Equilibrium Ring-Closing Metathesis

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Contents

1. Introduction

Ring-closing metathesis (RCM) of dienes is one of the most important methodologies now in use for the assembly of cyclic organic compounds. First employed by Villemin and by Tsuji nearly three decades ago,[1,2] the reaction has risen to astonishing prominence in organic synthesis over the past decade, owing largely to the development of easily handled catalysts that enable controlled reaction.[3] RCM represents a key step in many synthetic sequences: recent reviews describe its use in, inter alia, construction of synthetically valuable building blocks such as heterocyclic rings containing phosphorus,[4] sulfur,[4] oxygen,[5] or nitrogen,[5,6] including aromatic heterocycles;[7] spirocyclic,[8,9] cyclophane,[8] and polycyclic compounds;[8,9] and compounds of biological and medicinal relevance such as peptidomimetics,[10,11] carbohydrate derivatives,[11−14] alkaloids,[11,15−19] bioactive cyclic molecules,[20,21] and polycyclic ethers,[22] including macrocyclic aza-crown ethers[23] and topologically interesting molecules and "molecular machines".[24,25] While the common rings of 5−7 members have historically been dominant, owing in part to their greater ease of access, important advances have been made in the synthesis of medium[20,26−30] and macrocyclic[16,17,23,27,31−35] targets. One aspect of this review will examine the increased tendency of many medium and large rings to participate in equilibrium metathesis, and the resulting implications for selectivity and yields.

As with any other cyclization method, the synthetic efficiency of RCM is limited by the competition between intramolecular ring-closing and intermolecular oligomerization reactions. In the standard depiction of Figure 1, olefin metathesis is represented as a fully reversible set of [2 + 2] cycloaddition−cycloreversion equilibria, implying a thermodynamic distribution of "living" metathesis products.[36,37] The extent of reversibility in the various reaction manifolds in fact varies considerably, depending on the nature of the substrate and the extruded olefin, the competence of the catalyst, and the experimental conditions. In many cases, it will be seen that diene RCM and oligomerization reactions are irreversible. Where the RCM and oligomeric products are not able to interconvert, these competing pathways are terminal, and a kinetic product distribution results. Under these circumstances, it is crucial to limit oligomerization if RCM yields are to be maximized. The challenge is familiar from the classic, noncatalytic, cyclization methodologies in use since the early part of the last century.

Increasingly common, however, is the case in which these initial reactions are *not* terminal, because catalyst reactivity and lifetime suffice to enable sustained reaction at internal olefinic sites (section 3). A ring−chain equilibrium can then be established, involving cyclodepolymerization (CDP) of oligomers or polymers, or oligomerization of the intended

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Sebastien Monfette was born in Cap-de-la-Madeleine, QC, in 1982. He received his first research experience as the inaugural Inorganic Chemistry Exchange (ICE) student in 2004, under the supervision of Prof. Lisa Rosenberg at the University of Victoria, BC. He then returned to the University of Ottawa, where he completed his B.Sc. in chemistry in 2005. He is currently a fourth year doctoral student working with Prof. Deryn Fogg at the University of Ottawa, where he is developing new catalysts for applications in olefin metathesis and exploring the mechanistic behavior associated with ring-chain equilibria in ring-closing metathesis.

Deryn Fogg, a native of Sault Ste. Marie, Canada, obtained her Ph.D. in chemistry from the University of British Columbia (1995), where she worked with Prof. Brian James. After postdoctoral studies with Prof. Dick Schrock at MIT, she joined the University of Ottawa, where she has been a full professor since 2007. Honors include the Polanyi Prize in Chemistry (1997), the Strem Chemicals Award in Pure or Applied Inorganic Chemistry (2007), an NSERC Accelerator award (2007), and election as a Fellow of the Canadian Institute for Chemistry (2009). She is a founding member of the University of Ottawa Center for Catalysis Research and Innovation, and since 2000, she has chaired the "Bacon and Eggheads" series of science lectures for Canadian federal parliamentarians. Major research interests include the design and study of homogeneous catalysts for olefin metathesis and tandem catalysis, and the application of MALDI-TOF MS to the elucidation of problems in organometallic chemistry and catalysis.

RCM product. It is the CDP pathway to RCM targets that we shall describe as "equilibrium RCM" (ERCM). Studies of ring−chain equilibria go back to the early part of the last century, as discussed in excellent reviews by Semlyen and Suter.[38] The challenge when operating under such equilibrium conditions in metathesis lies in identifying the various factors that can be deployed to maximize RCM yields and gauging their impact on the lifetime of the catalyst species that enable equilibration.

The development of relatively robust, highly active "second-generation" Ru-NHC catalysts[39] (NHC = *N*-heterocyclic carbene), rightly seen as a milestone in expanding the scope of RCM methodologies to previously intractable substrates, has also led to fundamental changes arising from a greater

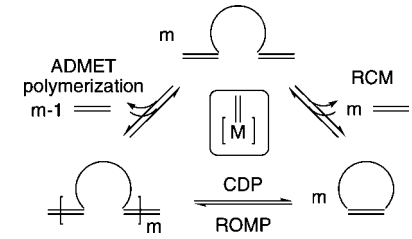


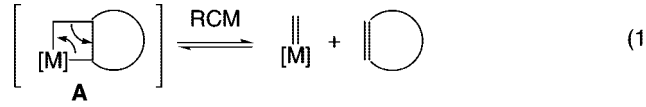
Figure 1. Conventional cartoon representation of olefin metathesis: equilibria relate all olefinic species. ADMET = acyclic diene metathesis, RCM = ring-closing metathesis, ROMP = ring-opening metathesis polymerization, CDP = cyclodepolymerization.

tendency toward equilibrium processes. Thermodynamic control is particularly relevant in the RCM synthesis of many medium-sized or macrocyclic targets via these catalysts. It is therefore important to understand when it can be expected, how it can be recognized (and monitored), and how to exploit it. The present review, covering the literature from 1968 to 2008, examines the physical properties of substrates and catalysts for which ERCM can be anticipated, experimental parameters that limit or promote establishment of equilibrium, and the implications of this behavior for organic synthesis.

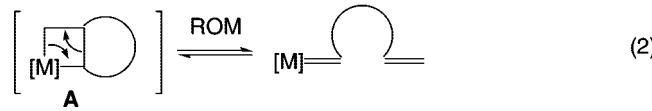
While RCM has seen major developments over the past 15 years, ROMP dates back four decades. One of the take-home messages of this review is that the two are inextricably related. We hope that the practicing organic chemist will find value in this back-to-back analysis of the molecular and macromolecular contexts of metathesis, which illustrates how long-established concepts in ROMP chemistry can offer insight into synthetic challenges in RCM.

2. Ring−Chain Equilibria in ROMP: Polymerization and Cyclodepolymerization

The mirror-image relationship between ring-closing and ring-opening metathesis (ROM) is evident from comparison of eqs 1 and 2, which depict the cycloreversion pathways available to the Chauvin metallacyclobutane intermediate **A**.[36]



(1)



(2)

For many ROMP monomers, including norbornene and cyclooctene, release of ring strain creates an enthalpic driving force for irreversible ring-opening. Importantly, however, backbiting to give cyclic oligomers (cyclic dimers, trimers, etc.) remains possible. The proportion of such low-strain species is governed by a delicately poised equilibrium, in which more subtle thermodynamic factors come into play. These factors, and their consequences, have been examined in detail in ROMP chemistry, in which a combination of high catalyst activity and mild reaction conditions gave early prominence to the possibility of equilibrium behavior. We therefore begin by examining ring−chain equilibria in the context of metathesis polymerization. The operative principles are then considered within the context of RCM synthesis. The catalysts cited here and subsequently are

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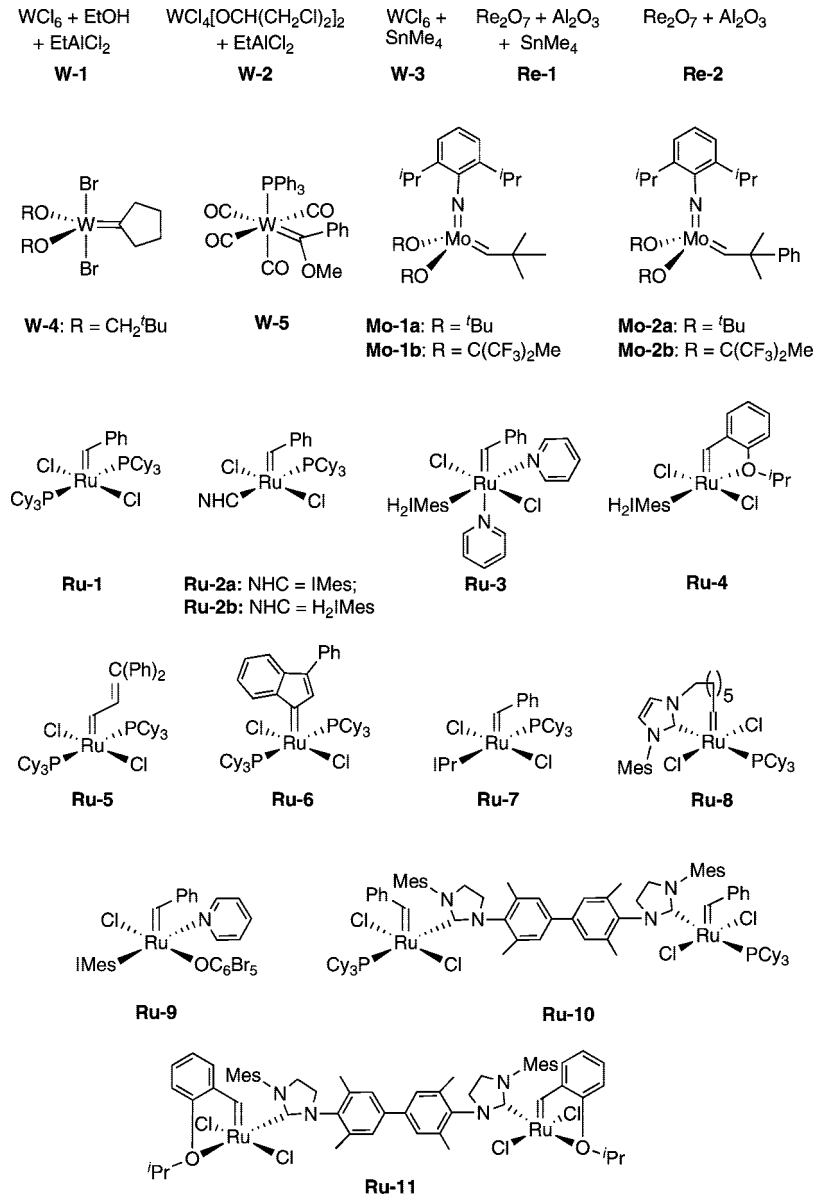

Figure 2. Metathesis catalysts cited in the following sections.

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summarized for convenience in Figure 2. It will be noted that these include classic as well as well-defined catalyst systems: while the former have diminished in popularity, owing largely to their limited functional-group tolerance, the implications of their equilibrium behavior are highly relevant to the present discussion.

Two distinct sets of ring−chain equilibria are operative during ROMP of cycloolefins (Figure 3). Equilibrium (i) relates the cyclic monomer and linear polymers. Equilibrium (ii) shows the relationship between the living, linear ROMP polymers and the cyclic oligomers formed by cyclodepolymerization. So-called ring−ring equilibria are necessarily mediated by the open-chain metal-alkylidene species and thus remain examples of ring−chain equilibria.[40]

A third equilibrium, not shown in Figure 3, involves interchain metathesis between linear polymers. This chain transfer process provides one means of equilibrating cis and trans olefin geometries: *E*/*Z* isomerization can also occur via an intramolecular pathway, as in (ii). Cis−trans ratios are thus often implicitly taken as a marker of equilibrium metathesis processes; see section 4.

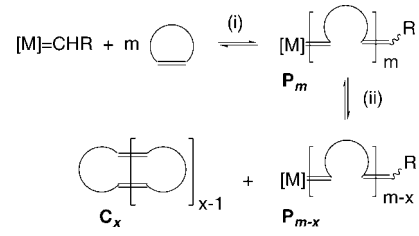

Figure 3. Initiation and ensuing polymerization−cyclodepolymerization equilibria in ROMP. (For high-strain monomers, ring-opening is irreversible). Here $\mathbf{P}_m$ and $\mathbf{P}_{m-x}$ are linear polymer chains of degree of polymerization m and $m-x$, respectively, and $\mathbf{C}_x$ is a cyclic oligomer of degree of polymerization x.

2.1. Observation of Cyclic Oligomers during ROMP

Formation of low-strain cyclic oligomers during ROMP of monocyclic olefins containing 5−12 carbon atoms (Figure 4; Table 1) was first reported 40 years ago. The reaction was quickly recognized as a ring−chain equilibrium, in which identical macrocyclic species were obtained by cyclooligomerization of monomer or by depolymerization

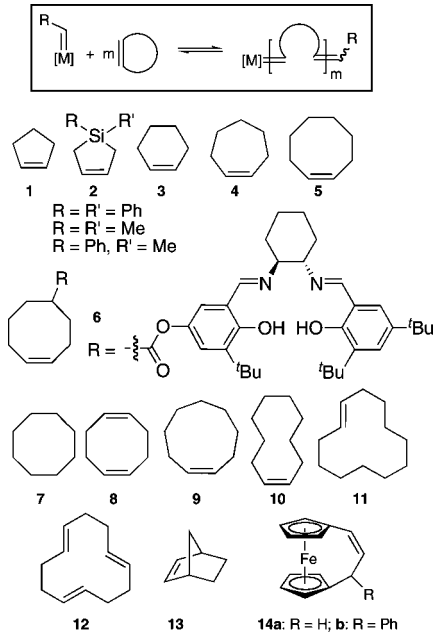

Figure 4. Representative monomers for which cyclooligomers have been reported during ROMP or ring-opening/ring-closing cyclooligomerization processes. For experimental details, see Table 1.

of high polymer.[41] The cyclic nature of these constituents and details concerning the equilibria were established by mass spectrometric characterization, including analysis of isolated fractions and in some cases their hydrogenated products.[42−46] The equilibrium concentration of the $\mathbf{C}_x$ oligomers was found to decline progressively with increasing degree of polymerization x and increasing cyclomonomer ring size n, as intuitively expected on the basis of the declining probability of encounter between chain ends, and consistent with Jacobson−Stockmayer theory, as discussed in the following section.[43] The specific proportions of the various cyclic olefins for the systems of Figure 4 were found, however, to vary even for a given cyclic monomer (Table 1). A number of workers have noted that the observed product distributions do not necessarily represent equilibrium values, owing largely to limitations in catalyst lifetime or activity.[47−49] In a detailed study, Thorn-Csanyi commented on the range of values reported for the 1,5-cyclooctadiene system and demonstrated that full equilibrium had not been established in all cases.[48]

In related recent work, Goldman, Scott, and co-workers reported the tandem dehydrogenation and metathesis of cyclooctane to yield cyclic and acyclic oligomers of cyclooctene, as well as ring-contracted products arising from isomerization.[50]

Formation of cyclooligomeric species during ROMP of norbornene was described by Reif and Höcker.[44] Although norbornene derivatives were long thought to resist cyclooligomerization,[40] advances in analytical methodologies (particularly electrospray mass spectrometry, ESI-MS) ultimately revealed that such species are indeed present.[71] Of note, formation of cyclooligomers during ROMP of norbornene by **W-3** was found to be suppressed by small amounts (0.2 mol %) of added isoprene.[72] The conjugated diene attenuates, but does not extinguish, the activity of the metathesis catalyst: the resulting catalyst system is reactive enough to effect linear polymerization of the strained bicyclic olefin but is unable to promote the nearly athermal (i.e., ergonically neutral) backbiting reaction. The importance of high catalyst activity in enabling backbiting will emerge as a central issue in RCM chemistry.

A key feature of these ring−chain equilibria, again with major implications for RCM, is their concentration-dependence. Early work by Chauvin and co-workers on ROMP of COD described the formation of cyclic oligomers at low monomer concentrations (0.65 M), but a mixture of low-molecular weight cyclic oligomers and high-molecular weight linear polymer at higher concentrations (1.35 M).[65] As this suggests, dilution plays a major role in shifting the equilibrium in favor of the smaller, cyclic species, which are favored by translational entropy (section 2.2.2). A related study, which underscores the futility of attempting to "push" these (equilibrium) reactions forward by simply adding more catalyst, demonstrated that the 1:2 ratio of cyclic oligomer and high polymer obtained at equilibrium was unaffected by a 10-fold increase in catalyst loading.[45]

Such bimodal molecular weight distributions, observable using appropriate GPC conditions, proved characteristic of these systems. The operation of a ring−chain equilibrium (i.e., (ii), Figure 3) was indeed initially deduced from the observation of a steady increase in the proportion of cyclic oligomers prior to formation of a measurable amount of polymer.[43] Höcker later noted that the approach to equilibrium may involve an initial bias toward either cyclic oligomers or linear polymer: that is, stepwise or chain growth mechanisms, respectively.[47] The favored pathway was proposed to correlate with the degree of ring strain and the reactivity of the catalyst. Metathesis of high-strain cycloolefins by catalysts of relatively low activity was reported to initially yield high molecular weight polymers, from which cyclic oligomers were subsequently extruded by cyclodepolymerization (i.e., backbiting). At the opposite extreme, metathesis of low-strain cycloolefins by highly reactive catalysts gave cyclic oligomers as the kinetic products, with cyclodimers and cyclotrimers being predominant. These cyclic species underwent conversion into high-molecular weight linear polymer through a stepwise chain growth mechanism once the equilibrium concentration of each $\mathbf{C}_x$ oligomer was exceeded (see next section). At equilibrium, linear polymer coexisted with a homologous series of cyclic oligomers. Where the early stages of reaction are dominated by linear polymer, the viscosity of the solution was shown to pass through a maximum, which declined as the cyclic oligomers were evolved.[37,73] The distribution and absolute concentration of homologous rings present at equilibrium are identical, however, irrespective of whether the starting point is the monomer, the polymer, or a mixture of cyclic oligomers.

2.2. Theoretical Context

2.2.1. Theories of Ring−Chain Equilibria

The Jacobson−Stockmayer (JS) theory of macrocyclization equilibria considers the distribution of cyclic and linear polymers present at equilibrium in concentrated solutions.[74] At a given concentration, increases in ring size lead to a decreasing probability of cyclization, for ideal chains within the Gaussian random walk approximation. In its original form, JS theory was based on the following assumptions: (1) all rings are strainless, and cyclization is athermal; (2) the end-to-end distances of linear chains obey Gaussian statistics; (3) the probability of cyclization is determined by

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Table 1. Cyclooligomers of Degree of Polymerization *x* Detected during ROMP of Monomers Containing *n* Ring Atoms[a]

n	mon.	cat.	conditions	detection method	*x*	ref
5	**1**	**W-1**	2.7 M, C_6H_6, 0−25 °C	GLC	3−8	51
5	**1**	**W-2**	3 M, C_7H_8, −20 °C	GC-MS, GPC	3−11	52
5	**2**	**W-3**	neat, RT	NMR	1, 2	53
5	**2**	**Mo-2b**	neat, RT	NMR	1, 2	53
6	**3**	**W-3**	4.2 M, C_7H_8, −77 °C	GC	2−6	54
7	**4**	**Re-1**	2.7 M,[c] *n*-pentane, 35 °C	GC, GPC, EI-MS	2−5	55, 56
7	**4**	**W-4** + $GaBr_3$	0.225 M, CD_2Cl_2, −38 °C to RT	^1H, ^{13}C NMR	2[b]	49
8	**5**	**W-1**	0.31 M, C_6H_6, 2 h, 5−20 °C	EI-MS	2−15	57
8	**5**	**W-1**	1.57 M, C_6H_6, 25 °C	GC, GLC, EI-MS	2−11	41
8	**5**	**W-1**	0.39 M, *n*-heptane, C_6H_6 or C_6H_5Cl, RT, 30 s to 20 min	NMR, MS, osmometry, viscometry	2−10	42, 43, 58−61
8	**5**	**Re-1**	1.4 M,[c] *n*-hexane, 50 °C	GC, GPC, EI-MS	2−5[c]	55, 56
8	**6**	**Ru-3**	0.10 M, CH_2Cl_2, RT, 1 h	NMR,[b] GPC, MALDI-MS	2−10	62
8	**7**	**Mo-2b**	neat,[f] 125 °C	GC-MS, GPC	1−9	50
8	**8**	**W-1**	1.57 M, C_6H_6, 25 °C	GLC, EI-MS	3−20[d]	41
8	**8**	**Re-2**	0.27 M, *n*-heptane, 40 °C	GC	3−14[d]	63, 64
8	**8**	**W-5** + $TiCl_4$	0.65 M, C_6H_5Cl, 30 °C (solely cyclooligomers)	GPC	3−12	65
9	**9**	**Re-1**	2.3 M,[c] *n*-hexane, 50 °C	bp, EI-MS	2−5[c]	56
10	**10**	**Re-1**	1.7 M,[c] *n*-hexane, 50 °C	bp, EI-MS	2−5[c]	56
12	**11**	**W-1**	0.01 M, *n*-pentane or *n*-octane, RT	GLC, GPC, MS	2−14[e]	66−68
12	**11**	**W-1, W-3**[g]	0.1 M, C_6H_6, *n*-heptane, cyclohexane, RT	GPC, MS	2−7	43, 60, 69
12	**12**	**Re-2**	10% (w/w), C_6H_6, 40 °C	GC, MS	3−14[d]	64
12	**12**	**W-1**	1.57 M, C_6H_6, 25 °C	GLC, EI-MS	3−8	41
5	**13**	**W-3**	0.05−0.33 M, C_6H_5Cl, 0 °C to RT	GPC (light scattering)	2−14	44, 61
6[h]	**14**	**Mo-2b**	0.11 M, C_6D_6, 40 °C, 3 d	NMR, GPC, EI-MS, ESI-MS	≥2	70

[a] For additional details, readers are referred to the excellent survey by Ivin and Mol.[37] [b] Routine NMR methods did not distinguish between larger cyclic oligomers and linear polymer. [c] Higher dilution achieved at catalyst surface by Soxhlet circulation of volatiles. Selectivity for cyclodimer: from cycloheptene, 80%; from COE, 34%; from cyclononene, 74%; from cyclodecene, 59%. [d] Concentration and degree of polymerization *x* for COD-, CDT-, or PBD-derived cyclooligomers given in units of C_4H_6. [e] Higher oligomers identified as catenanes. [f] Dehydrogenation of cyclooctane achieved using an Ir pincer catalyst to produce a low steady-state concentration of COE. [g] Other catalysts used: WCl_6 or $WCl_2(OPh)_4$ with EtOH or BuLi, and $EtAlCl_2$ or $AlBr_3$. [h] 1,1′-(1-Propene-1,3-diyl)ferrocene is a ring-tilted ferrocenophane: ring strain present. Specifics of *x* not reported.

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the fraction of all configurations for which the chain ends coincide; and (4) the reactivity of chain ends is independent of chain length.

