordination of the nitrogen donor, rather than phosphine [145a]. The inverse correlation was found for **C49**, suggesting activation by equilibrium formation of the monoruthenium species, which (as noted above) is kinetically accessible for edge-bridged dimers.

Aryloxide complexes **C50** and **C51** are a recent addition to the family of highly active metathesis catalysts; **C52**, in comparison, exhibits modest activity, but opens the door to Ru-catalyzed asymmetric metathesis, as discussed below [108,139,149]. The activity of **C50** and **C51** is due in part to the low steric constraints within these complexes: steric demand is minimized by the planarity of the aryloxide and pyridine donors, in conjunction with an essentially two-dimensional IMes ligand [150]. In contrast to the metathesis-inactive alkoxides **C43**, catalyst **C50** effects up to 41,000 turnovers in RCM of DEDAM, at exceptionally low catalyst loadings (5×10^{-4} mol % **C50**). In comparison, monoaryloxide complexes **C51** exhibit lower total turnover numbers, though lifetimes still exceed those of **C1**/**C2** (Table **1,2**) [65]. The decrease in total productivity is offset by heightened reactivity relative to **C50**. Catalyst **C51b**, in particular, effects efficient RCM of a range of substrates: in a number of cases, cyclization is complete within 15 minutes. A sampling of substrates is shown in Table **2**: these include a trisubstituted diene (linalool, **33**), ene-yne substrates (**35**, **37**), and macrocycle precursors (**1**, **39**). The 16-membered lactone **3** can be recognized as the macrocyclic core of epothilone A [9], and the unsaturated precursor to Exaltolide,

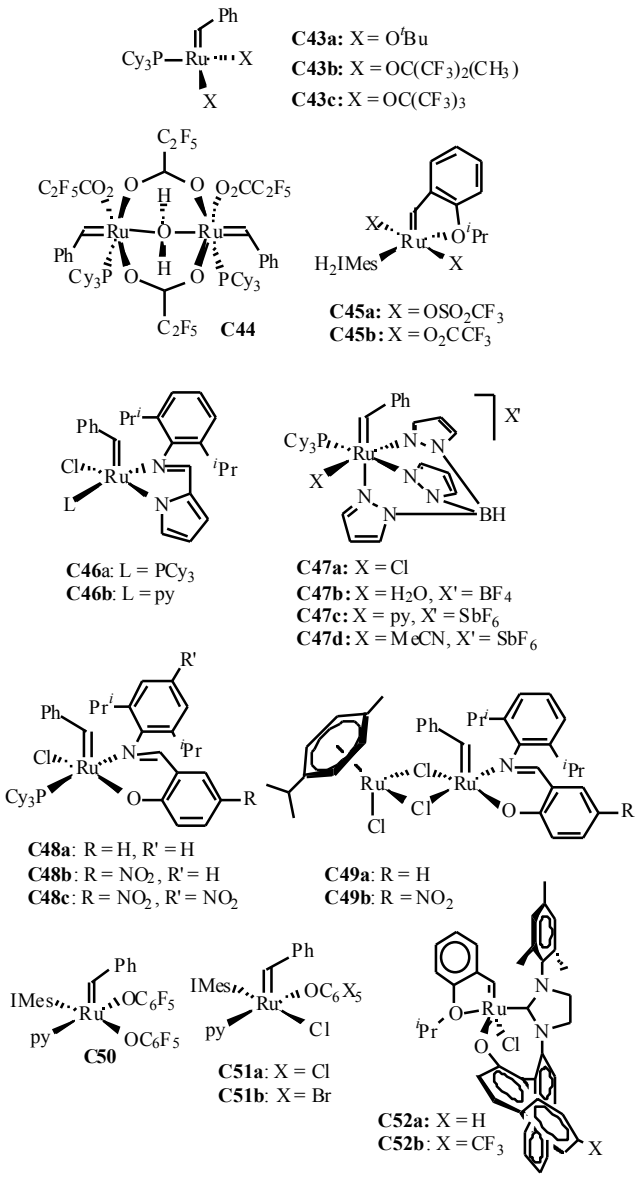


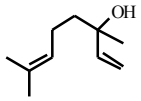
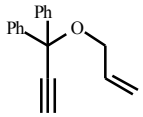
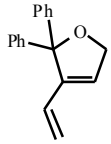
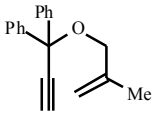
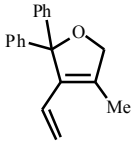
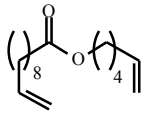
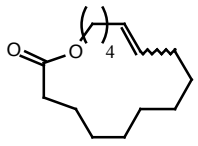
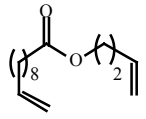
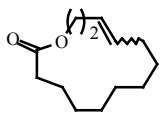
Fig. (11). Summary of Ru "pseudohalide" complexes relevant to olefin metathesis.

a musk-odoured component of the root oil of *Archangelica officinallis* [76].