JS theory predicts a critical monomer concentration $[M]_c$ (or "cut-off point") at equilibrium, below which a distribution of cyclic species is present, and above which the total concentration of cyclic oligomers remains constant and linear chains emerge.[37] Because enthalpic effects are neglected, and because the change in entropy for the chain is treated as essentially independent of chain length, the macrocyclization equilibrium constant K_x is determined solely by the change in configurational entropy associated with cyclization. The value of K_x (i.e., the critical monomer concentration, cmc) for the cyclic species $\mathbf{C}_x$ declines with increasing degree of polymerization *x*, and hence ring size, within a homologous series. This behavior is summarized in eq 3:

$$K_x = \left(\frac{3}{2\pi\langle r_x^2\rangle_0}\right)^{3/2}\frac{1}{N_A{\sigma_R}^2} \qquad (3)$$

where $\langle r_x^2\rangle_0$ is the mean-squared end-to-end length of the random chain, N_A is Avogadro's number, and σ_R is a symmetry number that takes into account indistinguishable configurations, being equivalent to 2*x* for cyclic species.

For long polymer chains, we can make the approximation $[\mathbf{P}_m] = [\mathbf{P}_{m-x}]$, where $\mathbf{P}_m$ is a linear polymer with *m* repeat units (see Figure 3). The cyclization equilibrium constant (eq 4) for extrusion of a cyclic oligomer with degree of polymerization *x* is then approximated by $[\mathbf{C}_x]$, and hence:

$$K_x = [\mathbf{C}_x] = A{\cdot}x^{-5/2} \qquad (4)$$

where *A* is a proportionality coefficient. Where JS theory is obeyed, plots of log $[\mathbf{C}_x]$ vs log *x* are linear, with a slope of −2.5, reflecting the decrease in the equilibrium concentration of cyclic oligomers for larger *x*. A slope approaching this theoretical value was recorded for cyclooligomeric species observed during ROMP of cyclooctene, cyclooctadiene, cyclododecene, and cyclopentadodecene.[75] (Deviations emerged for cyclic oligomers with $x < 4$, a point we return to below). The presence of additional unsaturation in the cyclic monomer shifted the line to the right, with the effect being equivalent to a lower $\mathbf{C}_x$ value or a more flexible chain.

Suter and Höcker improved on the original JS random flight model by using the rotational isomeric state (RIS) model to estimate the chain end-to-end distances. (This treatment considers the chemical structure of the chain in predicting the conformational behavior of macromolecules).[76] Values of K_x thus predicted agreed well with experimental values for macrocycles containing >30−40 backbone atoms.[77] Even once RIS assessments are incorporated, however, JS theory tends to overestimate values of K_x for shorter chains, as the ring strain increases, and the assumption of zero enthalpy of cyclization (and that K_x is determined solely by $[\mathbf{C}_x]$) becomes less tenable. While an inverse relationship between ring size and reaction concentration is maintained, the magnitude of the −5/2 scaling factor is affected, and hence estimates of the proportion of cyclics present. The theory remains useful for assessing the equilibrium proportion of relatively strain-free cyclooligomers formed through polymer backbiting, as in the examples to be considered in section 2.3.2. The limitations associated with consideration of solely entropic factors become more severe for medium rings, for which enthalpic factors are increasingly important (vide infra). Kornfield's updated treatment improves predictions of the distribution of cyclic and linear products by computing the enthalpy change through Monte Carlo methods.[78] Here the change in enthalpy is assumed to be due only to the strain energy, as the number of bonds and hence total bond energy in the ring−chain equilibrium remains constant, and intermolecular interactions are largely unaffected. Im-

Table 2. Thermodynamic Terms in ROMP or Ring-Opening Metathesis Oligomerization as a Function of Ring Size (Adapted from Refs 75 and 80)

ring size, n	common ($n = 5-7$)	medium ($n = 8-11$)	large ($n \geq 12$)
$\Delta H°$ ring strain	small or zero	large, negative	small or zero
$\Delta S°$ probability of encounter	high	intermediate	low
conformational motion (torsional/rotational)	low	intermediate	high
(overall) rotational entropy	high	intermediate	low
translational entropy	high	intermediate	low
net effect on $T\Delta S°$	small (negative)	small (negative)	positive[a]
$\Delta G°$	small (negative or positive),[b] enthalpy-driven	large (negative)	negative, entropy-driven
$[M]_e$	0.01−5 M	very low	low

[a] The magnitude of $\Delta S°$ is very sensitive to concentration for large rings. [b] For 5−7-membered rings, the thermodynamic susceptibility to intermolecular reaction (both sign and magnitude of $\Delta G°$) is highly sensitive to ring size and substitution, and to the reaction conditions.

portantly, this treatment also enables prediction of the polymerizability of cyclic monomers. A revised critical monomer concentration is proposed, $[M]_{c,\infty}$, which is defined as the total monomer lost to cyclic products.

As an alternative metric for the equilibrium ring−chain distribution, Thorn-Csanyi and Ruhland proposed the concept of the "turning point" to define the concentration at which rates of change in concentration of linear and cyclic species are equal.[48,79] For the question most relevant to organic synthesis—that is, the appropriate concentration for synthesis of a specific ring size—other methods have been developed, which relate to the value of K_x for that ring size. This point is discussed in more detail in section 3. Nevertheless, a key outcome of JS theory is the qualitative prediction, based on entropic effects, of higher proportions of cyclic species at lower concentration, with an increased bias in favor of smaller ring sizes as dilution increases.

2.2.2. Thermodynamics of Polymerization−Cyclodepolymerization Equilibria

Ivin, Höcker, and others have analyzed the thermodynamics of ROMP in terms of the Gibbs−Helmholtz equation, $\Delta G° = \Delta H° - T\Delta S°$.[37,75,80,81] For cyclic olefins—including RCM products—to undergo oligomerization or polymerization, the standard free energy change $\Delta G°$ must favor ring-opening and intermolecular coupling. Major contributions to the standard enthalpy and entropy of reaction are shown in Table 2. For ring−chain equilibria, the total number of bonds is conserved, and the enthalpic contribution is therefore determined by strain energy, as noted above. Entropic factors include simple encounter probabilities, conformational and rotational motion about bonds, overall rotation, and translational entropy. Experimental variables that favor ROMP are summarized in Table 3.

For common and medium-sized cycloolefins,[82] oligomerization incurs a high entropic penalty that must be compensated for by the release of ring strain. The limited strain present in 5−6-membered rings severely limits the enthalpic payoff available for polymerization.[75] Where $-\Delta H°$ is sufficiently large, $\Delta G°$ will change sign at some "ceiling temperature", above which depolymerization occurs and below which polymerization is favored.[80,81,83] For cyclopentene, for instance (for which the strain energy is only on the order of 17 kJ mol^{-1}), a ROMP-CDP study described an equilibrium concentration of ca. 0.8 M monomer at 25 °C but 95% polymer at −40 °C.[84] ROMP of cyclohexene provides an even more dramatic case: the absence of ring strain in this monomer results in a positive free energy of polymerization even at −77 °C, and only minor amounts of low molecular weight oligomers are formed. McCarthy and co-workers were able to isolate and characterize these species by quenching the catalyst at low temperature, thereby preventing cyclodepolymerization.[54]

Table 3. Experimental Variables That Can Create a Thermodynamic Bias toward ROMP[80]

parameter	effect
high [M]	increases $+\Delta S$ (or minimizes $-\Delta S$)
low T	beneficial, if ΔS is negative
high T	beneficial, if ΔS is positive
high P	beneficial if ΔH and the volume change ΔV are negative: increases negative value of ΔG at a given temperature

The corresponding seven-membered rings commonly undergo polymerization. Ivin has pointed out, however, that the presence of substituents makes ΔG less negative and can even change its sign.[80] Changing the solvent may likewise be sufficient to change the polymerizability of these species. The susceptibility of such compounds to ROMP is also constitution-dependent. The presence of heteroatoms or additional unsaturation within the ring, for example, can have a dramatic effect on strain energies.

Constitutional effects can also temper behavior in the medium-ring regime, but the much higher ring strain present creates a considerable enthalpic drive toward ring-opening. In contrast to the case of cyclopentene noted above, negligible amounts of the "cyclomonomers" are formed by backbiting. In the case of cyclooctadiene (COD) polymers, for example, the smallest ring formed on backbiting is cyclododecatriene[85] (section 2.3.2). Cyclooctene itself represents an unusual case in that polymerization is favored both entropically and enthalpically: it is thus polymerizable at any temperature.[75]

For ring-opening of macrocycles, enthalpic effects become insignificant, but the entropy of polymerization can also be favorable. This reflects the fact that the penalty arising from the decreased translational and overall rotational entropy diminishes with increasing ring size. This cost can ultimately be outweighed by the positive entropic contribution associated with the conformational flexibility of the polymer chain, relative to the cyclic monomer.[75] At high concentrations (in which viscosity limits expression of the higher translational mobility of the monomers), ROMP is entropically driven (section 2.3.1). In terms of JS theory, this extreme would correspond to operation above the cutoff point. Below the critical concentration, CDP is favored, and low-strain macrocycles can be extruded.

2.2.3. Solvation Effects

An influence of the solvent on the position of the ring−chain equilibrium, beyond simply concentration, is noted in several early papers.[43,61] ROMP of cyclooctene in

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heptane, for example, yielded a higher proportion of cyclic species than ROMP in benzene.[43] Similarly, Chauvin reported that use of heptane in place of benzene for ROMP of 1,5-cyclooctadiene increased the proportion of cyclic oligomer at equilibrium.[65] This raises the intriguing possibility that the theta character of the solvent affects the extent of backbiting. Kornfield has suggested that the solvent quality should be significant only for the entropic term, as differences in solvation energy between cyclics and linear chains are expected to be negligible.[78] One form of the JS relation takes solvent quality explicitly into account (eq 5: here n is the number and l the average length of bonds in the monomer, and a is the Mark−Houwink exponent).[147] This predicts a higher value of $[M]_c$ for the thermodynamically better solvent, consistent with the experimental data above. In a good theta solvent (particularly at high dilutions), polymer chains are expanded: this is expected to impede chain-end encounter, and hence liberation of cyclic species through backbiting.

$$K_x = \left(\frac{3}{2\pi}\right)^{3/2}\left(\frac{1}{N_A\sigma_R}\right)\left(\frac{1}{C_x n l^2}\right)^{3/2} x^{-(2+a)} \qquad (5)$$

Thorn-Csanyi has also reported significant solvent effects in the equilibrium E/Z ratios of 1,5,9-cyclododecatriene in studies of polybuta-1,4-diene polymers obtained by ROMP of COD.[85] This was attributed to the different dipole moments of the all-trans and the cis/trans/trans rings.

2.3. Exploiting Ring−Chain Equilibria in ROMP

2.3.1. Entropically Driven ROMP

As the discussion of section 2.2 indicates, an entropic driving force for ROMP of large, low-strain, or even strainless rings can be created at appropriately high concentrations of cyclic olefins. Examples of such behavior were established in early work.[51,75,86,87] Motivated by the attractive features of entropically driven ring-opening polymerizations (including the absence of volatile coproducts, minimal evolution of heat, and control over repeat unit stoichiometry), Hodge and co-workers developed routes to novel polyesters, polyamides, and polycarbonates via ED-ROMP of macrocyclic olefins prepared via RCM (Figure 5; Table 4).[88,89] In an illustrative example, ED-ROMP of 21-membered **19** (x = 1) was effected at 40 °C using **Ru-2b** (1 mol %), at a concentration of ∼700 mM. Reaction was carried out under a stream of nitrogen to induce evaporation of the CH_2Cl_2 solvent and further increase concentration. The polymer was obtained in 96% yield, with the balance being a mixture of cyclooligomers, indicating that these are evolved in the equilibration process.[88] Polymerization of macrolactones and carbonates ranging in size from 18 to 84 atoms (**20**−**24**) was reported, employing **Ru-1** or **Ru-2b** as initiator.[88,90] Mayer and co-workers recently applied this methodology to the synthesis of polypseudorotaxanes.[91] Reaction of cyclic **25** or **26** with catalyst **Ru-2b** in refluxing CH_2Cl_2 for 4 h yielded the corresponding polymers with a degree of polymerization (DP) of 83 or 63, respectively.

2.3.2. Entropically Driven Cyclodepolymerization of Metathesis Polymers

Table 1 illustrated a number of examples in which cyclic oligomers have been observed during ROMP. In other cases, ranging from simple polyalkenamers to polyesters and

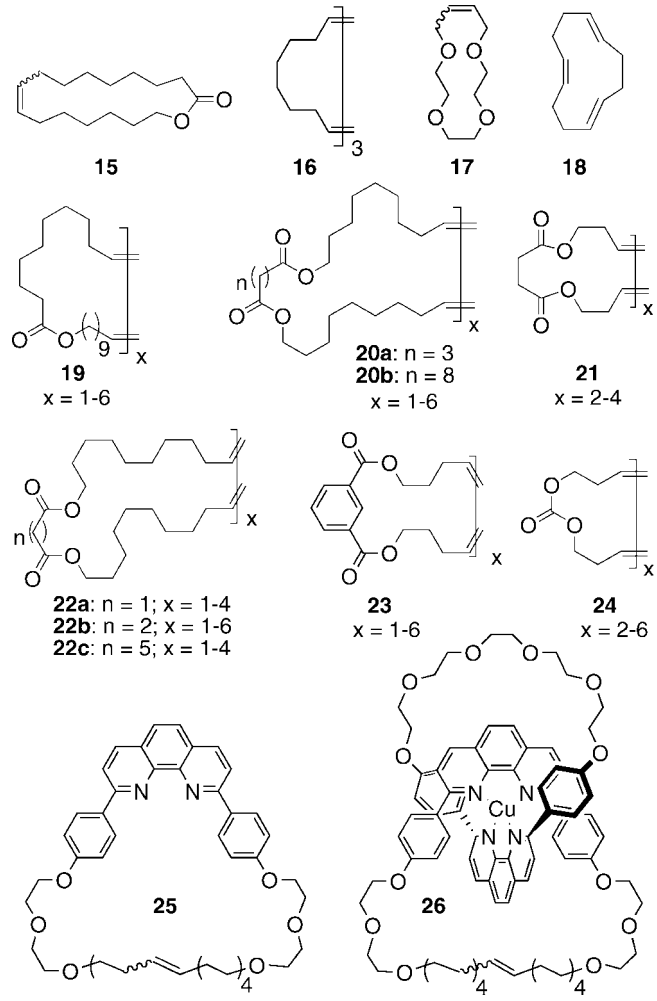

Figure 5. Representative cycloolefins subjected to ED-ROMP. For cyclic oligomers, only the repeat unit is shown. Experimental details appear in Table 4.

polyamides, ROMP (or indeed ADMET) polymers have been prepared deliberately and then cyclodepolymerized (Table 5; Figure 6). Polymer synthesis followed by CDP represents an unconventional route to RCM products, with the advantage (see section 3.2.3) of removing virtually all ethylene from the system at an early stage. The cyclic products attainable are limited to those for which ring strain is sufficiently low that entropic drivers prevail (section 2.1, 2.2.2). Where an enthalpic benefit can be derived, the equilibrium may be insensitive to temperature over some range.

The ring−chain (ring−ring) equilibria can sometimes be shifted in favor of a single product by external perturbation. In CDP of a ROMP polypentenamer, for example, Schrock and co-workers exploited the volatility of cyclopentene to remove it from the reaction mixture as it was formed, ultimately stripping the living polymer down to its tungsten end group.[84] Related approaches include the addition of a templating lithium ion to effect CDP of polyether **39**.[87] This and other examples of the deliberate use of CDP for the purposes of RCM are presented in section 4: for the present, we shall confine ourselves to considering the inherent bias present in the ring−chain equilibrium.

It will be noted from Table 1 that the cyclopentene system, when quenched, was found to contain a wide range of cyclic oligomers.[52] The presence of a heteroatom can reduce ring strain, as noted above. Thus, ROMP polymer **31** was reported

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Table 4. Examples of Entropically Driven ROMP[a]

substrate/monomer	catalyst	conc (M)	solvent	temp	time (h)	yield (%)	Mn ($\times 10^3$)	ref
15	**W-3**	neat				95	95.0	86
16	**W1**	0.3	C_6H_6	25 °C				51
17	**Ru-1**	1.2	CH_2Cl_2	RT	4.5	94	65.9, 129.2	87
18	**Ru-8**	5	CH_2Cl_2	45 °C	12	90	88	92
19	**Ru-2b**	0.7	CH_2Cl_2	40 °C	12	96	37	88
20a	**Ru-1**	1	CH_2Cl_2	25 °C	12	96	20.9	88, 90
20b	**Ru-2b**	1	CH_2Cl_2	40 °C	12	96	33.7	88, 90
21	**Ru-2b**	1	CH_2Cl_2	40 °C	12	92	15.0	90
22a	**Ru-2b**	1	CH_2Cl_2	40 °C	12	99	10.6	90
22b	**Ru-1**	1	CH_2Cl_2	25 °C	12	97	12.0	90
22c	**Ru-1**	1	CH_2Cl_2	25 °C	12	96	19.1	90
23	**Ru-1**	1	CH_2Cl_2	25 °C	12	75	12.2	90
24	**Ru-2b**	1	CH_2Cl_2	40 °C	12	98	21.2	90
25	**Ru-2b**	0.5	CH_2Cl_2	40 °C	4	93	116.0	91
26	**Ru-2b**	0.135	CH_2Cl_2	40 °C	4	93	93.0	91

[a] For compound structures, see Figure 5. Catalyst structures are shown in Figure 2.

Table 5. Inducing Cyclodepolymerization in Metathesis Polymers To Yield C_x Cyclooligomers Containing *n* Ring Atoms per Repeat Unit[a]

n	**P**	cat.	conditions[b]	detection method	*x*[c]	ref
4	**28**	**W-1**	4% w/w, C_6H_6, 25 °C	GLC, EI-MS	3−20	41
4	**28**	**W-5** + $TiCl_4$	0.65 M, C_6H_6 or C_6H_5Cl, 30 °C	GPC, GLC	3−12	65
4	**28**	**Mo-1b**, **Mo-2b**, **W-6b**	0.13−1.8 M, C_7H_8, 25 °C	GC, GPC, NMR	3−6	48, 93
4	**29**	**W-2**	6% (w/w), C_6H_6, RT	NMR	3	94
5	**27a**	**W-4** + $GaBr_3$	0.30 M, CD_2Cl_2, −38 °C to RT	^1H, ^{13}C NMR	1	49
5	**27a**	**W-1**	8% w/v, C_6H_6, 25 °C, 45 min	GLC	1 to ≥3	51
5	**27a**	**W-6a**	0.015 M to neat, C_7D_8, −40 °C or RT	NMR	1	84
5	**31**	**Mo-2b**	0.89 M, C_7H_8, RT,	NMR	2	53
6	**27b**	**W-3**	20% (w/v), C_7H_8, RT	GC	1	54
6	**30**	**W-2**	1−2% (w/v), C_7H_8, RT	GLC	1, 3−7	46
7	**27c**	**W-4** + $GaBr_3$	0.23 M, CD_2Cl_2, −20 to 0 °C	NMR	1−2	49
8	**27d**	**W-1**	4% (w/w), C_6H_6, 25 °C	GC, GLC, EI-MS	2−11	41
8	**27d**	**W-2**	2% (w/v), C_7H_8, 25 °C	viscometry[d]		46
12	**33**	**Ru-2b**	1% w/v, $CHCl_3$, 40 °C, 4 h	GPC, MALDI-MS[e]	2−5	90
13	**34a**	**Ru-2b**	0.06 M, CH_2Cl_2, 40 °C, 18 h	GPC, MALDI-MS	1−7	95
14	**39**	**Ru-1** + $LiClO_4$	0.02 M, CH_2Cl_2/THF (10:1), 45 °C, 75 min	NMR	1	87
15	**36**	**Ru-1**	1% w/v, CH_2Cl_2, 23 °C, 9 days	GPC, MALDI-MS	1−5	90
21	**34b**	**Ru-2b**	0.024 M, CH_2Cl_2, 40 °C, 2 h	GPC	1−5	88, 90
25	**35**	**Ru-2b**	0.25% w/v, THF, 56 °C, 4 days	GPC	1 to >4	89
28	**32a**	**Ru-1**	0.024 M, CH_2Cl_2, 23 °C, 9 days	GPC, MALDI-MS	1 to >5	90
28	**32a**	**Ru-2b**	0.024 M, CH_2Cl_2, 40 °C, 2 h	GPC	1 to >5[e]	88
30	**38**	**Ru-2b**	0.25% w/v, THF, 56 °C, 4 days	GPC	1 to >4	89
30	**37**	**Ru-2b**	0.25% w/v, THF, 56 °C, 4 days	GPC	1 to >4	89
32	**32b**	**Ru-2b**	1% w/v, $CHCl_3$, 40 °C, 4 h	GPC, MALDI-MS	1 to >5	90

[a] Linear polymer structures are shown in Figure 6; cyclic fractions may also be present. [b] Molar concentrations based on average repeat unit, where specified. [c] Higher cyclooligomers of unspecified *x* also observed, in diminishing proportions with increasing *x*. Maximum yield is for $x = 1$ in most cases. Exceptions: **28**, **29**, **31**, and **33**. Representative proportions: **32a**; $x = 1$ (48%), 2 (17%), 3 (8%), 4 (5%).[88] For **34b**: 51% yield cyclooligomers with $x = 1$ (52%), 2 (30%), 3 (7%), 4 (4%), >4 (7%).[88] [d] Intrinsic viscosity decreases from 3.5 dL/g to 0.3 dL/g after 1 h. [e] Isomerization observed for **32a** and **33** in $CHCl_3$, 40 °C, 4 h, isomerization (up to 35% for the cyclodimer of **32a**).[90]

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to undergo depolymerization to liberate a mixture of the silacyclopentene and the corresponding ten-membered cyclic dimer.[53] For the cycloheptene system, Kress reported that ROMP and backbiting of the living polymer afforded cyclotetradecadiene (i.e., the cyclic dimer) and the cyclic monomer as the principal products.[49]

Equilibrium selectivity can be high where one cyclic product is thermodynamically favored. Extensive studies of the CDP degradation of polyisoprene[94,96,97] and polybutadiene[48,93] (the latter obtained by ROMP of 1,5-cyclooctadiene (1,5-COD), among other methods; Figure 7) demonstrated that the most abundant cyclic species present at equilibrium were the all-trans isomers of 1,5,9-trimethyl-1,5,9-cyclododecatriene or 1,5,9-cyclododecatriene **12** (>90%). These species can be viewed as the "cyclotrimers" of the corresponding cyclobutane ring. Calculations by Tlenkopatchev and co-workers concur in predicting that the cyclic trimer is the dominant product in CDP of *cis*-polyisoprene (natural rubber),[98] but suggest that the cyclic tetramers and pentamers should be favored for the polybutadiene system.[99] Considerable discussion is found in much of this work about whether the observed product distributions indeed reflect thermodynamic control (vide supra): this is unsurprising given the very high sensitivity of the group 6 catalysts typically used. Issues of catalyst lifetime may also account for the somewhat surprisingly incomplete selectivity for the cyclohexene product in CDP of polybutadiene−propylene copolymers.[46]

Macrocyclic oligomers can undergo ring-contraction via ring-opening, followed by cyclodepolymerization (Figure 8), liberating thermodynamically stable smaller rings at appropriately high dilutions. A number of reports describe the extrusion of **12** or *all-trans*-1,5,9-trimethyl-1,5,9-cyclododecatriene from their higher cyclic oligomers.[41,48,65,93,94] Formation of the "cyclodimer" (i.e., cyclooctadiene) and cyclobutene itself is precluded by high ring strain; section 2.2.2.

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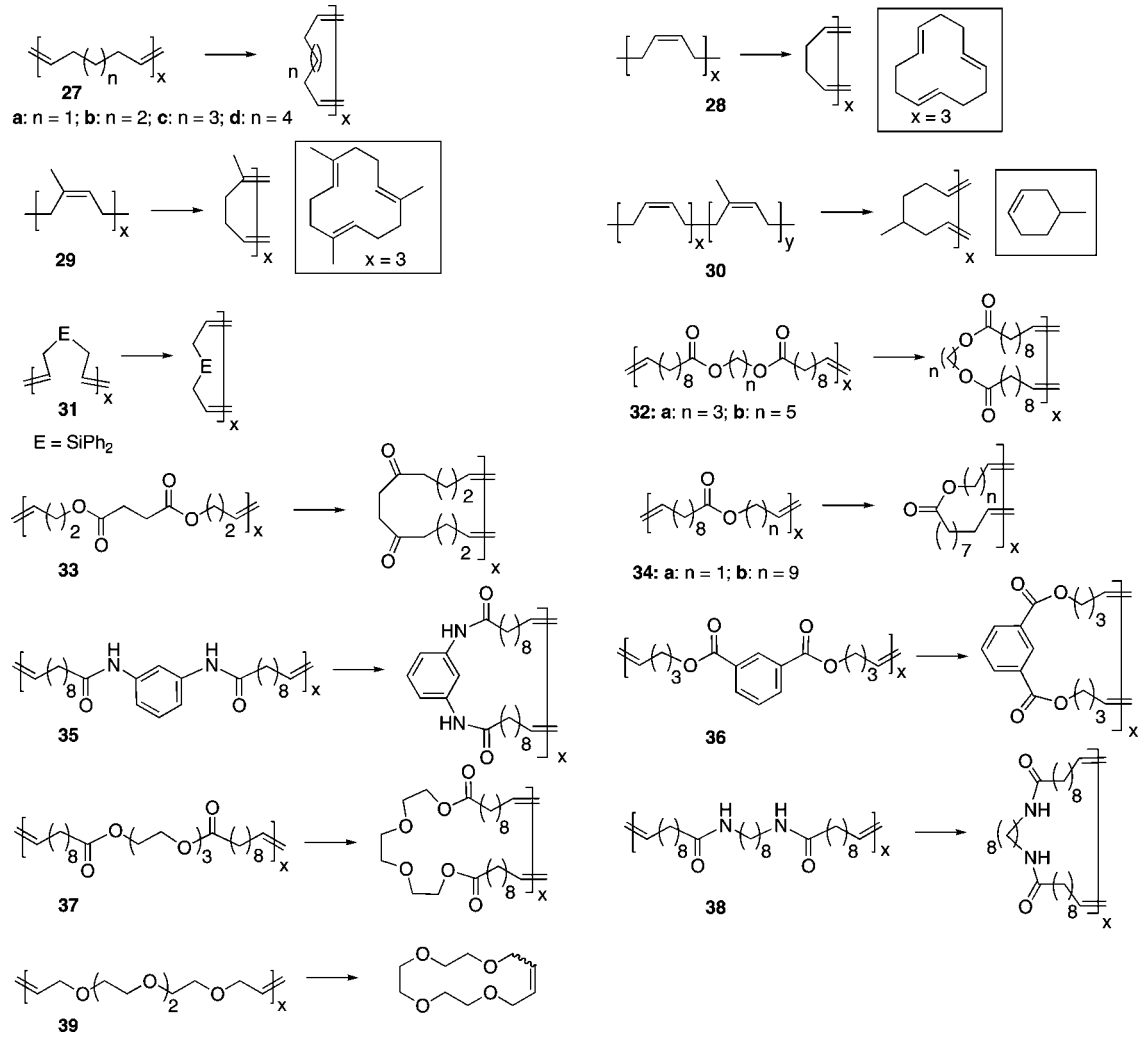

Figure 6. Representative linear metathesis polymers subjected to cyclodepolymerization to yield $\mathbf{C}_x$ cyclooligomers. Particularly stable products shown in boxes. For experimental details, see Table 5.

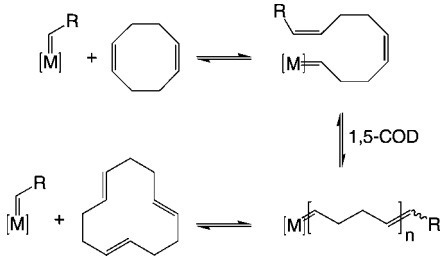

Figure 7. ROMP synthesis and cyclodepolymerization of polybutadiene.[93]

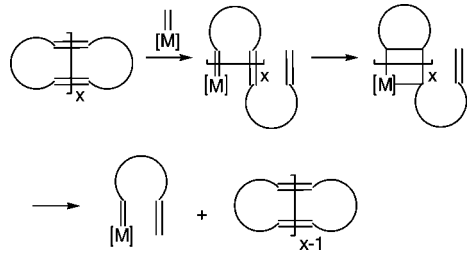

Figure 8. General representation of ring-contracting depolymerization of cyclic oligomers. For simplicity, degradation by a single repeat unit is shown.

For large, monounsaturated rings, the cyclic monomer dominates the product mixture at equilibrium, to an extent that increases with increasing ring size (section 2.2.1). The Hodge group has described the CDP of a range of metathesis polymers to yield macrocyclic rings. In a representative example, CDP of **32a** was carried out at a concentration of 24 mM (Table 5), to obtain as the dominant product cyclomonomer (48%), followed by smaller proportions of cyclodimer (17%), cyclotrimer (8%), and cyclotetramer (5%).[88] Higher oligomers were observed in diminishing amounts. In later work, the same group noted that while **Ru-2b** effected cyclodepolymerization faster than **Ru-1**, a broader distribution of ring sizes resulted from competing isomerization of the double bonds prior to backbiting, even under relatively mild conditions, i.e., refluxing CH_2Cl_2, 4 h.[90] Related examples of isomerization leading to such ring-contraction behavior have been reported (see also section 3.2.3).[41,50,53,64,88,89]

In other studies, Grubbs and co-workers described the synthesis of cyclic polyoctenamers via the NHC-chelated alkylidene catalyst **Ru-8**.[100] ROMP-CDP was proposed to occur through the formation of a transient, ring-expanded macrocyclic complex, in which both the alkylidene and the NHC ends of the growing polymer chain remain attached to the Ru center (Figure 9). Collapse of the ring through intramolecular backbiting at various sites in the conformationally flexible backbone would account for the formation of cyclic polymers with a wide range of degrees of polymerization. Intermolecular chain transfer processes may

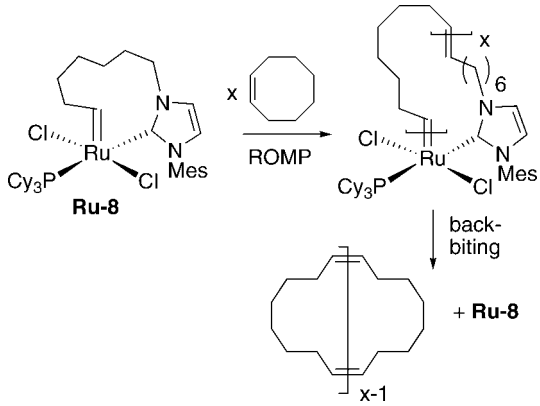

Figure 9. ROMP-cyclodepolymerization to afford cyclic polymers.[100] For simplicity, only the largest cyclic species hypothetically accessible are shown.

also occur. Formation of cyclic polymers clearly rests on the stability of the Ru-NHC bond, as well as the absence of any contaminants containing terminal olefins (i.e., chain transfer agents). That is, either NHC decoordination or chain transfer would result in coformation of conventional linear polymers.[92,101] Subsequent studies extended this approach to cyclooctadiene and cyclododecatriene.[92] More recently, reduction in the tether length of the NHC "arm" was shown to decrease the degree of polymerization *x* in the cyclic polymers.[102]

Synthesis of these catalysts itself provides an object lesson for some of the concepts discussed in this review. Yields proved highly dependent on both tether length and concentration: that is, the optimum conditions were strongly influenced by the size of the metallacyclic ring. For the ten-membered ring system **Ru-8**, for example, none of the desired cyclic product was observable at a concentration of 10 mM, vs 63% at a dilution 10-fold higher.[102]

3. Ring−Chain Equilibria in RCM

Section 2 examined the mirror-image relationship between ring-opening and ring-closing metathesis, and considered ring−chain equilibria in the context of ROMP (including cyclodepolymerization as an equilibrium pathway to cyclic products). In this section we will examine a number of features that distinguish RCM from ROMP processes, including the nature of the substrates, the resting state of the catalyst, and the reaction conditions, particularly as these relate to catalyst viability and the attainment of equilibrium. We will end with a summary of the parameters that increase the probability of ERCM. Examples of ERCM pathways in organic synthesis will be treated in section 4.

3.1. Substrate Properties and the Probability of Equilibrium RCM

3.1.1. Thermodynamic Factors

In ROMP applications, polymerization is typically driven by release of ring strain. Initiation of highly strained monomers is irreversible, though backbiting to form cyclic oligomers can occur. In RCM, no such enthalpic driver exists, barring strategies in which two reactions are coupled (e.g., ROM−RCM processes). RCM is thus entropy-driven, and the enthalpic costs that can be sustained are limited by the extent to which (in Gibbs−Helmholtz terms) the $T\Delta S$ term can be maximized. The entropic benefit associated with release and volatilization of ethylene on metathesis of vinylic α,ω-dienes is powerful but indiscriminate, driving both inter- and intramolecular reaction. Here we consider the thermodynamic role of substrate structure in controlling selectivity for cyclic vs acyclic products and, where the ring−chain equilibrium is accessible, how selectivity can be modulated.

A thermodynamic bias toward cyclization may arise from monomer destabilization (offsetting incipient ring strain, an enthalpic effect), restriction of rotors in the cyclization precursor (which reduces the entropic penalty incurred upon cyclization), or both. The influence of ring size on the susceptibility of cyclic olefins to ROMP was analyzed in section 2. The key parameters will be briefly recapitulated here, in the context of the corresponding bias toward cyclization. A key feature distinguishing the common rings (particularly those of five or six members) from their higher homologues is the strong thermodynamic bias toward their formation. The probability of encounter between reactive end groups is inversely proportional to ring size, and is therefore at a maximum in this size regime, relative to the larger systems. The higher translational and (overall) rotational mobility associated with molecules of smaller size likewise favors formation of common rings over larger rings, or acyclic oligomers, despite the loss in rotational and conformational flexibility. The cumulative effect is to render synthesis of common rings highly straightforward, to the extent that they are frequently accessible by direct RCM, and do not exhibit any tendency toward oligomerization under normal conditions of concentration and temperature. Appropriately substituted dienes can show a dramatically greater bias, and a now-classic paper by Forbes and Wagener demonstrated that, where aided by the Thorpe−Ingold effect, RCM of such substrates can be achieved even in neat diene.[104] Under more conventional solution conditions, the "benchmark" substrate diethyl diallylmalonate showed no evidence of oligomerization at diene concentrations of 100 mM, in contrast to dienes that afford larger rings.[105] (Oligomers were reported on metathesis of neat dimethyl diallylmalonate, however.[104])

The relevance of equilibrium RCM comes into sharper focus in the synthesis of medium and large rings. Ring strain increases sharply in the medium-ring regime, owing principally to imperfect staggering and transannular strain between atoms forced into proximity from opposite sides of the ring.[106] The precise position of the energy maximum with respect to ring size depends on the nature, substitution, and hybridization of the ring atoms. Of interest, given the degree of functionalization often characteristic of RCM substrates, is the finding that $\Delta G°$ for ROMP of some common and medium rings becomes less favorable as ring substitution increases (section 2.2.2).[37,80] This offers some promise for formation of strained medium-ring (or indeed small; vide infra) RCM targets. Strain diminishes as ring size increases further, but remains higher for macrocyclic compounds than for the common rings.

To place the discussion of section 2.2.2 into the present context, the relative weighting of the two key entropic factors, translational mobility (which favors small molecules) and conformational motion (which favors macromolecules), is sensitive to concentration, because translational mobility declines with increasing viscosity, while conformational motion is much less affected.[75] Two experimental variables of particular importance in creating an entropic bias toward cyclic products are therefore high

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dilutions and—in principle—high temperatures. The elevated temperatures[103] commonly employed in RCM (particularly in conjunction with the second-generation ruthenium catalysts), generally regarded as a kinetic requirement, play an additional thermodynamic role in ERCM. They favor cyclization by further reducing viscosity and maximizing thermal motion: they also serve to reinforce any entropic bias in the $T\Delta S$ term. It will be noted that the low temperature ceiling in refluxing CH_2Cl_2, a common RCM solvent, limits the extent of entropic weighting possible. Use of higher temperatures offers advantages in this regard (for examples, see section 4.3.2) but can adversely affect catalyst lifetimes (section 3.2.3). Use of high dilutions also comes at a cost, as discussed in sections 3.2.3 and 4.3.3.

3.1.2. Evaluating the Probability of Cyclization

Methods for gauging the probability of macrocyclization in ROMP were reviewed in section 2.2.1. Here we consider the extension of ring−chain theory from polymer to organic chemistry. In JS theory, the critical monomer concentration was used to define a "cut-off" concentration below which only cyclooligomers are present at equilibrium. Ercolani and co-workers have suggested, however, that the cmc is of limited utility in predicting the outcome of minimally exoergic reactions.[107] Furthermore, this concept has little predictive value in organic synthesis, where selectivity for a single ring size is normally desired. More broadly used is the related concept of effective molarity (EM), originally developed to assess the ease of cyclization of bifunctional molecules[106,108−110] and now widely used to evaluate the probability of self-assembly in a range of contexts.[111−117] Excellent overviews by Mandolini, Ercolani, Illuminati, and co-workers describe the evolution of EM concepts from JS theory.[106,109,110,118] The thermodynamic or equilibrium EM value is in fact equivalent to the macrocyclization equilibrium constant K_x[119] and is defined as the ratio K_{intra}/K_{inter}: the higher the value, the greater the ease of synthesizing a given ring free from competing polymerization reactions.[110]

EM values are extensively used in organic chemistry as an empirical predictor to assess the ease of cyclization reactions. They do not represent physically real concentrations,[120] in contrast to the "effective concentration" (which quantifies the bias toward intra- vs intermolecular reaction by evaluation of a physically real concentration of one reacting entity, as experienced by its partner). Effective concentrations, however, are not readily determined and are thus less commonly used in organic synthesis. Few thermodynamic EM values have been described,[118] for that matter, owing to the dominance of studies focusing on irreversible reactions. Much more common are kinetic EM values, in which the efficiency of cyclization is assessed from the ratio of the rate constants for the analogous intramolecular and intermolecular reactions under identical conditions (i.e., the kinetic EM value $= k_{intra}/k_{inter}$).

In a comparison of kinetic and thermodynamic EM values for saturated prolactones, Galli and Mandolini have noted that while the trends tend to track together, kinetic EM values are consistently higher, up to the limit of "strainless" large rings.[109,121] Where no strain energy is present in the transition states, the kinetic and thermodynamic EM values coincide.[109] Thus, while the difference diminishes as the difference in strain energy between the transition state and cyclic product decreases,[107] higher dilutions are required for cyclization under thermodynamic conditions for any ring where strain is present. The divergence between the two sets of values was thus proposed to be particularly acute in the strained, medium-ring regime.

In a study of equilibrium RCM, the reported EM values for saturated lactones, malonates, and catechol ethers were shown to provide a useful qualitative guide for trends in RCM yields of the corresponding, homologous 7−20 membered rings.[105] For the macrocyclic rings, the kinetic EM values proved a reasonable predictor for the trend in RCM yields at fixed concentration, despite operation under thermodynamic conditions. Deviations found in the medium-ring regime, in which much higher dilutions were required, could reflect the divergence between the trends in kinetic and thermodynamic values noted above.

As this study noted, however, EM values for saturated rings cannot be expected to apply with any quantitative precision to RCM substrates, if only due to the effect of the sp^2 centers on incipient ring strain in the latter.[106,109] Questions were also raised about the potential of the metal complex to perturb strain energies in the cyclic transition states. Although kinetic EM values have been shown to be largely independent of the nature of the reacting groups, reaction mechanism, and solvent for "strainless" rings, for which EM is entropically controlled,[118] the strain-free condition is violated in the large and (particularly) the medium-ring regime.

In an unrelated study of the cyclodepolymerization of poly(butylene terephthalate), Brittain and co-workers found that thermodynamic EM values were not able to accurately predict the critical monomer concentration.[122] Highlighted among the potential sources of error were limitations arising from ring strain or the extent of thermodynamic control.

Quantitative evaluation of effective molarities in the context of RCM could clearly be useful, and the problem is now beginning to receive attention. Two recent studies measure EM values by assessing the proportions of cyclic vs acyclic species. A report from Percy and co-workers examines substituted cyclooctenones bearing a ^{19}F marker. EM values were assessed in the presence of a Ti(IV) cocatalyst, the function of which is discussed in section 4.4.2. Oligomers were observed at diene concentrations above 20 mM (see, e.g., cyclodimer **56**, Figure 17).[123] The broad chemical shift dispersion characteristic of ^{19}F NMR can aid in overcoming the problem of peak overlap which plagues ^1H NMR analysis (see section 4.1). While overlap remained an issue, $^{19}F\{^1H\}$ signals for the "cyclomonomer", the desired RCM product, could be resolved from those due to other species remaining after diene consumption was complete, and identified as oligomeric products. Kinetic EM values were calculated from the integration ratios measured using appropriate relaxation delays, at a range of concentrations of the starting diene. The authors note that this approach requires that ROMP of the RCM product be slow under the experimental conditions; as well, it relies on the absence of side-products, such as those derived from isomerization. Most obviously, it requires the presence of a suitable (e.g., ^{19}F) reporter group.

In a very recent report, the Boehringer−Ingelheim group measured kinetic and thermodynamic EM values for a target macrocycle. Cyclic oligomers were identified by LC-MS analysis, and the product ratios were quantified by HPLC via UV detection.[124] The versatility of the analytical method used, and the capacity to unequivocally identify and quantify

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the diene precursor, the RCM product, and the various oligomeric species (see section 4.1), greatly simplify analysis.

3.1.3. Olefin Coproducts: Volatility and Reversibility

In the conventional depiction of Figure 1, olefin metathesis was represented as a fully reversible set of [2 + 2] cycloaddition−cycloreversion equilibria. In practice, complete reversibility is rare in RCM. Common restrictions include formation of olefinic products that cannot reenter the metathesis cycle by reason of efficient volatilization or low reactivity; inhibition of backbiting by rigidity, ring strain, or catalyst deactivation prior to establishment of equilibrium; and low catalyst reactivity toward internal olefins or nonmetathetical reaction pathways. While all of these factors can be important (and examples of many will be found in section 4), of greatest importance to the extent of reversibility in the *initial* stages of RCM or ADMET oligomerization is the nature of the diene.

In ROMP, extrusion of olefin is an intramolecular process, and the olefin remains subtended on the metal via the growing chain. In RCM, the olefin is released altogether, increasing the entropic driving force for reaction. Where the RCM substrate is a vinylic α,ω-diene (still the vast majority of substrates), this driving force is significantly amplified, owing to the release and volatilization of ethylene as the olefinic coproduct. Where RCM is carried out at elevated temperatures, in a vessel open to an atmosphere of N_2 or Ar, in organic solvents in which ethylene is poorly soluble[125,126] (especially as temperatures increase),[125] loss of ethylene is efficient. The initial reaction is therefore rapidly rendered irreversible. The same factors drive ADMET oligomerization, as noted in section 3.1.1. Because regeneration of the starting α,ω-diene is impossible, the metathesis equilibria simplify to the pathways shown in Figure 10. The only equilibrium then still operative is that between oligomeric and RCM products (providing that the catalyst is competent to effect both ROMP and backbiting), and its concentration-dependence can be exploited to manipulate product ratios, as discussed above.

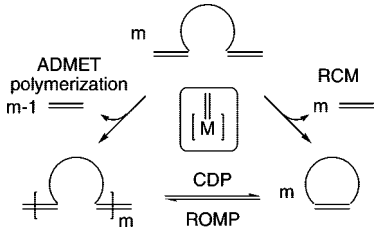

Figure 10. Cartoon depiction of olefin metathesis pathways involving irreversible loss of ethylene.

It should be noted that loss of ethylene can be retarded by use of sealed vessels with minimal headspace. Where ethylene is retained in solution, metathesis productivity is adversely affected by unproductive metathetical exchange[127,128] and by conversion of Ru-alkylidene species into shorter-lived and less reactive methylidene species; see section 3.2.1.[127,129,130] Weiler and co-workers reported only 24% yield, for example, on deliberate use of an ethylene atmosphere to convert a macrocyclic lactam into the corresponding acyclic diene **41** by ring-opening−cross-metathesis. The balance of material (60%) was recovered lactam: interestingly, however, 14% of the cyclic dimer **42** was also obtained (Figure 11).[131] Nosse,[132] Hanson,[133] and their co-workers have noted beneficial effects on RCM yields on deliberately sparging reaction solutions with an inert gas to accelerate loss of ethylene. (Ethylene pressure can have a beneficial effect, however, in enyne metathesis.)[134−136] As a corollary, retention of ethylene in solution for reactions in sealed small vessels can be expected to lead to significant discrepancies in reaction rates and product distribution, relative to the identical reactions in open vessels.

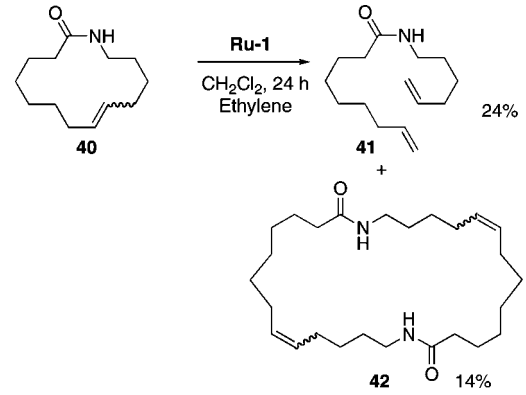

Figure 11. Example of reduced catalyst productivity under ethylene atmosphere.[131]

For metathesis of 1,2-disubstituted or tri- or tetrasubstituted dienes, in comparison, the lower volatility and increased solubility of the olefinic coproducts[137] increase the probability that they will participate in ring-opening−ring-closing equilibria (including reformation of diene) even under conventional synthetic conditions. For such substrates, the equilibria of Figure 1 are likely to be a more accurate description.