The selectivity and rate with which **C51b** effects macrocyclization, vs. ADMET, is notable. RCM of **1** using **C1a** and related catalysts is reportedly incomplete even after 30 h [151-154], while NHC catalyst **C2b** effects 72-87% ring-closing within 2-4 h [80,151]. In comparison, **C51b** effects quantitative formation of this value-added target molecule within 15 minutes [65]. Parallel experiments with **C2a** showed that at similar dilutions (5 mM), ADMET was kinetically preferred over cyclization, but that quantitative RCM could be achieved on 1 h reaction time in refluxing $CDCl_3$ (see Section 2.2.2).

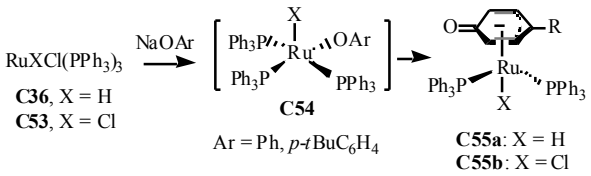
The electron-deficiency of the aryloxide ligands appears to be an important factor in their stability. $\sigma \rightarrow \pi$ Isomerization is very rapid in model phenoxide complexes (see **C54**, Scheme **20**) [155]. Isomerization can be arrested

Table 2. RCM efficiency of aryloxide catalysts vs. "second generation" catalysts

Substrate	Product	mol% Ru	Conditions	Catalyst	% Conv. (E:Z)
 **33**	 **34**	0.05 [a]	$CDCl_3$: Δ, 15 min	**C50**	100
				C51a	17
				C51b	34
				C2a	24
				C38a	29
 **35**	 **36**	0.5	$CDCl_3$: Δ, 15 min	**C51b**	100
		5	C_7H_8: 80 °C, 1 h	**C2b**	85
		1	CH_2Cl_2: 0 °C, 15 min	**C42a**	98 [110]
 **37**	 **38**	5	$CDCl_3$: Δ, 2 h	**C51b**	70
		5	CH_2Cl_2: 40 °C, 20 h	**C2b**	20 [110]
				C41b	17 [110]
				C42a	0 [110]
 **1**	 **3**	5	CH_2Cl_2: Δ, 15 min[b]	**C50**	9 (3:1)
				C51a	72 (4:1)
				C51b	100 (3:1)
				C38a	30 (4:1)
 **39**	 **40**	5	C_6H_6: Δ, 15 min[b]	**C50**	29 (4:1)
				C51a	100 (9:1)
				C51b	100 (9:1)
				C38a	63 (9:1)

[a] Each of these catalysts gives 100% conversion within 15 minutes at 0.5 mol%. [b] Substrate, catalyst added separately, dropwise; maximum diene concentration = 5 mM.

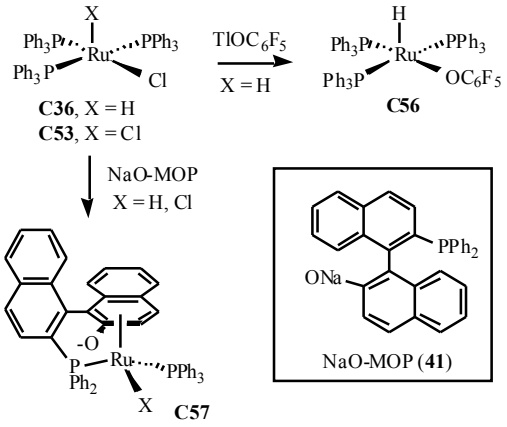
by attenuating the donor ability of the aryl ring (Scheme **21**), as indicated by the stability of **C56**, despite the simultaneous presence of a phenoxide ring and three labile PPh_3 ligands [156]. However, chelation appears insufficient to stabilize the σ-aryloxide structure, at least for seven-membered rings, if the ancillary ligands are sufficiently labile to permit access to the three coordination sites required to bind the phenolic ring. Thus, the corresponding reaction of labile precursors **C36** or **C53** with heterobifunctional phosphine-binaphtholate **41** yields piano-stool structure **C57**, in which the O-MOP ligand is bound in σ-fashion through phosphorus, and in π-fashion *via* the η^6-aryloxide ring [156]. The apparent stability of the binaphtholate derivative **C52** may reflect the rather low lability of the dative Ru-O (ether) bond (as indeed implied by the chromatographic stability and the slow initiation of this species) [108]. The *active* catalyst, of course, is coordinatively unsaturated, and may thus be unstable toward σ→π isomerization. Indeed, derivatives of **C52** modified to destabilize the ether chelate appear to decompose much more readily [139]. Conversely, the electron-deficiency of the two perfluorophenoxide ligands in **C50**, which disfavours isomerization, is presumably a key factor in the remarkable lifetime of this catalyst.