3.1.4. Substrate Dimerization

Unsymmetrically deactivated α,ω-dienes, in which one olefin is sterically hindered[138−140] or conjugated with an electron-withdrawing substituent,[141−144] typically undergo preferential dimerization at the other, unperturbed, olefinic site (Figure 12). Dimerization can be viewed as an arrested oligomerization reaction: where catalyst reactivity is insuf-

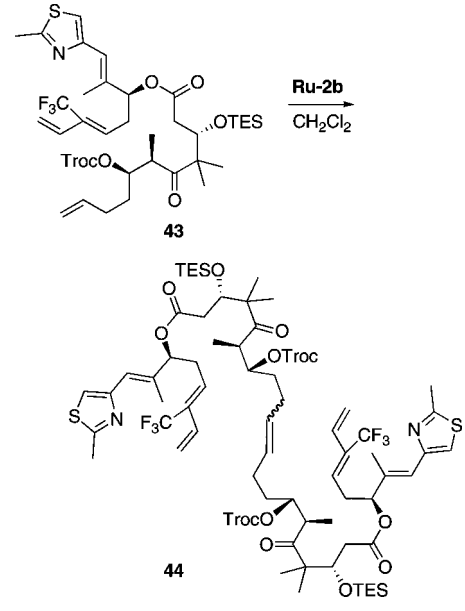

Figure 12. Example of preferential formation of an acyclic dimer by a diene bearing one deactivated vinylic site.[142]

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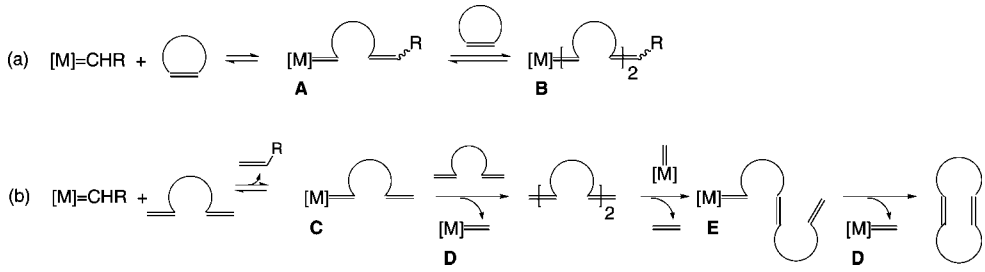

Figure 13. Comparison of resting states in (a) ROMP or (b) RCM of vinylic α,ω-olefins, showing key intermediates.

ficient to effect metathesis at the deactivated site, acyclic head-to-head dimers are formed.[133,138,140,144−152] Establishment of equilibrium will depend on whether the catalyst is competent to reinitiate metathesis at the internal olefinic site. The low reactivity of **Ru-1** toward internal olefins limits its efficacy in RCM of this class of dienes.[138−144,153] A number of studies have shown conversion of such ADMET dimers into the desired RCM products by treatment with a more reactive catalyst.[138−140] Selected examples of this behavior are described in section 4.3.4.

An interesting variant on this behavior comes from a Grubbs report describing the formation of cyclic dimers and trimers from a diene bearing an acrylate functionality at one terminus.[153] The cyclic nature of these products indicates that the activity of the **Ru-2b** catalyst used is sufficient to effect reaction of the electronically deactivated site. Their head-to-tail geometry contrasts with the head-to-head structure of their acyclic counterparts noted above, and the more usual formation of mixtures of head-to-head and head-to-tail cyclic dimers (see section 4.2). This selectivity was attributed to thermodynamic partitioning. Failure to observe the seven-membered lactone may be an artifact of operation at too high a concentration: these reactions were carried out between 2 and 100 mM, but closely related compounds were shown to be accessible only at dilutions of 0.5 mM.[105]

3.2. Catalyst Properties and the Probability of Equilibrium RCM

3.2.1. Catalyst Resting States

A fundamental difference between ROMP and the majority of RCM reactions lies in the nature of the catalyst resting state. In ROMP, these are metal alkylidene species (e.g., **A**, **B**; Figure 13a), which remain tethered to the polymer throughout chain growth and backbiting. Even in the extreme of end-to-end backbiting (i.e., a tail-biting,[154] "Ouroboros" reaction), the original metal alkylidene is regenerated: an example of such behavior in CDP of polypentenamers was described in section 2.3.2.[84] In RCM of the standard α,ω-diene substrates, the initially formed alkylidene complex **C** (Figure 13b) is expelled as the metal methylidene **D** in the subsequent dimerization step. Reinstallation of **D** on an oligomeric chain, or within a cyclooligomeric ring, is then a prerequisite for further reaction. The bimolecular nature of this reaction, and the stability of the methylidene complex, in the case of the Ru systems, have important consequences for catalyst deactivation which are discussed in section 3.2.3.

The lower reactivity reported for the [Ru]=CH_2 species, relative to their benzylidene or alkylidene counterparts,[155,156] constitutes an additional thermal barrier to propagation in RCM. For **Ru-2**, this is exacerbated by the lower lability of the PCy_3 ligand relative to **Ru-1**.[130] Elevated temperatures are therefore commonly required to re-enter metathesis and to enable equilibrium. The more labile first-generation catalyst **Ru-1** exhibits higher reactivity at ambient temperatures, though longer reaction times are often required, owing to the lower metathesis activity of the 14-electron active species.

3.2.2. Catalyst Activity and Kinetic Bias

High catalyst reactivity is essential to enable the backbiting reaction of a metal end group with the 1,2-olefinic sites present at internal sites in the metal-terminated oligomers (e.g., extrusion of cyclic monomer from **E**, Figure 13b). While efficient in RCM of vinylic α,ω-dienes, **Ru-1** shows low activity toward sterically congested olefins[139,140] and is reported to effect cyclodepolymerization[90] (or indeed chain transfer reactions[157]) of ROMP polymers relatively slowly. This limited activity often confines **Ru-1** to essentially irreversible oligomerization or RCM: that is, **Ru-1** can be expected to operate predominantly in the classic, kinetic regime. The much higher activity of **Ru-2** is illustrated by its capacity to effect RCM of trisubstituted (and in some cases tetrasubstituted) olefins.[158,159] The capacity of this and other second-generation Grubbs catalysts to enable efficient backbiting[88,90,105] is of central importance, given their kinetic behavior, which we consider next.

The influence of the inherent *kinetic* tendencies of metathesis catalysts on the approach to equilibrium in ROMP was briefly discussed in section 2.1. This summarized Höcker's division of catalysts into two classes: those with a kinetic bias toward formation of linear polymer, which approach equilibrium by CDP; and those with a kinetic bias toward formation of cyclics, which undergo subsequent ROMP at appropriate concentrations.[47] Of interest in this context is a recent report by Fogg and co-workers, describing a strong kinetic bias of the NHC catalysts **Ru-2a** and **Ru-3a** toward oligomerization of dienes that function as precur-

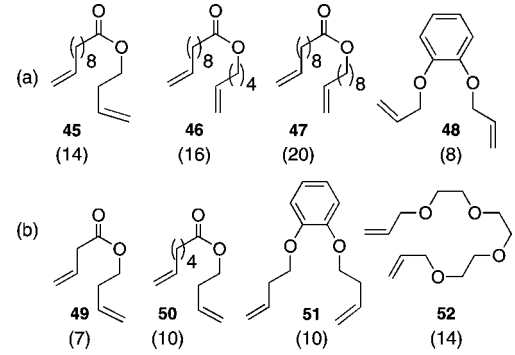

Figure 14. Examples of dienes found to undergo oligomerization−cyclodepolymerization to yield RCM products on reaction with **Ru-2a** or **Ru-3a** (a) at 5 mM or (b) at 0.5 mM.[105] For specifics regarding the concentration-dependence of these reactions, see section 4.3.3.

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sors to large and medium rings, even in dilute solution (<5 mM; dropwise addition).[105] Significant oligomerization was observed at 15 min for α,ω-vinylic prolactones, catechol ethers, and a polyether (Figure 14). Backbiting (i.e., CDP) was also efficient, however, enabling high yields of RCM products over a time scale of hours. The dilutions required varied from 0.5 to 5 mM, depending on ring strain (see sections 3.1.2 and 4.3.3); reactions at 0.05 mM showed incomplete consumption of diene, owing to competing catalyst decomposition (see next section).

The limited capacity of **Ru-1** to react with internal olefins, and by implication to participate in backbiting, was noted above. It is fortunate, therefore, that **Ru-1** exhibits a minimal kinetic tendency toward oligomerization. Thus, RCM of the substrates shown in Figure 14 was found to proceed principally by direct RCM, albeit at rates generally slower than those found for **Ru-2**.[160]

The difference in performance of the first- and second-generation Ru catalysts demonstrates that the mechanistic pathway to RCM products can be controlled through choice of catalyst. Other evidence suggests the possibility of influencing the position of the equilibrium. These ring−chain equilibria are unusual in that the metal complex functions as a partner in the equilibrium, rather than simply a facilitator. "Pseudohalide" analogues of **Ru-3a**, in which a chloride ligand is replaced by a perbromoaryloxide group (e.g., **Ru-9**), exhibited a kinetic preference for RCM, over oligomerization, under conditions of dropwise addition.[161] Whether this represents improved selectivity for RCM over oligomerization, as for **Ru-1**, or simply faster backbiting, is not yet clear. Lemcoff and co-workers recently reported that diruthenium catalysts **Ru-10** and **Ru-11** yield a much larger proportion of cyclic dimer in RCM of 1,12-tridecadiene (**27**; $n = 9$) than **Ru-2b** and **Ru-4**.[162] These studies raise intriguing questions concerning the potential to modulate EM values, and hence selectivity for RCM, through catalyst tuning.

3.2.3. Catalyst Deactivation

A common feature of the early ROMP studies noted in section 2.1 was the observation of nonequilibrium product distributions owing to catalyst deactivation. The same issues apply in diene RCM: deactivation of the catalyst after complete consumption of substrate, but prior to equilibration, can result in isolation of polymeric material even if the reaction is carried out at appropriately high dilutions. This need for high dilutions exacts a price in terms of reaction rates and productivity, however. First, the necessarily bimolecular reaction between substrate and catalyst means that rates of metathesis will decline as concentration decreases. High temperatures or long reaction times are therefore required. Second, the deleterious effect of adventitious contaminants becomes much more significant as catalyst concentration declines. The higher relative concentration of catalyst-noxious components, including "trace" air and water, is a particular risk for oxophilic, hydrolytically sensitive catalysts based on the early and midtransition metals. Catalyst decomposition may account for the somewhat surprisingly poor performance of the Schrock catalyst **Mo-2b** in backbiting of ADMET oligomers, which their high reactivity should be competent to address.[163] The thermal sensitivity of these group 6 catalysts may also be a factor. Catalyst decomposition almost certainly accounts for the failure to observe "oligomerization−cyclodepolymerization" behavior in Villemin's early macrolactonization work using a $WCl_6/SnMe_4$ catalyst system (**W-3**), despite explicit recognition of the importance of substrate concentration (Figure 15).[1] Complete conversion to the macrolactone was achieved at very similar dilutions (5 mM, vs 6 mM) using **Ru-2a**.[105]

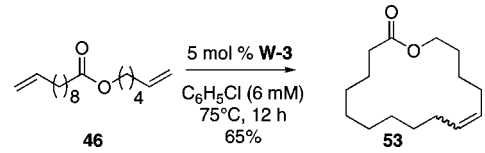

Figure 15. An early example of RCM via an air- and water-sensitive tungsten catalyst.[1]

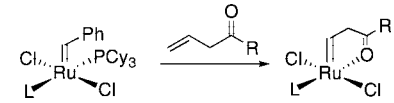

Figure 16. Example of catalyst deactivation through formation of a stable chelated alkylidene.

The Grubbs-class Ru metathesis catalysts, while more robust than their early transition metal and group 6 predecessors, are not long-lived. Within this important family of catalysts, the methylidene intermediate is particularly vulnerable.[129,164,165] The half-life of the methylidene derivative of **Ru-1**, for example, is reported to be only ca. 40 min at 55 °C in C_6D_6; that of the corresponding methylidene complex of **Ru-2b** is ca. ∼6 h.[127,129,164] The half-lives of the benzylidene parents, in comparison, are reportedly 8 days (**Ru-1**)[129] and >1 month (**Ru-2b**),[164] respectively. An important added complication arises from the unimolecular decomposition of these Ru-methylidene complexes.[129,164] This implies that rates of catalyst *depletion* will be unaffected as dilutions increase, but the corresponding rates of RCM will decline. Kinetics evidence[129] and model studies[166,167] suggest a bimolecular decomposition pathway for the Ru-alkylidene precursors. While low turnon efficiency can result in a reservoir of unreacted catalyst, which can be drawn on for demanding transformations in, e.g., total synthesis,[16,31−34] the 14-electron active species formed by ligand loss is much more vulnerable. Again, rates of (bimolecular) ligand rebinding will decline as dilutions increase. As a cumulative effect of high dilutions and elevated temperatures, competing catalyst decomposition can become much more problematic, increasing catalyst loadings, and the burden of purification. A recent review of the RCM macrocyclization literature cites standard catalyst loadings of 2−25 mol %.[33]

The Grubbs-class ruthenium metathesis catalysts, while less sensitive to oxygen or water than the group 6 systems, are nevertheless susceptible to deactivation through formation of stable chelate rings, particularly rings of five or six members (Figure 16).[168−172] Chelation of appropriately located carbonyl or ether groups on RCM or ROMP substrates to the Ru center has been shown by the groups of Fürstner and Khosravi,[168,173−175] and the issue of chelate ring size and stability has been usefully discussed.[173,176] (For approaches that have been used to disrupt chelation, see section 4.4.2). Instances of sensitivity to alcohol or amine functionalities have also been reported.[177−179] Observation of unconverted starting material is a common marker for such deactivation. Reported as a further risk for metathesis of acrylates, particularly for **Ru-1**, is formation of Ru═CHC(O)R species of low metathesis activity.[180,181] (Successful RCM of acrylate substrates by more active catalysts has been described).[140,181−183] Metathesis of vinyl ethers likewise yields Ru products (Fischer carbenes) of low metathesis activity.[184,185]

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Vinyl halide substrates trigger decomposition: Johnson and co-workers have presented compelling evidence that this is due to formation of metathesis-inactive Ru carbides.[186,187]

Nonmetathetical pathways can disrupt equilibrium RCM by depleting the concentration of the metathesis-active catalyst species, as noted above, or by altering the product distribution. Among the wide range of nonmetathesis pathways promoted by the Grubbs catalysts,[188] olefin isomerization is particularly common as an unintended side-reaction. Isomerization of the diene precursor can alter the product ring size or disrupt RCM completely.[182,189−191] Isomerization of ADMET polymers (i.e., double bond migration along the polymer backbone), well documented by the Wagener group,[192−196] can likewise result in ring contraction or expansion upon backbiting, as described in section 2.3.2. Such behavior has been observed in the presence of both Ru[90,182,189−196] and Mo[50,191,197,198] catalysts. The problem is particularly severe for the second-generation Ru systems, relative to **Ru-1**.[182,190,192] The correlation between high metathesis activity and high double-bond isomerization activity was pointed out by Thorn-Csanyi and co-workers in a study of the Schrock catalysts (both Mo and W).[199]

3.3. Summary: When Is ERCM Operative?

Fundamental to the question of whether equilibrium RCM or direct RCM will be operative is the ring size and extent of strain in the product. Common rings, in many cases, will favor DRCM; for others, the equilibrium pathway must be considered. Critical in the latter case is the kinetic bias of the catalyst (or, more properly, intermediate **C** in Figure 13) toward oligomerization, vs cyclization. For catalysts characterized by a kinetic bias toward oligomerization, mobilization of the ERCM pathway requires that the catalyst activity and lifetime are adequate to support sustained backbiting.

ERCM product distributions are governed by concentration and temperature. If dilutions are insufficient, the equilibrium will favor oligomers over the desired RCM products. Suitable dilutions for ERCM synthesis of targets with a range of ring sizes and strain energies were noted in section 3.2.2. Catalyst deactivation through poisoning, thermal decomposition, or substrate chelation can arrest the reaction before equilibrium is reached, however: the former issues become increasingly problematic as dilutions increase beyond ca. 0.1 mM.

In short, ERCM can offer the opportunity to exploit the ring−chain equilibrium to "correct" initial product distributions resulting from a kinetic bias toward oligomerization of diene substrates. Where ERCM functions as the dominant route to RCM products, an advantage has been proposed to the initial use of high concentrations (i.e., above the "cut-off point"), thus forcing the resting state to the metal-terminated oligomer rather than the shorter-lived methylidene.[105] This requires a second dilution stage to trigger backbiting CDP and shift the ring−chain equilibrium in favor of the cyclic RCM product.

4. Operation and Disruption of Ring−Chain Equilibria in RCM: Case Studies

4.1. How To Identify Oligomers Formed during RCM

Detection of oligomers during ERCM (or intended RCM) reactions is essential in order to assess the extent and progress of reaction, and to identify the need for intervention (e.g., increasing reaction time, increasing dilution, or, as a last resort, adding catalyst). Oligomeric species formed during RCM have typically been characterized following chromatographic isolation, usually by mass spectrometry (MS), where the molecular ion is observable. Ionization methods range from conventional electron impact[138,146−148,200−205] (including GC-MS)[140,162,206] and FAB[145,203,207−209] methods—these limiting observation to suitably volatile species, often cyclic dimers or trimers of complex precursors—to electrospray ionization[149,151,152,201] (sometimes in conjunction with HPLC separation)[148,207,210] and MALDI[88,90,191] (matrix-assisted laser desorption−ionization), for less volatile materials. GPC (SEC) characterization of reaction products can give insight into the degree of oligomerization, where appropriate columns are employed.[87,88,90] Viscometry measurements, utilized in early ROMP studies (section 2.1) are also of interest in this context, but we are aware of no study exploring their utility in RCM.

Surprisingly little attention has focused on monitoring the formation and disappearance of oligomeric species *in situ* during RCM reactions. Qualitative evidence for oligomeric species can be afforded by simple TLC (thin-layer chromatography) analysis.[139] ^{1}H NMR analysis, while convenient and much used to monitor the extent of RCM reactions, is frequently misleading, owing to the difficulty in distinguishing between the signals for the starting diene, oligomers, and RCM products. Examples of such difficulties in ROMP chemistry were presented in Table 1. In the context of RCM, a number of workers have made similar observations. In a representative example, Christoffers and co-workers described an NMR spectrum consistent with the desired product during the attempted RCM synthesis of a 7-membered lactone, but GC-MS analysis (subsequently confirmed by X-ray analysis) indicated formation of the cyclic dimer.[206] Similarly, Srikrishna and co-workers reported that while both ^{1}H and ^{13}C NMR spectra of an isolated RCM product were consistent with the expected cyclic monomer, X-ray analysis revealed that the product of the reaction was cyclic trimer **74** instead of the RCM product.[211] Mass spectroscopic analysis was inconclusive, owing to fragmentation. Fogg and co-workers reported difficulties in monitoring macrolactonization by ^{1}H NMR analysis, owing to the strong similarity between the spectra of oligomers and the composite spectrum of starting diene and RCM product.[105] The Weck group likewise commented on the inability to evaluate rates of backbiting in the cyclodepolymerization of salen-functionalized ROMP polymers (see **6**, Figure 4) by ^{1}H NMR analysis.[62] Multinuclear NMR methods can sometimes aid in chemical shift dispersion, where a convenient reporter nuclide is present, provided that the spectroscopic signatures of the various components can be established.

GC methods have been extensively used to quantify the progress of RCM reactions: they offer advantages over NMR methods for separation and quantification of diene and RCM products. Low-molecular weight oligomers can also be observed in some cases. Table 1 illustrates a number of examples in which GC methods were successfully used to characterize cyclic oligomers formed in ROMP of cyclopentene and related monomers. The greater degree of functionalization common in RCM substrates limits the volatility of their oligomeric derivatives, however. GC analysis of ERCM reactions thus requires accurate quantification of the amount of missing material to evaluate the progress of the reaction. This carries the usual hazards of

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negative evidence, and unless appropriate calibration curves are constructed to measure both disappearance of diene and appearance of RCM products, formation of involatile material can go unrecognized. Conventional EI-MS and FAB-MS methods can be useful in identifying both volatile and (comparatively) involatile reaction components. LC and SFC (supercritical fluid chromatography) methods facilitate resolution of individual constituents irrespective of their volatility, but again the progress of the reaction requires rigorous attention to detector calibration for accurate quantitation. LC-MS identification of oligomers, in conjunction with HPLC-UV quantitation, enabled a recent breakthrough in the measurement of EM values in the context of RCM, as described in section 3.1.2.[124]

The limited attention paid to oligomer quantification in the broader RCM literature to date presumably reflects the widespread assumption that formation of polymeric/oligomeric species in RCM is a dead end. Recognition of the capacity of ERCM to improve product distributions will doubtless focus new attention on monitoring methods. With the intention of demonstrating the scope of the phenomenon, as well as best practices, the following sections describe intended RCM reactions in which oligomers have been identified and instances in which these have been converted into RCM products.

4.2. Examples of Oligomers Identified during RCM

The RCM literature is rife with reports of the unwanted formation of oligomeric products. More rarely, these species are isolated and characterized. Examples of well-defined cyclodimers or cyclooligomers are shown in Figure 17; those of linear dimers or oligomers are shown in Figure 18. Details of the experimental conditions associated with their formation appear in Table 6. Many of the oligomers intercepted, whether cyclic or acyclic, exhibit a low degree of polymerization. This reflects the relatively low concentrations in general use, which correspond to operation well below the critical monomer concentration, and the inverse dependence of cyclooligomer concentration on ring size (section 2.2.1). In some cases, cyclic trimers (see, e.g., **61**, **65**) have been isolated as major products from RCM reactions even at concentrations of 2−5 mM, suggesting a high degree of strain in the cyclic monomer and dimer. A potential caveat worth noting in this context concerns the potential for dimerization or polymerization during workup, particularly for strained rings or where high catalyst loadings are used. These issues are discussed in section 4.3.3.

Deliberate recycling of oligomeric species into RCM targets through backbiting is still not common, despite reports that describe the success of such strategies (for specifics, see Table 6). This is somewhat surprising, given the conventional perception that olefin metathesis is accurately represented by the series of equilibria shown in Figure 1. The well-recognized changes in *E*/*Z* ratios over time, for example, are generally attributed to secondary metathesis reactions that result in a thermodynamic distribution of products.[212] A brief summary of factors that create a bias toward ERCM is shown in section 3.3. Examples of conditions designed to favor CDP of oligomers and liberate RCM products are shown in the next section.

Several insights can be extracted from Table 6. First, CDP of linear oligomers is considerably more common than ERCM of cyclic oligomers. This may reflect a lower barrier to reinstallation of the metal end group for the terminal olefin (a necessary prerequisite to backbiting). Second, a number of these RCM reactions are carried out at room temperature or in refluxing CH_2Cl_2 over several hours. As Danishefsky has noted,[143] and as discussed in section 3.1.1, such low temperatures limit the extent to which the entropic bias can be leveraged. Finally, it should be noted that the product distributions tabulated may not reflect equilibrium values, given the issues of decomposition discussed above (section 3.2.3).

4.3. Inducing ERCM by Modifying Experimental Conditions

When evidence for oligomerization is observed during intended RCM reactions, ERCM yields can often be improved through the simple expedients of increasing reaction time, dilution, or temperature. Selected examples of each are described below. Methods used where these prove insufficient are described in section 4.4.

4.3.1. Reaction Time

To maximize yields of ERCM reactions, sufficient time must be allowed for the CDP process to occur (presupposing operation in the appropriate concentration regime). Figure 19 depicts a representative plot showing the evolution of products in an RCM macrolactonization.[105] While involatile oligomers dominated the product mixture at 15 min (ca. 70%), cyclodepolymerization was complete at 1 h using 5 mol % **Ru-3a**, at a maximum diene concentration of 5 mM (CH_2Cl_2, reflux).

Another illustrative example described by Blechert and co-workers is depicted in Figure 20.[144] A 5:1 ratio of linear dimer **91** to RCM product **92** was found after 2 h, but **92** was dominant after 2 days (50 mM, refluxing CH_2Cl_2; catalyst **Ru-4**). This report is particularly notable given the characteristically high strain of cyclobutene rings.[219] The absence of ROMP products implies a strong stabilizing influence of the ring substituents in **92** (see sections 2.2.2 and 3.1.1), which inhibits ring-opening.