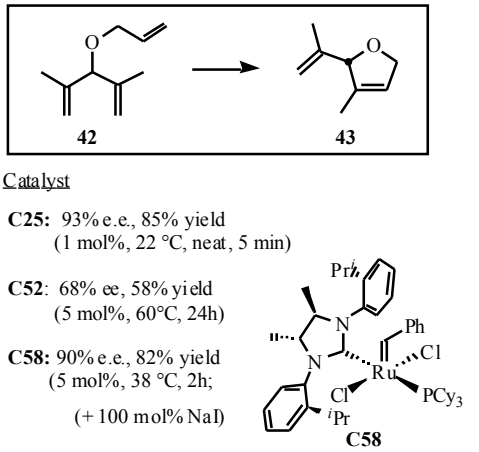
Scheme 20.

Asymmetric RCM is a major goal in Ru-catalyzed metathesis: few chiral Ru catalysts have yet been developed, but this situation will undoubtedly change significantly over the next few years. Both **C52** [139] and chiral NHC derivative **C58** [157] (Scheme **22**) show somewhat modest activity for the standard probe reaction, desymmetrization of triene **42** to chiral cyclic ether **43**. Enantioselectivities of 68% and 90% were achieved with **C52** and **C58**, respectively. The "gold standard" at this stage remains the Schrock-Hoveyda catalysts exemplified by **C25** [158], albeit

with the drawback of high sensitivity inherent in Mo catalysis.



Scheme 21.



Scheme 22. Comparison of chiral catalysts for asymmetric RCM.

5. REMOVAL OF RUTHENIUM RESIDUES

The majority of the Ru metathesis catalysts exemplified by in current use decompose into highly coloured byproducts that are difficult to separate from the desired organic products. Attempts to remove the organic fraction by distillation can trigger olefin isomerization, as well as other undesirable reactions catalyzed by the ruthenium species present (see Section 3.2). Several ingenious anchoring strategies have been devised in pursuit of metathesis methodologies that could circumvent these problems [143,151,159-166]. Use of an *anionic* donor ligand to tether the catalyst [143] obviates limitations associated with anchoring *via* a labile L-donor ligand, as well as those inherent in anchoring *via* the alkylidene itself (the latter strategy necessitating a "release-recapture" mechanism) [159]. The utility of immobilization strategies is ultimately determined by the lifetime of the anchored catalyst, and the relevance of unimolecular and substrate-induced deactivation pathways is thus a concern. Of particular interest in this context are recent findings describing TON values for supported catalysts greater than those for the homogeneous parent (although it should be recognized that the formal concentration of a catalyst on a support can differ significantly from the corresponding solution concentration, even at equivalent substrate: catalyst ratios) [163a,b]. Alternative reaction media, including ionic liquids [167,168], fluorous media [169], and supercritical CO_2 [170], can also offer attractive opportunities for both purification and catalyst recycling.

Several extraction techniques have been devised for removal of ruthenium after metathesis reactions carried out using conventional catalysts and reaction conditions (Table **3**). Additives used to modify or sequester the spent ruthenium following RCM with **C1a** include lead tetraacetate [171], DMSO or triphenylphosphine oxide [172], or water-soluble phosphines [173]. An interesting new approach is the use of a polymer-bound diarylphosphine scavenger [174]. These methods enabled a reduction of the ruthenium content to 200-1200 ppm (0.2-1.1 μg/mg). Citing concerns about the toxicity and expense of some of these reagents, Cho and Kim developed an alternative method in which crude RCM products were incubated with activated charcoal for 12 hours, then subjected to two cycles of chromatography, decreasing the Ru content to ca. 60 ppm [175]. In comparison, the high affinity of the Ru-aryloxide