Cyclooligomerization of kinetically favored RCM products can also occur, at appropriate concentrations. During the synthesis of radicicol precursors, for example, Danishefsky and co-workers reported higher yields of the RCM product (**96**, vide infra) when the reaction with **Ru-2b** was terminated after only 5−10 min. Longer reaction times resulted in formation of cyclic dimers through the ring-opening−ring-closing pathway.[143]

An important example from the Fürstner group described the ring-expanding equilibration of cyclic products during the synthesis of the 16-membered macrodiolide **94** (Figure 21).[140] Thus, when RCM of **93** (2 mM in refluxing CH_2Cl_2; 5 mol % **Ru-2b**) was quenched at 50 min, after complete consumption of diene had been confirmed by TLC analysis, the desired **94** was obtained in 37% yield, accompanied by 27% of cyclic trimer **61** and 11% of higher cyclic oligomers. These products were identified by GC-MS analysis. The mass balance (25% "missing" material) reflects the volatility limitations inherent to GC methods, discussed in section 4.1. The involatile products clearly contain higher oligomers, as they undergo partial conversion to cyclic trimer **61** when the reaction was allowed to evolve for 15 h. After this period, **61** was isolated in >80% yield, thus requiring both cyclodepolymerization of the higher oligomers and ring-expansion

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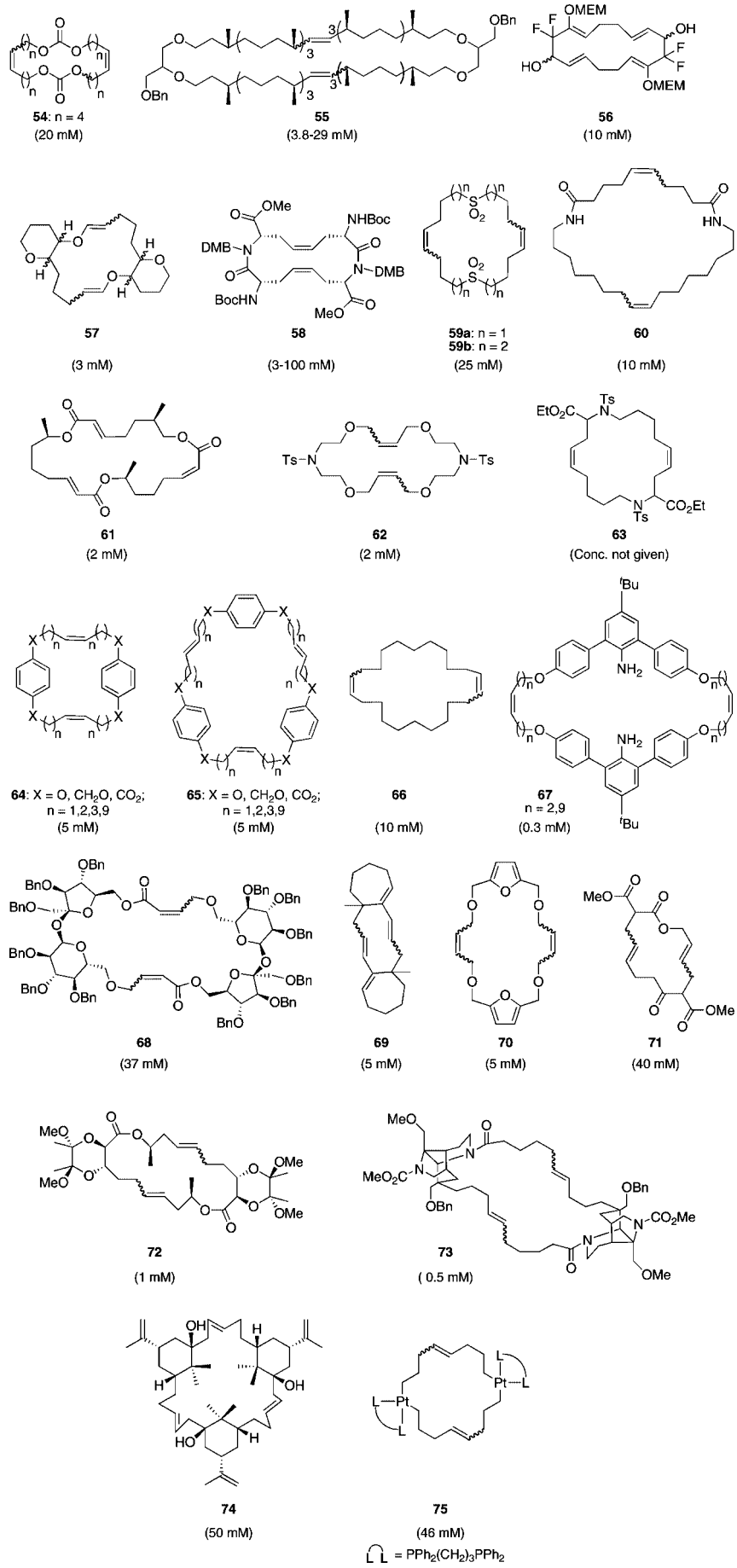

Figure 17. Examples of cyclic dimers or oligomers isolated during RCM. For experimental details, see Table 6. Compounds are obtained as a mixture of head-to-head and head-to-tail isomers, unless otherwise stated (see text). Substrate concentrations are shown in parentheses, where reported.

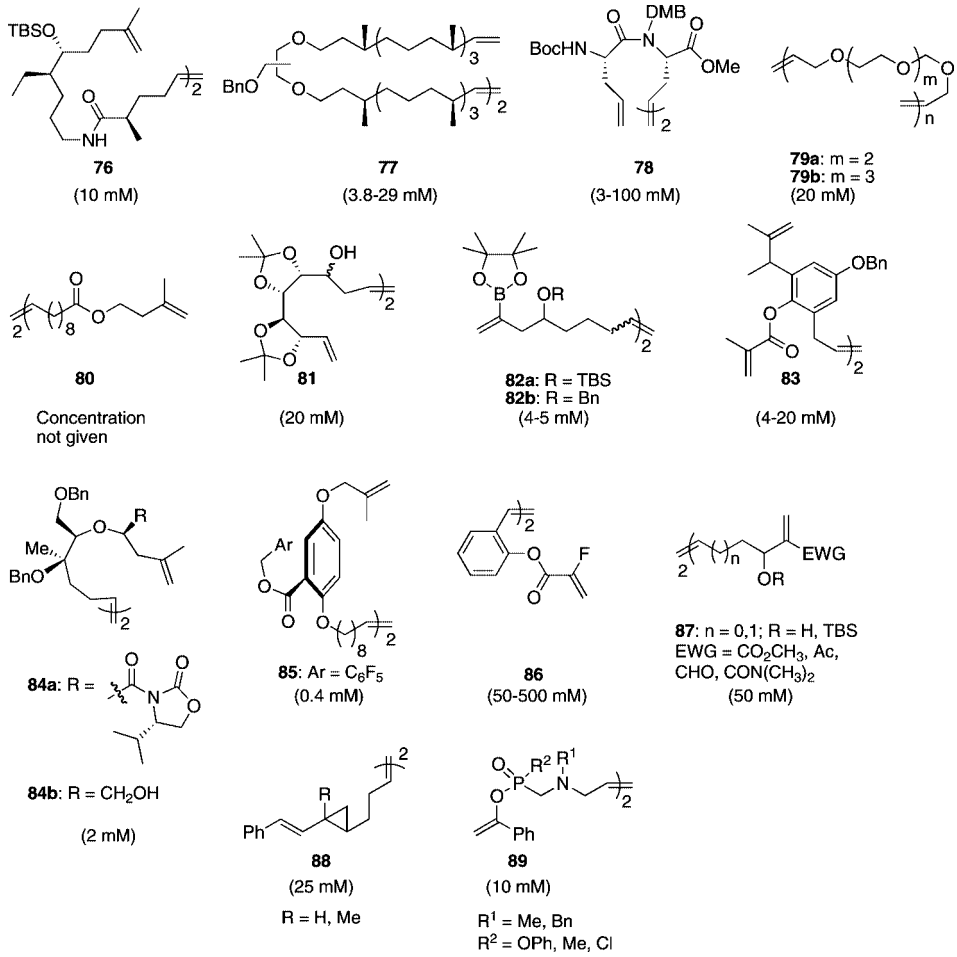

Figure 18. Examples of linear oligomers or polymers isolated during RCM, identified by NMR analysis, accompanied by MS or GPC (**79**) data for all but **84**.[213] Substrate concentration is shown in parentheses, where reported. For experimental details, see Table 6.

of **94**. One of the first detailed examples of equilibrium RCM, this behavior finds many precedents in ROMP chemistry: section 2.3.2.

4.3.2. Temperature

Danishefsky and co-workers[143] have commented on the potential to control product distributions in RCM macrocyclization reactions by increasing reaction temperature; section 3.1.1. In the reaction of Figure 22, the relative proportions of the desired RCM product **96** vs the cyclic dimer were found to increase from ca. 1:2 at 40 °C, to 1:1 at 80 °C, at a constant dilution of 0.5 mM **95** in benzene or toluene, respectively.

Similar effects were described by Crimmins and co-workers during the synthesis of 9-membered cyclic ether **98** (Figure 23).[149] A 3:1 mixture of monomer **98** to dimer **84b** was observed at 40 °C (**Ru-2b**; 2 mM diene in refluxing CH_2Cl_2). The corresponding reaction at 80 °C afforded a >15:1 mixture, in 89% isolated yield, although the potential impact[182] of the change in solvent was not discussed. Of note, subjecting the isolated dimer **84b** to these conditions afforded **98** in >90% yield after 5 h. Grela and co-workers likewise commented that carbonate-containing dienes showed a significantly greater proportion of oligomers in RCM via **Ru-1** at room temperature vs refluxing CH_2Cl_2, even at a concentration of 10 mM.[201]

During the synthesis of 14-membered macrolactone **100** (Figure 24), Grubbs and co-workers observed that dimerization competed with RCM at room temperature at diene concentrations as low as 3 mM.[212] RCM of **99a**−**d** in refluxing CH_2Cl_2 enabled isolation of **100** in >75% yield, however. Reaction of hydroxyl derivative **99e**, in comparison, afforded only 23% **100**, though complete consumption of starting diene was noted. High proportions of oligomers were observed in the latter case, perhaps indicating deactivation of the catalyst by the α,β-unsaturated alcohol before significant CDP can occur.

4.3.3. Concentration

Concentration is one of the key experimental factors affecting ring−chain (ring−ring) equilibria in olefin metathesis,[74] and one of the major tools available to manipulate product distributions in ERCM, as highlighted throughout this review. It should be recognized, however, that high dilutions come at a cost. Indeed, from the industrial perspective,[220] high dilutions are not a viable solution to the challenges of ERCM, given the high direct costs of the large volumes of solvent required, and further costs associated with waste disposal, longer reaction times, and the problems of product purification that commonly result from high catalyst loadings.[124,221,222] Farina, Shu, Senanayake, and co-workers have cited a target concentration of at least 100 mM in scaling up BI's BILN 2061 process (cf. the standard range of 0.2−8.5 mM reported by Gradillas and Perez-Castells in a recent review of RCM macrocyclization).[33]

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Table 6. Linear Oligomers or Polymers Isolated during RCM[a]

product	catalyst	conc (mM)	solvent	temp (deg)	time (h)	ERCM operative[b]	ref
54	**Ru-1**	20	CH_2Cl_2	reflux	2−24	N.I.	201
55	**Ru-1**	3.8−29	CH_2Cl_2	reflux	12−42	+ (cyclic dimer)	200
56	**Ru-2b**	10	CH_2Cl_2	reflux	48	N.I.	123
57	**Mo-2b**	3	C_5H_{12}	RT	5	N.I.	214
58	**Ru-1**, **Ru-2b**	3−100	CH_2Cl_2	RT	23	N.I.	148
59	**Ru-1**, **Ru-2b**	25	CH_2Cl_2	reflux	4	N.I.	8, 215
60	**Mo-2b**	10	C_6H_6	50	18	N.I.	138
61	**Ru-2a**, **Ru-2b**	2	CH_2Cl_2	reflux	15	+	140
62	**Ru-1**	2	CH_2Cl_2	RT	15	N.I.	216
63	**Ru-2b**	N.A.	CH_2Cl_2	reflux	N.A.	N.I.	8
64	**Ru-1**, **Ru-2b**	5	CH_2Cl_2	reflux	14−32	N.I.	209
65	**Ru-1**, **Ru-2b**	5	CH_2Cl_2	reflux	14−32	N.I.	209
66	**Ru-2b**, **Ru-4**, **Ru-10**, **Ru-11**	10	CH_2Cl_2	N.A.	1−4	N.I.	162
67	**Ru-1**, **Ru-2a**	0.3	CH_2Cl_2	reflux	48	N.I.	203
68	**Ru-2b**	37	CH_2Cl_2	reflux	3.5	N.I.	208
69	**Ru-2b**	5	CH_2Cl_2	reflux	3	N.I.	204
70	**Ru-1**	5	CH_2Cl_2	reflux	18	N.I.	202
71	**Ru-2b**	40	CH_2Cl_2	reflux	24	N.I.	206
72	**Ru-2b**	1	CH_2Cl_2	18	16	N.I.	205
73	**Ru-1**	0.5	CH_2Cl_2	reflux	48	N.I.	217
74	**Ru-2b**	50	C_6H_6	reflux	1	N.I.	211
75	**Ru-1**	46	CH_2Cl_2	reflux	8	N.I.	218
76	**Ru-5**	10	C_6H_6	N.A.	N.A.	+	138
77	**Ru-1**	3.8−29	CH_2Cl_2	reflux	12−42	+ (cyclic dimer)	200
78	**Ru-1**, **Ru-2b**	3−100	CH_2Cl_2	RT	23	N.I.	148
79	**Ru-1**	20	CH_2Cl_2/THF (10:1)	45	1	+	87
80	**Ru-1**, **Ru-2a**, **Ru-2b**	N.A.	CH_2Cl_2	reflux	4−40	+	140
81	**Ru-1**	20	CH_2Cl_2	RT	30	N.I.	147
82	**Ru-1**	4−5	C_6H_6	RT	76−118	N.I.	145
83	**Ru-2b**	4−20	CH_2Cl_2	reflux	20	+	151
84	**Ru-2b**	2	CH_2Cl_2 C_6H_6	reflux	5	+	149
85	**Ru-1**, **Ru-2b**	0.4	CH_2Cl_2	reflux	15	N.I.	152
86	**Ru-2b**	50−500	C_7H_8	80	2	N.I.	150
87	**Ru-4**	50	CH_2Cl_2	reflux	48	+	144
88	**Ru-1**	25	CD_2Cl_2	25	21	N.I.	146
89	**Ru-2b**	10	CH_2Cl_2	reflux	6−48	N.I.	133

[a] For structures, see Figures 17 and 18. [b] N.I. = not investigated.

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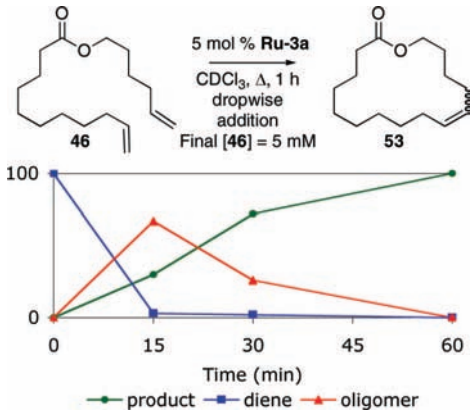

Figure 19. Monitoring oligomerization and backbiting as a function of time. GC-FID analysis.[105] Reaction carried out by dropwise addition of catalyst and diene; maximum diene concentration 5 mM.

In an elegant exposition of the use of concentration effects to bias selectivity in the construction of topologically complex molecules, Leigh and co-workers described the conversion of cyclic **102** into catenated rings using **Ru-1** (Figure 25).[207] At a concentration of 200 mM, the [2]-catenane was obtained in >95% yield (realizing a goal that dates back to the earliest days of metathesis chemistry; Table 1).[66−68] Lowering the concentration increased the proportion of the noninterlocked, 29-membered macrocycle **102**. Above 200 mM, higher cyclic oligomers could also be detected by analytical HPLC and FAB-MS. The capacity of **Ru-1** to

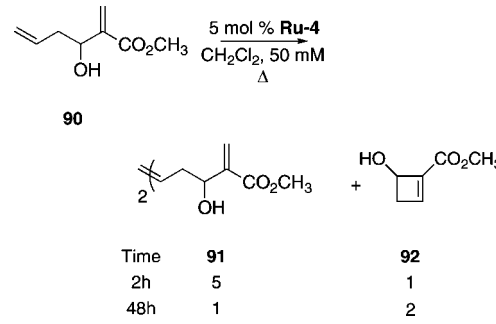

Figure 20. Evolution in ERCM product distributions: equilibration of linear and cyclic products.[144]

"unlock" the rings in **102** and **103** is noteworthy, given its relative inactivity toward 1,2-disubstituted olefins. The key to successful reaction presumably lies in the prolonged reaction times (up to five days), as well as the large difference in size between **102** and **103**.

Danishefsky and co-workers examined use of Ziegler "infinite dilution"[106] methodologies in RCM via **Ru-2b**.[143] Dropwise addition of diene **95**, over a 7-h period, to a solution of the catalyst in refluxing benzene had no effect on the yield of **96** (for structures, see Figure 22), relative to reactions in which all of the diene was added at the outset. The isolated yield of **96** was solely dependent on the final concentration. This unexpected result was attributed to the susceptibility of **96** to ring-opening and dimerization, culminating in a thermodynamic distribution of products.

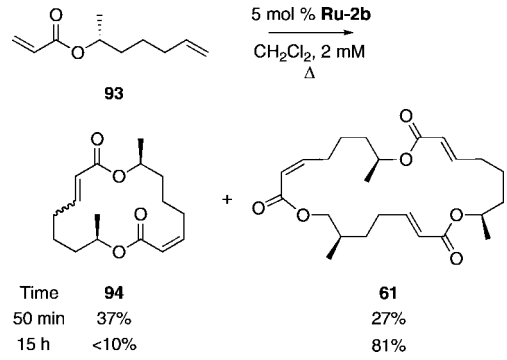

Figure 21. Evolution in ERCM product distributions: equilibration of cyclic products.[140]

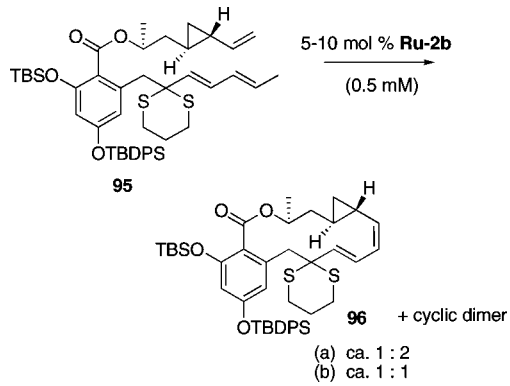

Figure 22. Manipulating ERCM yields by use of elevated temperatures: (a) 40 °C, 19 h; (b) 80 °C, 35 min.[143]

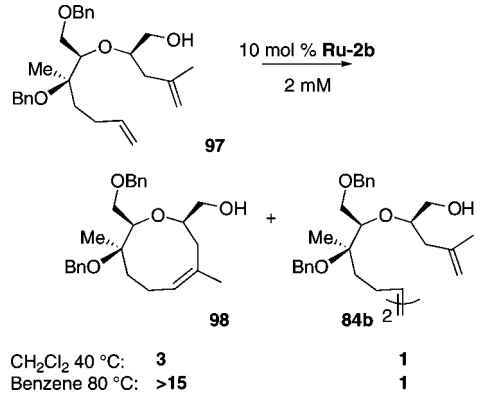

Figure 23. Manipulating ERCM yields by use of elevated temperatures.[149]

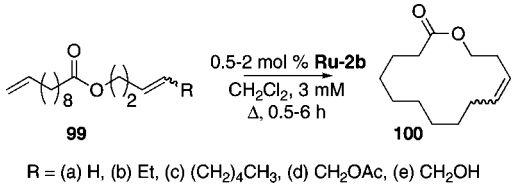

Figure 24. Use of elevated temperatures to suppress dimerization in RCM of **99a**−**d**.[212]

The influence of concentration in the RCM synthesis of macrocyclic lipids was described by Kakinuma and coworkers. A mixture of "cyclic monomer" and the cyclic and linear dimers (the latter two are shown as **55** and **77**, respectively, in Figures 17 and 18),[200] was obtained on RCM using **Ru-1** (refluxing CH_2Cl_2, 3.8 mM diene). The RCM target was isolated in 79% yield, accompanied by a small proportion of the cyclic dimer (6%). On increasing concentrations to 29 mM, yields of desired product dropped to 15%,

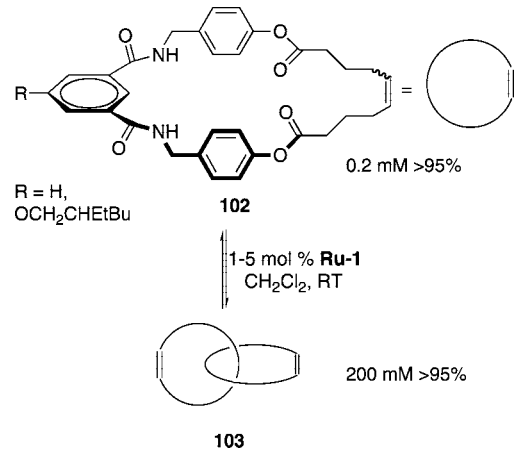

Figure 25. Formation of catenane **103** via concentration-dependent ERCM.[207]

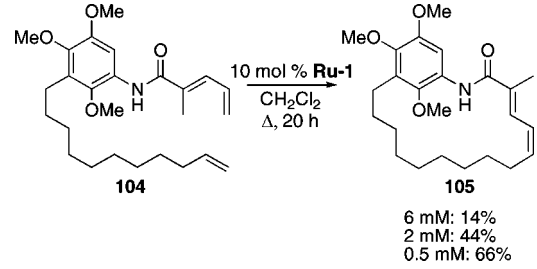

Figure 26. Concentration-dependent formation of *ansa*-bridged lactams via RCM.[141,223]

while the linear and cyclic dimers were isolated in 12 and 11% yield, respectively. In contrast with the example of Figure 25, however, this effect is almost certainly kinetic in origin, as no ring-opening was observed on resubjecting the isolated RCM product to this treatment.

Work from the Fogg group demonstrating the concentration-dependence of ERCM yields for a range of lactones, malonates, and a polyether was shown in Figure 14.[105] High yields (>90%) of the smallest ring size were observed for the 14−20-membered lactones **45**−**47** and the vinylic catechol ether **48**, at a diene concentration of 5 mM. Relative yields within homologous series agreed well with the trends in EM values reported for the corresponding saturated rings, despite the approximations involved in this comparison (see section 3.1.2). Higher dilutions were required to maximize cyclization of **49**−**52**: the selectivity for "cyclomonomer" vs cyclic oligomers was incomplete for these higher-strain rings even at 0.5 mM (section 3.1.2). For *ansa*-bridged vinylic ethers (cyclization of which would yield 11- and 13-membered rings), solely oligomers and the starting dienes were observed. Very low EM values were reported[107b] for the corresponding saturated species (≤2 mM). Bach and coworkers reported that larger, 16−20-membered *ansa*-bridged macrocyclic lactams could be obtained with use of **Ru-1**, in yields that were highly sensitive to concentration. A representative example is shown in Figure 26.[141,223] Yields of macrolactam **105** varied from 14%, at a diene concentration of 6 mM, to 66% at a concentration of 0.5 mM.

In a rare example of ERCM in formation of five-membered rings, the Grubbs group described a concentration-dependent cyclodimer−"cyclomonomer" equilibrium during RCM of a diene in which one of the olefinic sites was trisubstituted (i.e., sterically deactivated; see section 3.1.4).[139] Using either **Ru-1** or **Mo-2b**, significant amounts of dimer were observed

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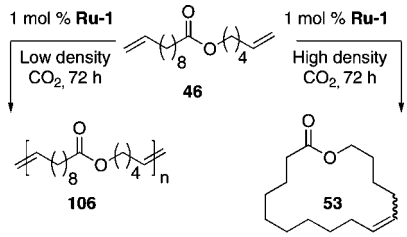

Figure 27. Olefin metathesis in $scCO_2$ to yield cyclic or oligomeric products, depending on the CO_2 density.[224,225]

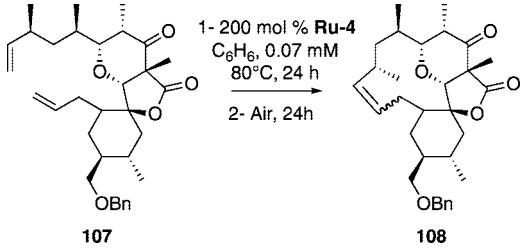

Figure 28. Avoiding concentration-induced ROMP by catalyst quenching prior to workup.[226]

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at 100 mM concentrations, but the equilibrium was shifted in favor of the smaller ring at 10 mM.

Work by Fürstner and Leitner highlights the potential of supercritical CO_2 ($scCO_2$) as an environmentally benign, relatively low-cost alternative to the use of conventional organic solvents to achieve high dilution.[224,225] Increasing the density of $scCO_2$ effectively mimics the effect of dilution by decreasing the ratio of reactants relative to inert molecules. In RCM of **46** via **Ru-1** at low CO_2 densities (0.55 g mL^{-1}), oligomer **106** predominated. Increasing the density to 0.83 g mL^{-1} enabled formation of **53** in ca. 90% yield (Figure 27).[224,225] As with other reactions involving **Ru-1**, this bias may be kinetic in origin: nevertheless, it indicates a potentially important solution to the dilution problem.

The concentration-dependence of the oligomerization−CDP equilibrium can result in degradation of RCM products during workup. The problem is exacerbated at high catalyst concentrations or on large-scale synthesis. In the synthesis of (−)-okilactomycin, containing a 13-membered macrocyclic core (Figure 28), Smith and co-workers noted that satisfactory yields of **108** required quenching the **Ru-4** "catalyst".[226] Polymerization of the macrocycle was otherwise observed during evaporation of the benzene solvent. This is perhaps unsurprising, given the very high ruthenium loadings used (200 mol %). Air-exposure for 24 h prior to concentration at a bath temperature below 25 °C was found to effectively arrest this behavior. The efficacy of the aerobic treatment is somewhat unexpected, given the established stability of **Ru-4** to oxygen and water (indeed, the groups of Hoveyda and Grela describe purification of **Ru-4** and related species by column chromatography in air).[227,228] It indicates considerable loss of the chelated styrenyl ether in **Ru-4** despite the low turnon efficiency usually characteristic[229] of this catalyst. The use of a sealed reaction vessel and consequent retention of ethylene may be relevant.

Catalyst quenching was also essential in the **Ru-4** catalyzed synthesis of BILN 2061 by Boehringer-Ingelheim researchers (Figure 29).[221,230] Again, evaporation of the solvent following synthesis of the macrocycle on a large scale triggered extensive degradation. Mercaptonicotinic acid **109** was identified as a suitable quenching agent, which offers the advantage of facile removal by extraction with aqueous

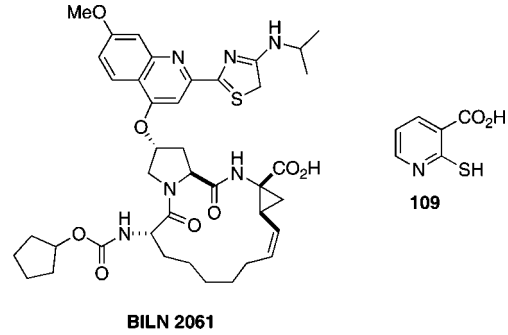

Figure 29. Structure of BILN 2061 and quenching agent **109**.[221,230]

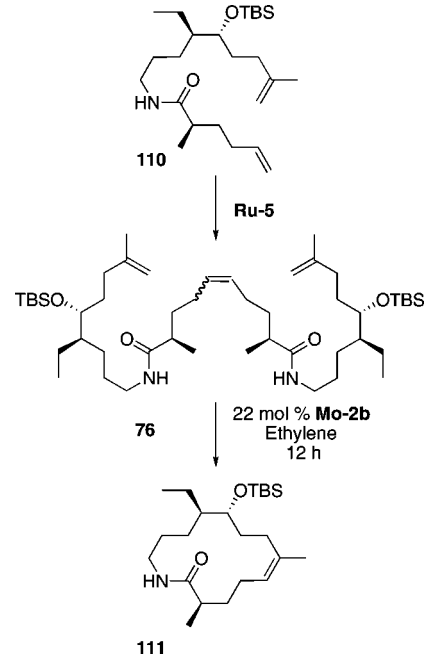

Figure 30. ERCM of a linear dimer achieved by use of a more reactive catalyst.[138]

bicarbonate. Decomposition was not observed in small-scale reactions, possibly because of the much shorter evaporation time required.

For strained rings, these problems can be much more severe, and quenching prior to workup is important even on the conventional bench scale at standard catalyst loadings. A range of quenching agents has been explored in addition to **109**,[123,231−235] which offer alternatives to the widely used ethyl vinyl ether.[236] The latter is reported to promote thermal decomposition of the Ru catalysts to isomerization-active Ru hydrides.[184,237,238]

4.3.4. Addition of a More Reactive Catalyst

Where modulation of time, temperature, and concentration fail to induce backbiting of oligomers to enable ERCM, addition of a second, more reactive catalyst can sometimes give access to the desired product. This strategy has been widely used to induce RCM of acyclic head-to-head dimers formed from unsymmetrically deactivated dienes (section 3.1.4).[133,138,140,144−152] Low catalyst activity inhibits metathesis at the internal, 1,2-disubstituted olefinic site. Hoveyda and co-workers reported that dimer **76** (Figure 30) could not be induced to undergo backbiting with **Ru-5**, for example. In contrast, the Schrock catalyst **Mo-2b** was successful in

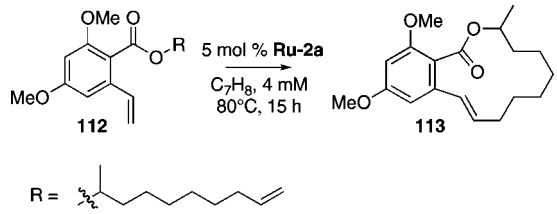

Figure 31. Favoring RCM by using a more reactive catalyst.[239]

converting **76** into the desired macrolactam **111**, after pretreatment of the Mo catalyst with ethylene to remove the unwanted alkylidene end group.[138] Isolated yields of **111** approached 60−65% over 12 h in benzene at 50 °C at a diene concentration of 10 mM. Importantly, use of freshly reprecipitated, bright orange **Mo-2b** increased yields to 90% at the same concentration, within 4 h at room temperature. This highlights the remarkable reactivity of **Mo-2b** when handled appropriately.

Fürstner and co-workers likewise exploited the higher activity of the second-generation Grubbs catalysts for macrolactonization reactions.[140] Linear dimer **80** (see Figure 18) was isolated in 79% yield from reactions of its diene precursor with **Ru-1**.[139] Use of **Ru-2a** or **Ru-2b** in refluxing CH_2Cl_2, however, afforded the desired macrolactone in ca. 60% yield after 40 h, with only trace amounts of **80**. Isolated **80** could also be induced to cyclize in 60% yield by reaction with the IPr catalyst **Ru-7** in boiling CH_2Cl_2 for 28 h (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazolyl-2-ylidene). In another example from the Fürstner group, styrenyl olefin **112** proved resistant to RCM via **Ru-1** but could be quantitatively converted into the desired ring **113** using **Ru-2a** (Figure 31).[239] Failure of the **Ru-1** reaction is consistent with the electronic and steric deactivation of the styrenic olefin.

4.3.5. Limitations on Entropic Tuning

A remarkable example of equilibrium RCM was reported by Smith and co-workers in the synthesis of macrocycle **116**, a precursor to (−)-cylindrocyclophanes A and F (Figure 32).[240−242] Attempts to generate **115** by RCM of **114** afforded solely cyclic dimer **116** at equilibrium, as the head-to-tail isomer. The stability of **116** relative to the corresponding head-to-head dimer **115** was confirmed by Monte Carlo calculations.[241] A series of "self-editing" ring-opening−ring-closing metathesis equilibria was proposed to account for the regioselectivity of the reaction. The failure to obtain **115**, despite exhaustive manipulation of experimental parameters, illustrates the limitations of ERCM when confronted by a thermodynamically favored alternative to the desired target.

4.4. Perturbing Equilibria

The preceding section described ways to bias ERCM reactions in favor of the desired cyclic products by manipulating experimental variables that have an impact on the overall entropy of reaction. These strategies are not always successful. In this section we examine additional approaches that have been used either to complement ERCM or to inhibit the initial oligomerization pathways that create the need for ERCM. We shall not consider the many strategies that have been employed to create a conformational bias toward cyclization by covalent modification of the substrate. For such methods, readers are referred to several recent reviews.[5,222,243,244] Instead, we shall focus on the use of external agents and additives that can aid cyclization. Importantly, however, these approaches do not appear to offer a general solution to the need for high dilutions. In rare cases, they enable RCM at substantially higher concentrations than would otherwise be possible, but in most cases, low concentrations appear to remain essential.

Two distinct strategies have been adopted, which we classify as templating or capping approaches, respectively. Templating agents (whether Lewis acids or bases; Figure 33a) are used to bring together dienes separated by two or more donor or acceptor sites: these can act either to amplify a bias in ERCM or to inhibit oligomerization. Capping agents operate only in the latter mode: these are Lewis acids, used in conjunction with substrates containing an appropriately placed donor group, which act to block off one quadrant or hemisphere of the molecule, thus reducing the conformational flexibility of the substrate and hence the entropic penalty associated with cyclization (Figure 33b). Examples of both strategies appear in the following sections.

4.4.1. Use of Templating Agents

Templating agents that have proved effective in RCM range from simple alkali[32,87] or alkaline earth metals[245,246] to transition metal ions,[246] transition metal complexes,[198,247−255] and charged or neutral organic molecules.[191,256−260] Binding of the template to the polar site of the substrate increases the probability of intramolecular reaction by bringing the olefinic groups into close proximity. An added advantage can be the selective formation of *Z*-olefin geometries.[87,246]

Organic Templates. Both neutral and cationic organic molecules have been used. Of interest is the capacity of the former to interact with acceptor sites on the substrate (i.e., they are complementary to the more commonly used Lewis acid templates). Either is readily modified in size and shape, facilitating tuning. Examples of RCM products obtained using this approach range from simple crown ethers to molecules exhibiting a range of complex topologies (Figure 34; Table 7); representative organic templates are shown in Figure 35.

Grubbs and co-workers described the **Ru-1**-catalyzed synthesis of crown ether analogue **117** via a hydrogen-bonded [2]rotaxane assembly, in which the template is a dumbbell-shaped secondary ammonium ion **124**.[256] The rotaxane was also accessible in 95% yield starting from **117** itself, via a **Ru-2b** catalyzed magic ring synthesis involving ring-opening and ring-closing (see also catenane **103**, Figure 25). In the case of the **Ru-1**-catalyzed reaction, the resistance of **117** to reopening limits the ability of the catalyst to correct the initial product distribution, and the bias exerted by the ammonium template is thus critical. Yields of ca. 70% were obtained at 100 mM, relative to ca. 50% at 5 mM for the untemplated reaction.[256]

More recently, the same group reported cyclotrimerization of a dibenzo [24]crown-8-diene to form **118**, using a template containing three dialkylammonium ions **125**.[257] The enforced proximity of the three sets of dienes yielded a mixture of the desired cyclodimer and cyclotrimer (39% and 55%, respectively) at a concentration of 1 mM (4 h, 20 mol % **Ru-4**; refluxing CH_2Cl_2). In the absence of the template, only cyclodimer was obtained.

Nguyen and co-workers exploited the capacity of neutral amines to function as templates for RCM substrates bearing Lewis acidic sites, in a synthesis of hollow porphyrin prisms **119**.[258] Use of either **126** or **127** as template, in conjunction with **Ru-1**, afforded the desired trimer in greater than 70%

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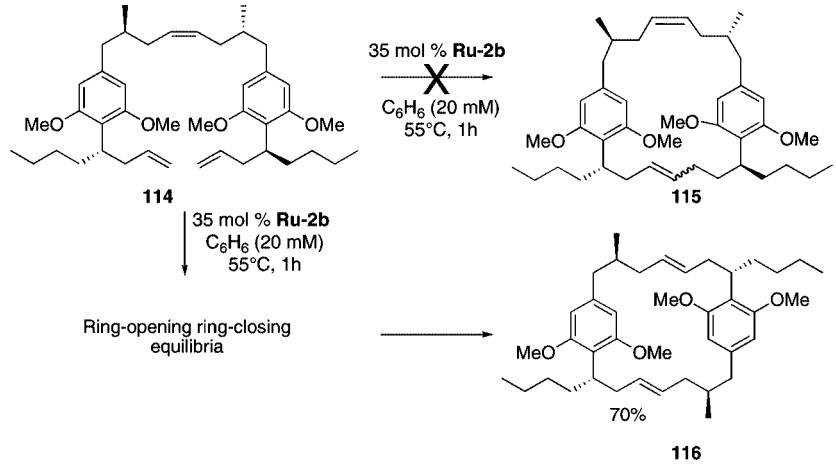

Figure 32. Substrate "self-editing" to afford a single thermodynamically stable cyclic product.[242]

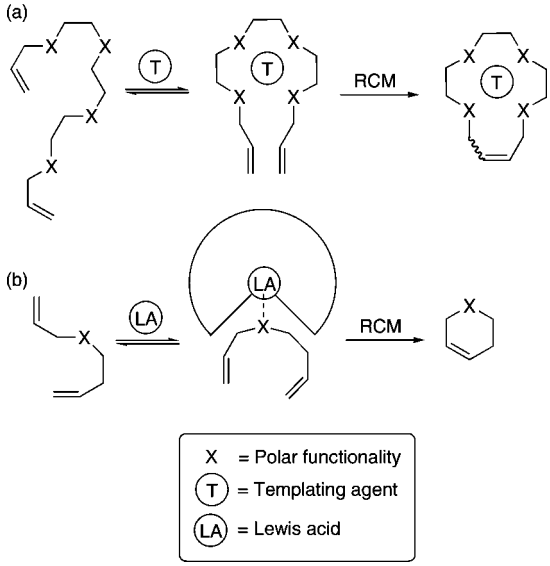

Figure 33. Strategies used to favor RCM. Use of (a) templating agents or (b) bulky Lewis acid capping agents.[281]

yield; in its absence, solely dimers were obtained. Dilutions of 0.3 mM were essential to limit formation of ADMET products. Likewise, Takeuchi and co-workers reported the use of diamines **128** or **129** to promote formation of a tetrameric assembly of zinc porphyrins; see **120**.[259] In the absence of the template, only one pair of olefins reacted; addition of 2.4 equiv of either diamine afforded the desired product in ca. 70% yield, at a concentration of 0.25 mM. High loadings of **Ru-4** were required (25 mol %). In a related approach, tetrameric Zn "boxes" **121** were assembled by Nolte and co-workers, utilizing porphyrin template **130**. In the absence of template, a mixture of linear and cyclic oligomers was obtained. Yields of the "zinc-boxes" were strongly catalyst-dependent. Thus, **Ru-1** was effectively poisoned by the amine functionalities on the template; use of **Ru-2b** led to competing isomerization, resulting in low isolated yields of **121** (28%) accompanied by other products with a range of ring sizes (MALDI-MS evidence). In an ingenious "back-door" approach to **121**, the substrate was first deliberately oligomerized via **Ru-1** in the absence of template. Subsequent treatment of the mixture of linear and cyclic oligomers with **Ru-2b** and template **130** induced ERCM. The desired tetramer was then isolated in 62% yield (CH_2Cl_2, room temperature, 6 h). The concentration required to enable the backbiting reaction was not reported.

In another example demonstrating the synergy between equilibrium RCM and templating strategies, Sanders and co-workers described satisfactory yields of macrocycle **122** only in the presence of template **131**.[210] When a 10 mM mixture (2:1) of diene and **131** (2:1 molar ratio) was reacted with **Ru-1** at room temperature for 3 days, catenane **122**−**131** was obtained in ∼50% yield after hydrogenation. As evidence of the equilibrium pathway, these workers cited the near-identical yields of **122** obtained following deliberate oligomerization of the diene *in the absence* of **131**, followed by addition of the template and fresh **Ru-1**.

Synthesis of catenanes and pseudorotaxanes using a neutral calyx[4]arene template (see **132**) was described by Beer and co-workers.[261] This templating strategy relies on hydrogen-bonding interactions between the substrate and **132**. Catenane **123**−**132** was obtained in 40−60% yield (once corrected for recovered starting material) at a concentration of 1 mM (CH_2Cl_2, room temperature, ca. 16 mol % **Ru-1**). The ca. 50% of missing material points toward extensive oligomerization despite use of the template and high dilutions. The interlocked cyclization product was not obtained when the bromide or chloride counteranions on the substrate were changed to either iodide or PF_6^-. The larger size of these anions was proposed to disrupt the hydrogen-bonding interaction.

Metal Ions As Templates. Many examples have been reported of metal-templated RCM since the 1997 report by the Grubbs group, describing the RCM synthesis of unsaturated 14- and 17-membered crown ethers via catalyst **Ru-1** (e.g., **17**, Table 8 and Figure 36).[87] While the RCM yield of the nontemplated reaction ranged between 40 and 60% at a concentration of 20 mM, use of a lithium ion template increased the yields of both crown ethers to >90% at the same concentration. Other alkali metal ions were also explored. While Li^+ and Na^+ gave similar yields of the 17-membered crown ether, yields of the 14-membered crown ether dropped with increasing size of the alkali metal cation, from 95% for Li^+, to 42% for Na^+, and 36% for K^+. Use of the Li^+ and Na^+ templates resulted in preferential formation of the *Z* isomer for both crown ethers. Later work demonstrated that **17** was accessible in 92% yield in the absence of a template, but higher dilutions were then required (0.5 mM), and *E*/*Z* mixtures were obtained.[105]

In related work by Nabeshima and co-workers, the *E* isomer of 32-membered macrocyclic tetraoxime **133** was isolated in 94% yield in the absence of a template, at diene concentrations of 1 mM (5 mol % **Ru-1**, 30 h, room-

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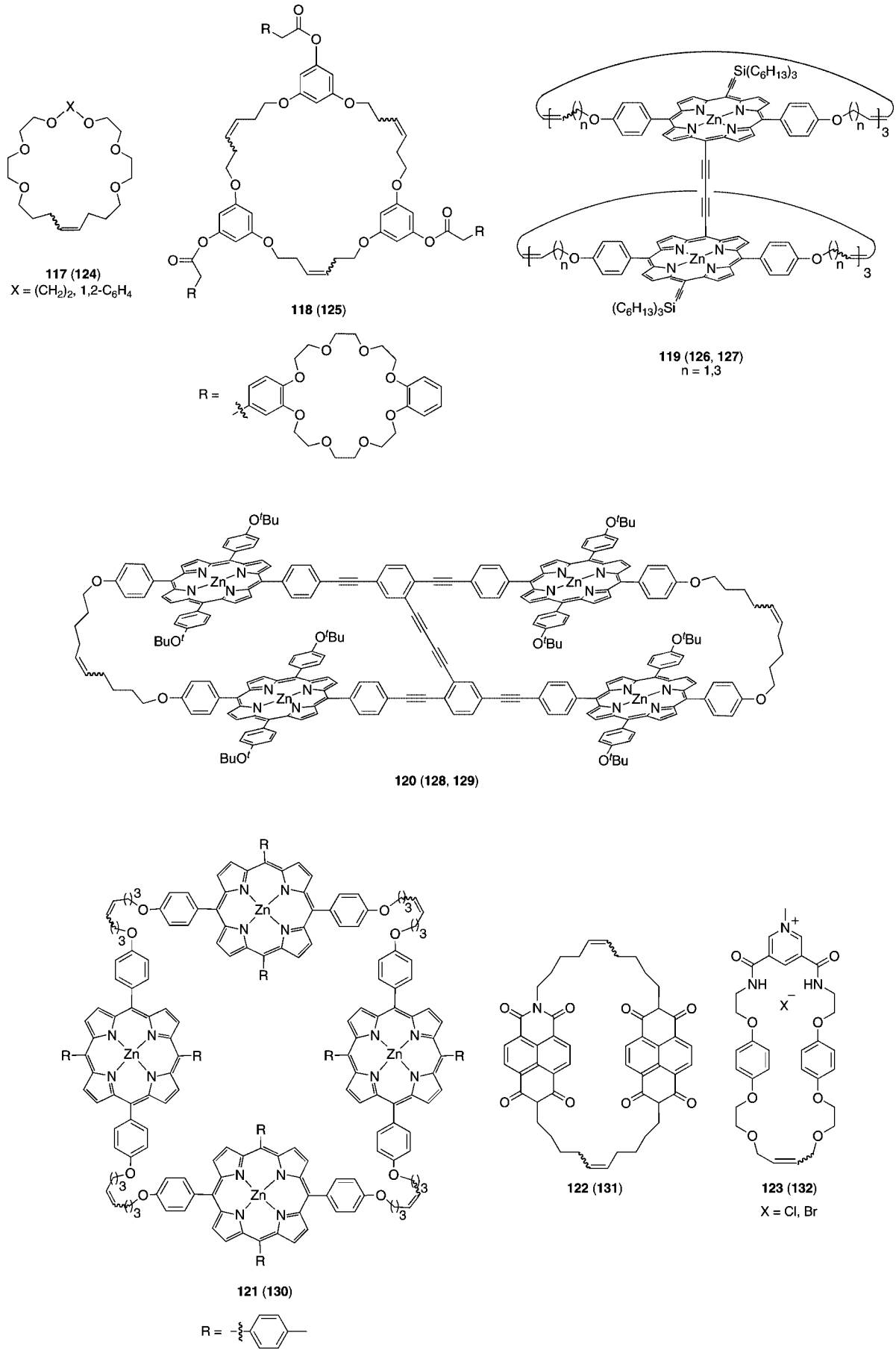

Figure 34. Topologically complex molecules synthesized using the organic molecules of Figure 35 as templates. Templates are specified in parentheses beside the appropriate RCM target. For experimental details, see Table 7.