Table 3. Methods for removal of Ru residues following RCM

Ref.	Catalyst	Purification Method	Yield	ppm Ru
[65]	**C50, C51**	One cycle of flash chromatography (silica gel; 5% EtOAc / hexanes)	92-97	<100[a]
[172]	**C1a**	1. Stir with 100 equiv DMSO for 12 h 2. Chromatography (silica gel; 10% EtOAc / hexanes; one cycle)	80-90	382
[172]	**C1a**	1. Stir with 50 equiv PPh_3O for 12 h 2. Chromatography (silica gel; 10% EtOAc / hexanes; one cycle)	80-90	240
[173]	**C1a**	1. Stir with 86 equiv $P(CH_2OH)_3$ and 160 equiv NEt_3 in CH_2Cl_2 for 10 min 2. Add H_2O and silica gel, then filter		206
[175]	**C1a**	1. Stir with activated carbon for 24 h 2. Chromatography (silica gel; 10% EtOAc / hexanes; one cycle)	91	60
[171]	**C1a**	1. Stir with 1.5 equiv $Pb(OAc)_4$ for 12 h 2. Filter through silica gel (10 g : 0.5 mmol **C1a**)		310
[174]	**C1a**	1. Stir with resin-bound phosphine for 17 h 2. Filter through activated charcoal	81	1120

[a] Identical treatment of solutions following RCM of DEDAM with **C1a** or **C2a** resulted in > 50,000 ppm Ru.

complexes for silica gel significantly aids their separation from nonpolar organic compounds. Thus, a *single*, routine, chromatographic pass afforded colourless oils in which the residual Ru content was below the ICP-AES detection limit (<100 ppm, or 0.1 μg/mg; ICP-AES = inductively coupled plasma atomic emission spectroscopy) [65].

6. CONCLUSIONS

Major advances in synthetic organic chemistry have resulted from the deployment of ruthenium catalysts for olefin metathesis. Further advances will undoubtedly accrue as we develop a better understanding of the complex interrelationships between the targeted metathesis transformations and the underlying inorganic chemistry. In this Review, we have highlighted the importance of both substrate and catalyst parameters in examining the continuing evolution of RCM methodologies. Limitations in the ring-closing of dienes are commonly viewed as arising largely from thermodynamic restrictions associated with diene structure, such as ring size or the presence of conformational constraints. While these issues are clearly of fundamental importance, catalyst properties (beyond mere reactivity!) also have an important role to play. While reactivity – taken as the capacity to effect RCM – is obviously a minimum requirement, equally relevant are issues of catalyst selectivity, lifetime, and decomposition to products that may themselves trigger unwanted catalytic activity. Catalyst lifetime, for example, plays a key role in determining the balance between kinetically favoured ADMET oligomerization, and thermodynamically favoured macrocyclization.

The search for catalysts that are both highly active and longer-lived is particularly important for challenging metathesis reactions. Remarkable recent advances in catalyst activity have resulted from development of catalyst precursors that dramatically accelerate the rate of formation of the key methylidene species, $RuCl_2(NHC)(CH_2)$ (**C17b**). Increased activity goes hand in hand with decreased lifetime, however, underscoring the need for better insight into deactivation pathways. Incorporation of "pseudohalide" donors, particularly aryloxide and carboxylate ligands, has led to the first highly active Ru metathesis catalysts that do not proceed through **C17**. These offer new opportunities in terms of catalyst lifetime, selectivity, and ease of removal from organic products. Most fundamentally, however, they represent an expansion in catalyst diversity which – in view of the structural diversity in the organic targets – can be expected to afford new opportunities in Ru-catalyzed olefin metathesis.

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ABBREVIATIONS

ADMET	=	acyclic diene metathesis
Bn	=	Benzyl
CM	=	cross-metathesis
COE	=	cyclooctene
COD	=	1,5-cyclooctadiene
DEDAM	=	diethyl diallylmalonate
equiv	=	equivalents
GC	=	gas chromatography
H_2IMes	=	N,N'-bis(mesityl)imidazolin-2-ylidene
ICP-AES	=	inductively coupled plasma atomic emission spectroscopy
IMes	=	N,N'-bis(mesityl)imidazol-2-ylidene
Mes	=	Mesityl
NHC	=	N-heterocyclic carbene
py	=	pyridine
RCM	=	ring-closing metathesis
ROM	=	ring-opening metathesis
ROMP	=	ring-opening metathesis polymerization
Troc	=	trichloroethoxycarbonyl

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[19] A distinction should be drawn between air-stable catalysts, and air-stable catalyst precursors. Precatalysts containing non-labile ligands often display higher stability to oxygen, but initiate slowly (see, for example, Refs. 20, 21.) The active catalyst formed by ligand loss is more oxygen-sensitive, by virtue of the greater accessibility of the metal, and the inherent susceptibility of Ru(II) toward oxidation to Ru(III). The activating effect of oxygen sometimes noted for phosphine-containing precatalysts implies a

dissociative mechanism, with efficient trapping of released phosphine as the phosphine oxide, a weaker donor ligand (see Ref. 22, and references therein). The productivity of any Ru catalyst in aerobic metathesis is determined by the relative rate of metathesis vs. decomposition, accounting for the typically low yields for challenging RCM reactions carried out in air.

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