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Table 7. RCM Formation of Topologically Complex Products by Use of Organic Templates To Bias Reactions toward DRCM[a]

product	template	catalyst	solvent	temp	conc (mM)	ref
117	**124**	**Ru1**, **Ru-2b**	CH_2Cl_2	reflux	100	256
118	**125**	**Ru-1**, **Ru-2b**	CH_2Cl_2	reflux	1	257
119	**126−127**	**Ru-1**	CH_2Cl_2	RT	0.3	258
120	**129−129**	**Ru-4**	$CHCl_3$	40 °C	0.25	259
121	**130**	**Ru-1**, **Ru-2b**	CH_2Cl_2	RT or reflux	0.1−10	191
122	**131**	**Ru-1**	$CHCl_3$	RT	5	210
123	**132**	**Ru-1**	CH_2Cl_2	RT	2	261

[a] For RCM targets, see Figure 34; for templates, see Figure 35.

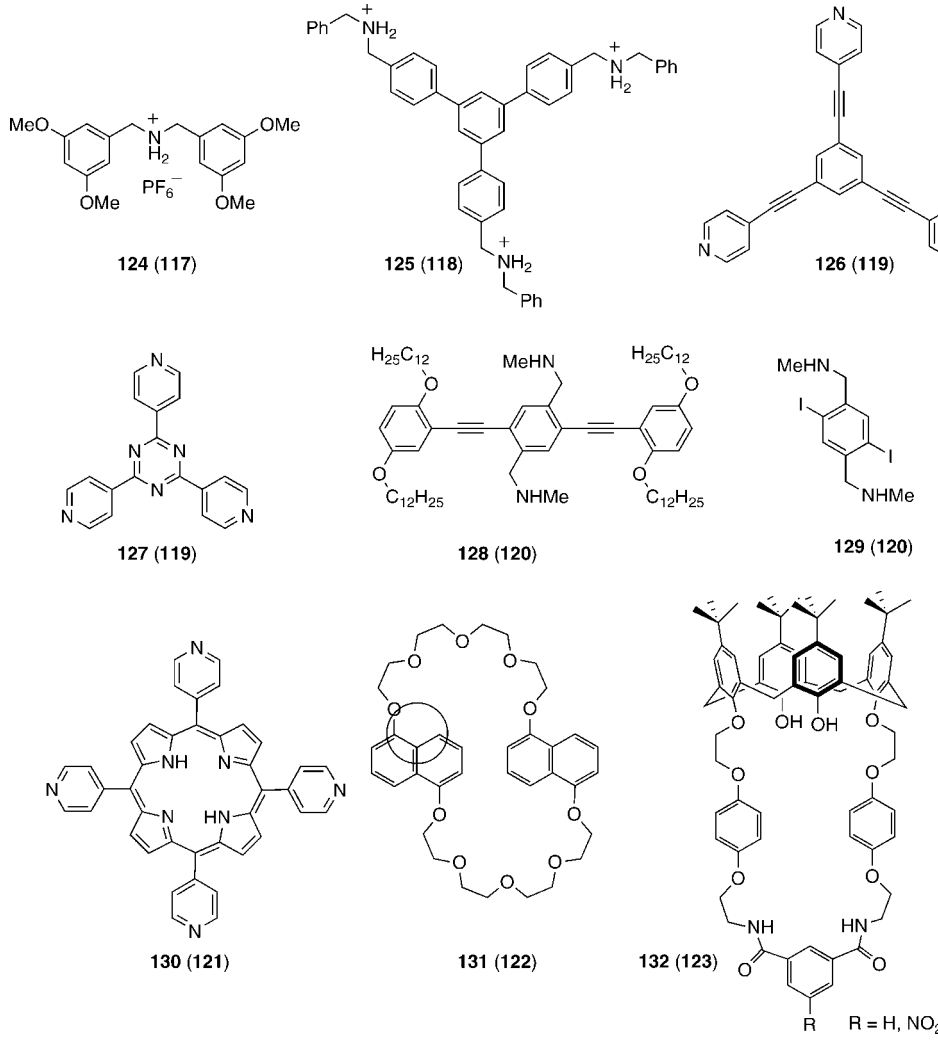

Figure 35. Organic templates used to promote RCM assembly of targets shown in Figure 34. Targets are specified in parentheses beside the appropriate template. For experimental details, see Table 7.

Table 8. RCM Conditions Yielding Molecules of Figure 36

product	metal ion	catalyst	solvent	temp	conc (mM)	ref
17	Li^+, Na^+, K^+	**Ru-1**	CH_2Cl_2/THF (10:1)	45 °C	20	87
133	Ca^{2+}, Zn^{II}	**Ru-2b**	THF	reflux	5	246
134	Ca^{2+}	**Ru-1**, **Ru-2b**	CH_2Cl_2	reflux	N.G.	245
135	Cs^+	**Ru-1**	CH_2Cl_2	reflux	4	262
136	Cu^I, Ru^{II}	**Ru-1**	CH_2Cl_2	RT	10	263, 264, 266, 267
137	Fe^{II}, Cu^I	**Ru-1**	CH_2Cl_2	RT	10	265, 268
138	Cu^I	**Ru-1**	CH_2Cl_2	RT	1	252, 253

temperature CH_2Cl_2).[246] Solely the *Z* isomer was obtained in the presence of divalent Zn and Ca ions, at a concentration of 5 mM; in this case **Ru-2b** was used as catalyst.

In a related approach, Rychnovsky and co-workers described the failure of a Ca^{2+}-templated approach in the attempted synthesis of dimeric macrolides.[245] A mixture of the unreacted diene and the cyclomonomer (i.e., the conventional RCM product **134**) was obtained using either **Ru-1** or **Ru-2b** in refluxing CH_2Cl_2. Details regarding concentration were not described, but an intriguing inference is the potential use of *excessive* dilution, or the inappropriate size of the Ca^{2+} template.

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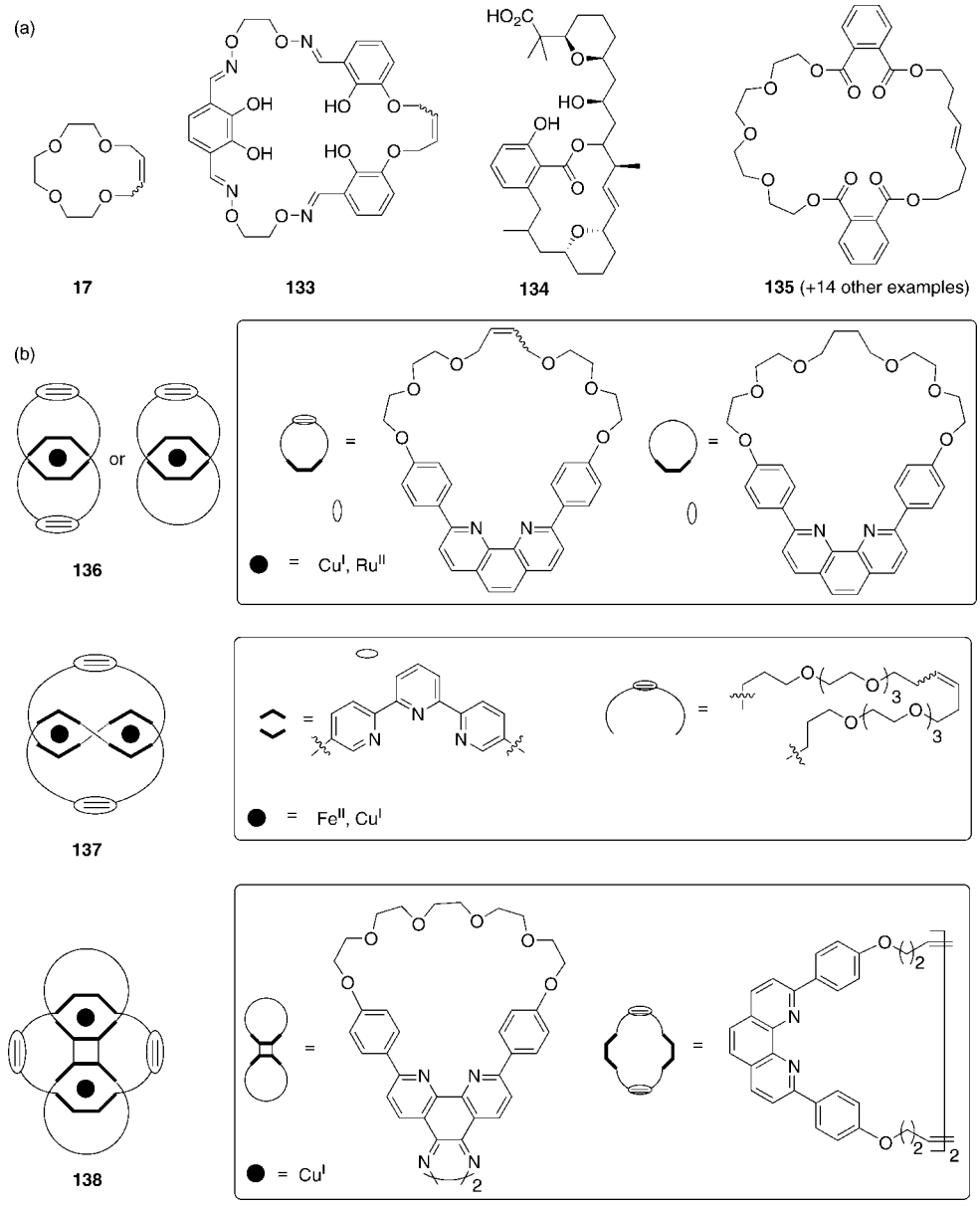

Figure 36. Favoring RCM formation of (a) macrocycles or (b) interlocked molecules using metal ion templates. For experimental details, see Table 8.

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Muthusamy and co-workers recently described the CsCl-assisted synthesis of tetralactones bearing oxyethylene spacers (**135**; Figure 36).[262] Reactions with **Ru-1** carried out at 5 mM in refluxing CH_2Cl_2 afforded **135** in 20−30% isolated yield in the absence of the templating ion, a figure that increased to 60−88% on introduction of 2 equiv of CsCl. The higher yields were attributed to the enforced proximity of the olefin groups resulting from coordination of the Cs^+ ion to the oxyethylene spacer.

A series of papers from the Sauvage group describes the application of metal ion-templated RCM to the synthesis of interlocked molecules such as catenanes,[263,264] molecular knots,[265] and even handcuff-like molecules[252,253] (**136**−**138**). For a comprehensive overview and a discussion of the relevance of these structures to the assembly of molecular machines, readers are referred to two excellent reviews.[24,25] The key structural motif is a self-assembled metal complex containing two rigid polydentate Lewis bases such as phenanthrolines, the relative orientation of which sets the topology of the target molecules. Orthogonal binding of the two donor ligands to Lewis acids such as Cu^I, Fe^{II}, or Ru^{II} orients the dienes, which can then be locked in place by RCM. Products were obtained in >80% yield at diene concentrations of 1−10 mM (**Ru-1**, CH_2Cl_2, room temperature). These interlocked molecules were prepared using the first-generation Grubbs catalyst at room temperature, albeit at high catalyst loadings (10−100 mol %) and long reaction times (up to ten days). The kinetic bias of this catalyst toward RCM (section 3.2.2), coupled with its low reactivity toward 1,2-disubstituted olefins, may be key to the selectivity for cyclic products and the resistance to reopening of the interlocked rings once formed. The propensity of the second-generation Ru catalysts toward oligomerization was noted above, as was their tendency to promote olefin isomerization (section 3.2.3). Either would reduce total yields, as indeed observed by van Koten on use of **Ru-2b** in related work described below.

Metal Complexes as Templates. A related approach utilizes transition metal *complexes* as highly modular templates to enable the construction of a wide range of topologically challenging molecules. Here RCM is carried out on olefinic groups on the periphery of large, typically

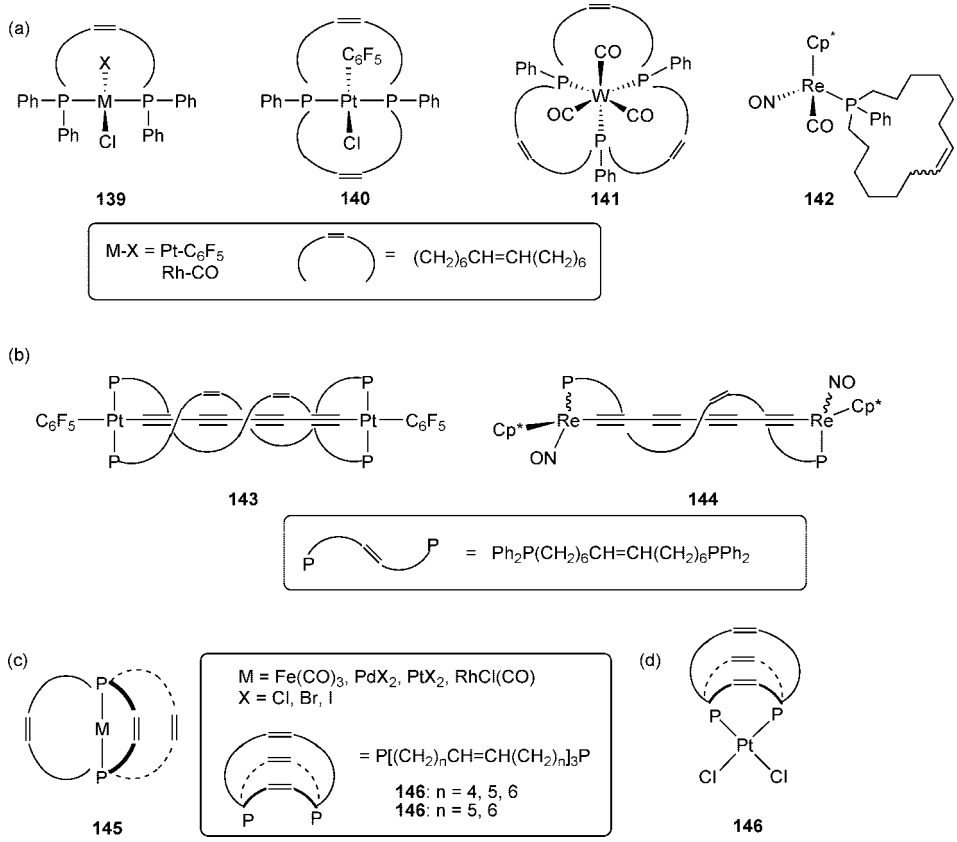

Figure 37. Promoting RCM assembly of topologically complex targets by use of metal complexes as templates: (a) phosphine macrocycles; (b) molecular wires; (c) gyroscopes; (d) parachutes. For experimental details, see Table 9.

Table 9. RCM Conditions Yielding Molecules of Figure 37[a]

product	solvent	temp	conc (mM)	ref
139	CH_2Cl_2	reflux	2.5−2.7	269−272
140	CH_2Cl_2	reflux	∼15	269−272
141	CH_2Cl_2	reflux	0.4	269, 270
142	CH_2Cl_2	RT	0.7−1.3	269, 278
143	N.G.	N.G.	N.G.	249, 273, 274
144	CH_2Cl_2	reflux	1	273−275
145	CH_2Cl_2	reflux	7−8	247, 248, 276, 277
146	CH_2Cl_2	reflux	0.8−1	250

[a] Catalyst **Ru-1** used in all cases; catalyst loadings range from 4 to 20 mol %.

metalloorganic, substrates. In contrast to the work of Sauvage and co-workers, where templating of the substrate is typically carried out by self-assembly at a simple metal ion center immediately prior to RCM, these core structures are synthesized independently, often in a series of steps, and then subjected to RCM. This work highlights the topological versatility attainable by use of metal complexes as core structural elements and the capacity to modulate molecular topology through ligand emplacement.

The Gladysz group has described the RCM assembly of a series of complex structures containing diverse metallic cores as templates, examples of which are shown in Figure 37. A common element is again the near-exclusive use of catalyst **Ru-1**, along with the expected high dilutions to curb oligomerization (1−15 mM; other experimental details given in Table 9). Phosphine-containing macrocycles were synthesized using a variety of metallic supports, including Pt, Rh, Re, and W.[269−272] An intriguing feature of the multiring macrocycles (e.g., **140**, **141**) is the very low tendency toward cyclization of olefins on the same phosphorus atom. The bias may indicate greater ring strain in the loop formed by homocyclization onto a single ^{31}P site than in a ring spanning two ^{31}P centers. That such loop structures are indeed accessible is illustrated by the successful synthesis of **142**. Gladysz and co-workers note that the selectivity in these systems is kinetic in origin, with the initial product distribution being trapped by the low reactivity of **Ru-1** toward internal olefins.[269] By analogy to the gem-dialkyl effect, they suggest that the bulk and geometrical preferences of the MPPh and PPh_2 groups may contribute to the initial conformational bias.[269,271] The intriguing possibility is raised of a further templating effect arising from π-stacking of the C_6F_5 ligand with the arylphosphine. Also of interest are potential advantages in **139**−**142** arising from the electron-withdrawing effect of the perfluorophenyl ligand, which could minimize oligomerization reactions associated with phosphoalkene decoordination. The high isolated yields of these macrocycles (generally >80%) are notable given the potential for formation of isomeric and oligomeric species. In fact, only modest amounts of dimers or oligomers are formed at dilutions of 1−15 mM, again highlighting the kinetic bias of **Ru-1** toward cyclization over oligomerization and its consequent ability to favor direct RCM over ERCM pathways.

More complex structures such as "molecular wires" **143** and **144**, in which the alkene chain is twisted around the central polyynediyl support, have also been prepared.[249,273−275] In contrast to the phosphorus macrocycles, the "twisted" structures **143** and **144** are formed in competition with structures such as **140**, although strikingly high selectivity was observed for **143**, in particular, which was formed in near-quantitative yield.[274] The shape of these cyclic molecules can be tailored further by appropriate choice of ligand geometry and orientation. Thus, trigonal bipyramidal Fe-

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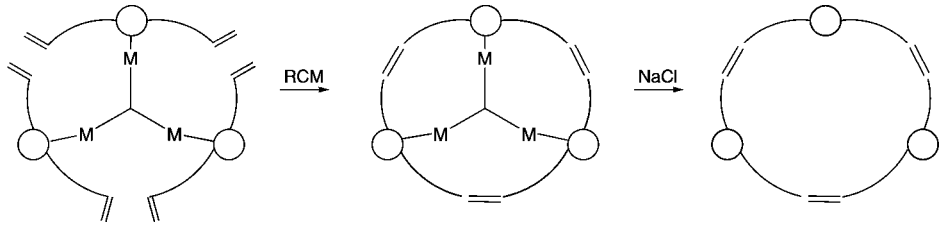

Figure 38. Substrate−template interactions in formation of macroheterocycles.[198]

$(CO)_3$, bearing two trans-disposed phosphines, was used as the stator of a molecular gyroscope, following RCM to lock in the rotor.[247,248,276,277] In contrast, a "molecular parachute" was obtained using a square planar platinum center bearing cis-oriented phosphine ligands.[250] The range of structural possibilities within these molecular wires (including nonhelical or partially twisted products) adds to the complexity of characterization, but the wealth of NMR handles in these complexes is a major advantage. MS methods are of value in confirming the presence of dimers and oligomers.[269]

In some cases (e.g., ether-functionalized analogues of **143**), reactions with **Ru-1** proved sluggish, and **Ru-2b** was used instead. The target molecular wire was obtained, albeit in modest yields (27% after chromatography),[249] owing to polymerization during workup (see also section 4.3.3).[274] Of interest in the **Ru-2b**-mediated reaction is the significant difference in size between the RCM products and those formed by ADMET oligomerization, which should increase sensitivity to dilution. The relative merits offered by the important catalyst types represented by **Ru-1** and **Ru-2** and, by implication, offered by the DRCM vs ERCM pathways are now being explored in the synthesis of these and related giant molecules.[249,278]

Macroheterocyclic membrane materials have been prepared via metal-templated RCM by van Koten and co-workers.[198,254,279] Here a rigid platinum-pincer ligand complex was used to preorganize the olefinic "tails" prior to RCM (Figures 38 and 39). The target macrocycles, which have been used as preorganized host molecules for the selective binding of specific guests,[254] can be released by reaction with NaCl. The RCM step, carried out using **Ru-1** (5−15 mol %) at a concentration of 1 mM in refluxing CH_2Cl_2, afforded various macrocycles in 20−70% yield following purification by preparative TLC. While substrates **147a/b** and **148a/b** were converted into the desired tris-pyridyl macrocycles, 3,5-disubstituted pyridines such as **149a/b** afforded solely the monopyridine macrocycles. Yields were highly dependent on the catalyst used. Thus, **148a** was obtained in 44% isolated yield on use of **Ru-1**, vs only 20% on use of **Ru-2b** under the same conditions. The latter was accompanied by extensive amounts of oligomeric species, consistent with the kinetic bias of the second-generation catalysts toward oligomerization noted above. In contrast, RCM synthesis of **147c** was only effective with **Ru-2b**, and isolated yields reached ca. 60%. Failure of the corresponding reaction with **Ru-1** was attributed to the less reactive nature of the styrene olefins and the higher stability of the stilbenoid double bond, which inhibits secondary metathesis.

In another showcase example, Ko and co-workers recently described the RCM synthesis of the 90-membered hexa(pyridyl)macrocycle **154** using a $Pt(PEt_3)_2$ template, at a dilution of 0.1 mM (Figure 40).[255] Competing catalyst decomposition imposed a requirement for high loadings of **Ru-1** (30 mol %), but the desired product could be isolated by preparative TLC in 80% yield after 3 days at room temperature. The template was removed by treatment with NaI to afford the free macrocycle, which was isolated in 74% yield.

4.4.2. Perturbing Equilibria by Reducing Conformational Motion

Lewis acids have been widely used as cocatalysts in RCM, typically to inhibit chelation of polar functionalities that can poison the catalyst (e.g., alcohols, esters, amides, etc.), as noted in section 3.[169,170,181,183,280] Most commonly used is $Ti(O^iPr)_4$, first shown by Fürstner and co-workers to facilitate formation of macrocyclic targets en route to (−)-gloeosporone.[169] The possibility of using Lewis acids to facilitate RCM by blocking the conformational mobility of the substrate is a strategy of more recent interest. The Percy group showed that $Ti(O^iPr)_4$ was effective in promoting RCM of a variety of eight-membered rings by **Ru-2b**, and they pointed out that use of the Lewis acid completely suppressed formation of oligomers (Figure 41).[123] The effective molarity of substrate **155** in the presence of 30 mol % $Ti(O^iPr)_4$ increased by 5-fold, as judged by $^{19}F\{^1H\}$ NMR analysis. While the role of the Lewis acid was not discussed, a possible explanation comes from the interaction in Figure 33b above.[281]

A related recent example from Nguyen and co-workers described the use of the bulky Lewis acid aluminum tris(2,6-diphenylphenoxide) (ATPH; **159**, Figure 42) to promote RCM of seven-membered prolactones such as **49**.[281] Formation of such essentially *unsubstituted* rings in high yields is particularly challenging (see section 3.1), owing to the bias toward formation of the lower-strain cyclic dimers. In contrast to the Percy findings with **155**, RCM of **49** (20 mM, refluxing CH_2Cl_2, 10 mol % **Ru-2b**) resulted in sole formation of cyclodimer **158** in the presence of 1.05 equiv of $Ti(O^iPr)_4$. Use of **159**, in contrast, enabled formation of seven-membered **157** in 87% yield, under otherwise identical conditions.

Ring-closing to form such medium-sized lactones requires prior isomerization of the preferred *Z*-ester into the *E* form (Figure 42). For **49**, the *Z* isomer is reportedly favored by ca. 5 kcal/mol, with an exchange barrier of ca. 10 kcal/mol.[281] The efficiency of cyclization was attributed to the capacity of bulky **159** to bring the olefinic groups into close proximity by enforcing the *E*-ester conformation. The effect of **159** is dramatic, enabling a 9:1 selectivity for **157** over **158** even at a 100 mM concentration of diene. While this methodology has not yet been demonstrated beyond a narrow range of 7-membered lactones, these results point toward a potentially very powerful, versatile strategy in which Lewis acids are used as sterically tunable additives to address the low EM values characteristic of strained medium rings.

Issues of additive−catalyst compatibility must also be considered, however. Low RCM yields have been reported in the presence of strong Lewis acids such as $La(OTf)_3$ or $AlCl_3$.[170] Other Lewis acids, such as LiBr, have been reported

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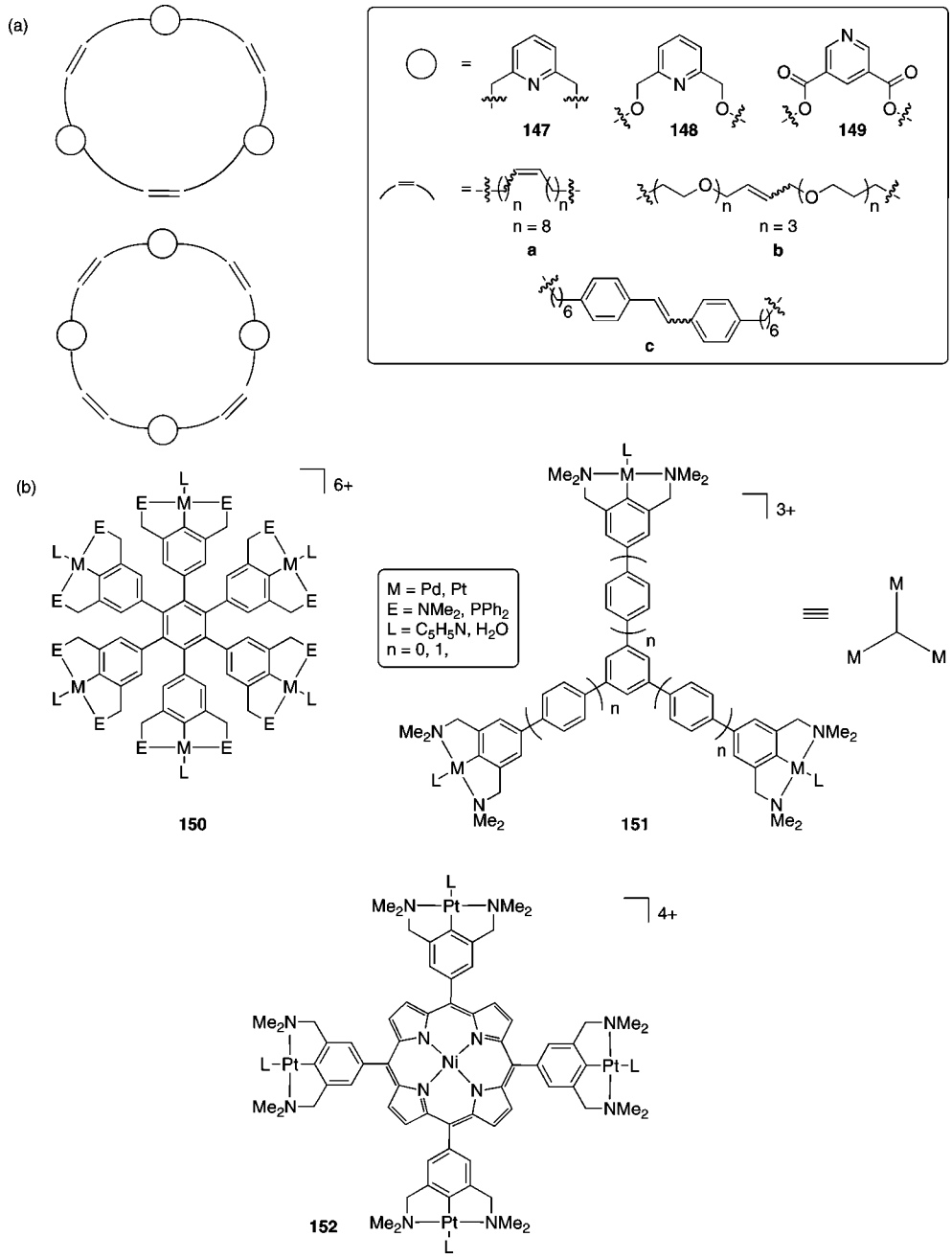

Figure 39. (a) Strategy for favoring RCM formation of macroheterocycles; (b) nature of transition metal support.[198,254,279]

by Fürstner and co-workers to retard cyclization: this was suggested to arise from salt metathesis with the Ru−Cl bond.[169] Catalyst decomposition by stronger Lewis acids ($TiCl_4$, $SnCl_4$) may be due to scavenging of the Lewis basic ligands of the catalyst. The rapidity with which these additives can be screened, particularly using high-throughput screening methods, may offer a significant asset in optimization of RCM reactions of appropriately functionalized dienes.

5. Conclusions and Future Prospects

Thermodynamic control of metathesis reactions, first documented in ROMP chemistry more than 40 years ago, can also be important in enabling RCM via an indirect, oligomerization−backbiting pathway. While direct RCM is favored for dienes that form five- or six-membered rings, or for which restricted rotation reduces the entropic penalty incurred upon cyclization, ERCM can be key to the synthesis of conformationally more flexible large and medium rings.

The increasing incidence of equilibrium RCM is due in part to the growing dominance of ruthenium metathesis catalysts. Because these are less susceptible to decomposition by trace air and water than are the molybdenum catalysts which remain their chief rivals, their use increases the likelihood that equilibrium can be achieved. A second key factor is the high activity characteristic of the Ru-NHC catalysts now in most common use. These second-generation Grubbs catalysts and their descendants have greatly expanded the range and scope of substrates that can be successfully subjected to metathesis. One aspect of this expanded scope lies in their capacity to effect metathesis at internal olefinic sites. This is essential for ERCM, as it enables low-energy backbiting pathways. The first-generation Grubbs catalyst, in comparison, exhibits limited activity toward such sites,

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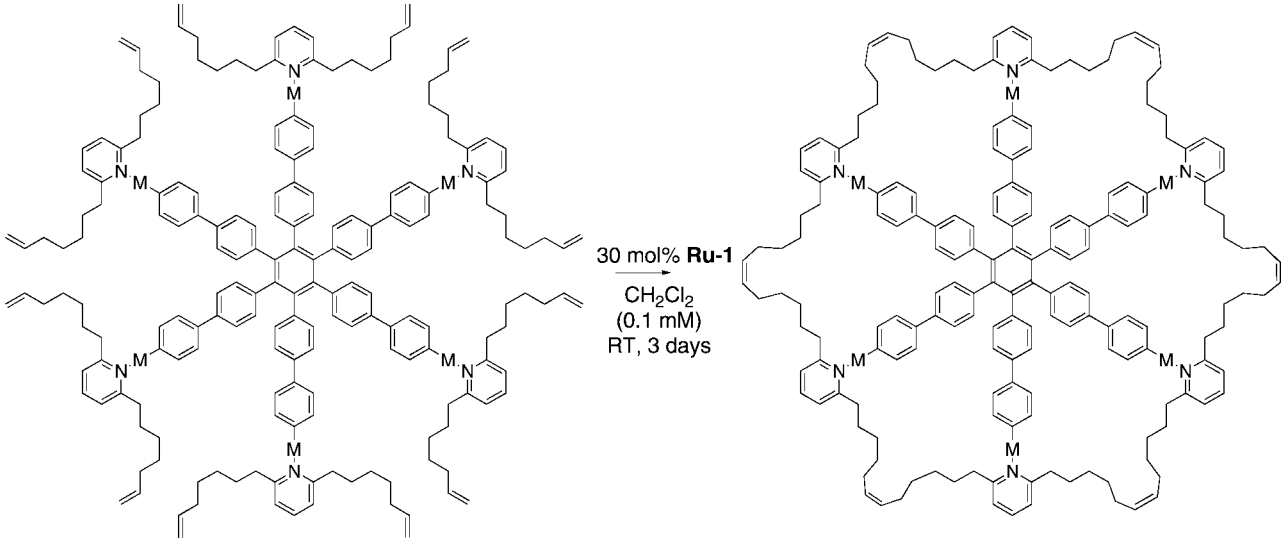

Figure 40. Template-directed synthesis of a 90-membered macroheterocycle (M = *trans*-Pt(PEt_3)$_2$).[255]

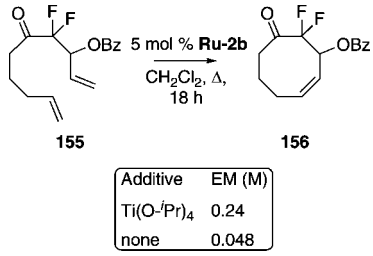

Figure 41. Increasing EM by addition of Ti(O^iPr)$_4$.[123]

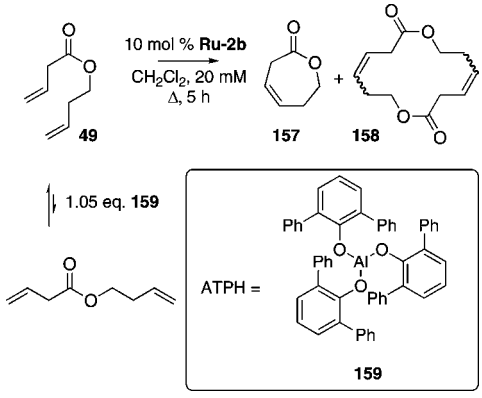

Figure 42. "Substrate encapsulation" by a bulky Lewis acid.[281]

in the absence of a strong driving force for reaction, and thus typically affords a kinetic distribution of products.

Equally important, however, are the kinetic proclivities of the catalysts themselves toward intramolecular vs intermolecular reactions. Emerging evidence suggests that a striking difference between the first- and second-generation catalysts is the kinetic bias of the former toward RCM and of the latter toward oligomerization, even in dilute solution. It is this kinetic bias toward oligomerization that creates the need to "correct" product distributions through backbiting. Of great interest, therefore, is the potential to develop catalysts that combine high activity with a high kinetic bias toward direct RCM, which would circumvent the need for ERCM.

While the chief detriment of the Ru-NHC catalysts is thus their kinetic bias toward intermolecular reactions, their high activity means that oligomeric products are not a dead end. Formation of unwanted oligomers during RCM does not imply failure of the reaction but the need to optimize reaction conditions. Under appropriate conditions, the ring−chain equilibrium can be exploited to "recycle" unwanted oligomers and cyclic oligomers into the desired cyclic species. Thermodynamic control is thus central to RCM performance.

Loss of ethylene creates a powerful, but indiscriminate, driving force for intra- and intermolecular metathesis. More subtle entropic parameters govern the ring−chain equilibrium. Chief among these is translational entropy, which can be maximized by use of high dilutions. High reaction temperatures aid in weighting the favorable entropic factor, as well as by decreasing the viscosity of the reaction medium. A corresponding risk, however, lies in the shorter catalyst lifetimes at elevated temperatures. Achieving equilibrium requires not merely sufficient reaction times at appropriate dilutions but also a supply of viable catalyst. Finally, where manipulation of experimental parameters gives inadequate selectivity for the desired ring, use of additives can be valuable in tilting the equilibrium further toward cyclic species or in inhibiting oligomerization and thus favoring direct RCM.

While these approaches are practical and often highly useful in small-scale benchtop synthesis, equilibrium metathesis creates major challenges for the industrial application of RCM. Probably most significant is the large volume of solvent required, which represents a major impediment to sustainable and economical synthesis on industrial scales. A need is clear for efficient methodologies that enable cyclization at elevated concentration or use of alternative, environmentally more benign diluents such as supercritical CO_2. Greater control arising from advances in flow-through and microreactor technologies may also aid in adaptation of RCM and ERCM methodologies to industrial applications.

6. Acknowledgments

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7. References

(1) Villemin, D. *Tetrahedron Lett.* **1980**, *21*, 1715–1718.
(2) Tsuji, J.; Hashiguchi, S. *Tetrahedron Lett.* **1980**, *21*, 2955–2958.

Downloaded by UNIV MAASTRICHT on August 28, 2009 | http://pubs.acs.org
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Downloaded by UNIV MAASTRICHT on August 28, 2009 | http://pubs.acs.org
Publication Date (Web): June 19, 2009 | doi: 10.1021/cr800541y

(3) (a) Schrock, R. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 3748–3759. (b) Grubbs, R. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 3760–3765.
(4) McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239–2258.
(5) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238.
(6) Collins, S. K. *J. Organomet. Chem.* **2006**, *691*, 5122–5128.
(7) Donohoe, T. J.; Fishlock, L. P.; Procopiou, P. A. *Chem.—Eur. J.* **2008**, *14*, 5716–5726.
(8) Kotha, S.; Lahiri, K. *Synlett* **2007**, 2767–2784.
(9) Schmidt, B.; Hermanns, J. *Curr. Org. Chem.* **2006**, *10*, 1363–1396.
(10) Brik, A. *Adv. Synth. Catal.* **2008**, *350*, 1661–1675.
(11) Martin, W. H. C.; Blechert, S. *Curr. Top. Med. Chem.* **2005**, *5*, 1521–1540.
(12) Plumet, J.; Gomez, A. M.; Lopez, J. C. *Mini-Rev. Org. Chem.* **2007**, *4*, 201–216.
(13) Madsen, R. *Eur. J. Org. Chem.* **2007**, 399–415.
(14) Jorgensen, M.; Hadwiger, P.; Madsen, R.; Stutz, A. E.; Wrodnigg, T. M. *Curr. Org. Chem.* **2000**, *4*, 565–588.
(15) Arisawa, M.; Nishida, A.; Nakagawa, M. *J. Organomet. Chem.* **2006**, *691*, 5109–5121.
(16) Gaich, T.; Mulzer, J. *Curr. Top. Med. Chem.* **2005**, *5*, 1473–1494.
(17) Brenneman, J. B.; Martin, S. F. *Curr. Org. Chem.* **2005**, *9*, 1535–1549.
(18) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693–3712.
(19) Delgado, A. *Eur. J. Org. Chem.* **2008**, 3893–3906.
(20) Van de Weghe, P.; Eustache, J. *Curr. Top. Med. Chem.* **2005**, *5*, 1495–1519.
(21) Schall, A.; Reiser, O. *Eur. J. Org. Chem.* **2008**, 2353–2364.
(22) Clark, J. S. *Chem. Commun.* **2006**, 3571–3581.
(23) Ibrahim, Y. A. *J. Mol. Catal. A* **2006**, *254*, 43–52.
(24) Collin, J. P.; Dietrich-Buchecker, C.; Hamann, C.; Jouvenot, D.; Kern, J. M.; Mobian, P.; Sauvage, J. P. *Compr. Coord. Chem. II* **2004**, *7*, 303–326.
(25) Champin, B.; Mobian, P.; Sauvage, J.-P. *Chem. Soc. Rev.* **2007**, *36*, 358–366.
(26) Chattopadhyay, S. K.; Karmakar, S.; Biswas, T.; Majumdar, K. C.; Rahaman, H.; Roy, B. *Tetrahedron* **2007**, *63*, 3919–3952.
(27) Nishida, A.; Nagata, T.; Nakagawa, M. *Top. Heterocycl. Chem.* **2006**, *5*, 255–280.
(28) Kaliappan, K. P.; Kumar, N. *Tetrahedron* **2005**, *61*, 7461–7469.
(29) Rassu, G.; Auzzas, L.; Battistini, L.; Casiraghi, G. *Mini-Rev. Org. Chem.* **2004**, *1*, 343–357.
(30) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073–2077.
(31) Prunet, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 2826–2830. *Angew. Chem., Int. Ed.* **2003**, *42*, 3322.
(32) Fürstner, A. *Eur. J. Org. Chem.* **2004**, 943–958.
(33) Gradillas, A.; Perez-Castells, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6086–6101.
(34) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490–4527.
(35) Majumdar, K. C.; Rahaman, H.; Roy, B. *Curr. Org. Chem.* **2007**, *11*, 1339–1365.
(36) Hérisson, J. L.; Chauvin, Y. *Makromol. Chem.* **1971**, *141*, 161–176.
(37) Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Metathesis Polymerization*; Academic Press: New York, 1997.
(38) (a) Semlyen, J. A. *Adv. Polym. Sci.* **1976**, *21*, 41–75. (b) Suter, U. W. In *Comprehensive Polymer Science*; Allen, G., Bevington, J. C., Eds.; Pergamon: New York, 1989; Vol. 5, Chapter 6, pp 91−96.
(39) (a) Weskamp, T.; Schattenmann, W. C.; Spiegler, M.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2490–2493. (b) Weskamp, T.; Kohl, F. J.; Hieringer, W.; Gleich, D.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 2416–2419. (c) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247–2250. (d) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956. (e) Huang, J.; Stevens, E. D.; Nolan, S. P.; Peterson, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674–2678.
(40) Ivin, K. J. *NATO Sci. Ser. II* **2002**, *56*, 1–15.
(41) Scott, K. W.; Calderon, N.; Ofstead, E. A.; Judy, W. A.; Ward, J. P. *Adv. Chem. Ser.* **1969**, *91*, 399–418.
(42) Höcker, H.; Musch, R.; Jones, F. R.; Luederwald, I. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 430.
(43) Höcker, H.; Reimann, W.; Riebel, K.; Szentivanyi, Z. *Makromol. Chem.* **1976**, *177*, 1707–1715.
(44) Reif, L.; Höcker, H. *Makromol. Chem., Rapid Commun.* **1981**, *2*, 183–185.
(45) Chauvin, Y.; Commereuc, D.; Zaborowski, G. *Recl. Trav. Chim. Pays-Bas* **1977**, *96*, 131–133.
(46) Korshak, Y. V.; Dolgoplosk, B. A.; Tlenkopachev, M. A. *Recl. Trav. Chim. Pays-Bas* **1977**, *96*, 64–69.
(47) Höcker, H. *J. Mol. Catal.* **1991**, *65*, 95–99.
(48) Thorn-Csanyi, E.; Ruhland, K. *Macromol. Chem. Phys.* **1999**, *200*, 1662–1671.
(49) Kress, J. *J. Mol. Catal. A* **1995**, *102*, 7–21.
(50) Ahuja, R.; Kundu, S.; Goldman, A. S.; Brookhart, M.; Vicente, B. C.; Scott, S. L. *Chem. Commun.* **2008**, 253–255.
(51) Ofstead, E. A.; Calderon, N. *Makromol. Chem.* **1972**, *154*, 21–34.
(52) Witte, J.; Hoffmann, M. *Makromol. Chem.* **1978**, *179*, 641–659.
(53) Anhaus, J. T.; Gibson, V. C.; Clegg, W.; Collingwood, S. P. *Organometallics* **1993**, *12*, 1780–1789.
(54) Patton, P. A.; Lillya, C. P.; McCarthy, T. J. *Macromolecules* **1986**, *19*, 1266–1268.
(55) Warwel, S.; Kätker, H.; Rauenbusch, C. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 702–703.
(56) Warwel, S.; Kätker, H. *Synthesis* **1987**, 935–937.
(57) Wasserman, E.; Ben-Efraim, D. A.; Wolovsky, R. *J. Am. Chem. Soc.* **1968**, *90*, 3286–3287.
(58) Höcker, H.; Musch, R. *Makromol. Chem.* **1972**, *157*, 201–218.
(59) Höcker, H.; Musch, R. *Makromol. Chem.* **1974**, *175*, 1395–1409.
(60) Höcker, H.; Reif, L.; Reimann, W.; Riebel, K. *Recl. Trav. Chim. Pays-Bas* **1977**, *96*, 47–53.
(61) Reif, L.; Höcker, H. *Macromolecules* **1984**, *17*, 952–956.
(62) Zheng, X.; Jones, C. W.; Weck, M. *J. Am. Chem. Soc.* **2007**, *129*, 1105–1112.
(63) Kumobayashi, H.; Ogura, T.; Akutagawa, S.; Saito, K.; Yamaguchi, T.; Tanabe, K. *Chem. Lett.* **1976**, 317–320.
(64) Saito, K.; Yamaguchi, T.; Tanabe, K.; Ogura, T.; Yagi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3192–3197.
(65) Chauvin, Y.; Commereuc, D.; Zaborowski, G. *Makromol. Chem.* **1978**, *179*, 1285–1290.
(66) Wolovsky, R.; Nir, Z. *Synthesis* **1972**, 134–135.
(67) Wolovsky, R. *J. Am. Chem. Soc.* **1970**, *92*, 2132–2133.
(68) Ben-Efraim, D. A.; Batich, C.; Wasserman, E. *J. Am. Chem. Soc.* **1970**, *92*, 2133–2135.
(69) Höcker, H.; Riebel, K. *Makromol. Chem.* **1978**, *179*, 1765–1771.
(70) Arisandy, C.; Cowley, A. R.; Barlow, S. *J. Organomet. Chem.* **2004**, *689*, 775–780.
(71) Saf, R.; Schitter, R.; Mirtl, C.; Stelzer, F.; Hummel, K. *Macromolecules* **1996**, *29*, 7651–7656.
(72) Reif, L.; Höcker, H. *Makromol. Chem., Rapid Commun.* **1983**, *4*, 693–695.
(73) Dolgoplosk, B. A.; Makovetskii, K. L.; Korshak, Y. V.; Oreshkin, I. A.; Tinyakova, E. I.; Yakovlev, V. A. *Recl. Trav. Chim. Pays-Bas* **1977**, *96*, 35–46.
(74) Jacobson, H.; Stockmayer, W. H. *J. Chem. Phys.* **1950**, *18*, 1600–1606.
(75) Höcker, H.; Reimann, W.; Reif, L.; Riebel, K. *J. Mol. Catal.* **1980**, *8*, 191–202.
(76) Rehahn, M.; Mattice, W. L.; Suter, U. W. *Adv. Polym. Sci.* **1997**, *131/132*, 1–19.
(77) Suter, U. W.; Höcker, H. *Makromol. Chem.* **1988**, *189*, 1603–1612.
(78) Chen, Z.-R.; Claverie, J. P.; Grubbs, R. H.; Kornfield, J. A. *Macromolecules* **1995**, *28*, 2147–2154.
(79) Thorn-Csanyi, E.; Ruhland, K. *Macromol. Symp.* **2000**, *153*, 145–150.
(80) Ivin, K. J. *J. Polym. Sci., Part A* **2000**, *38*, 2137–2146.
(81) Höcker, H.; Keul, H. *Adv. Mater.* **1994**, *6*, 21–36.
(82) Throughout this discussion, we adopt the following terminology for different ring sizes: common rings are those containing 5−7 members; medium rings, 8−11 members; and large or macrocyclic rings, 12 or more. Small rings (3−4 members), which are not routinely accessible by RCM methods, will not be treated in this review, beyond a heavily functionalized example in section 4.3.1, which illustrates one of the arguments in section 2.3.2. For a discussion of new advances in this area, readers are directed to a recent overview. See: Grela, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 5504–5507.
(83) An alternative statement of this relationship posits an equilibrium monomer concentration $[M]_e$ at any given temperature, below which long-chain polymer cannot be formed. Kornfield and Grubbs distinguish between this term and the critical monomer concentration, noting that $[M]_e$ can be a poor indicator of polymerizability in the context of metathesis. They contrast the $[M]_e$ value of 0.002 M for ROMP of cyclooctene (see: Ivin, K. J. *Makromol. Chem., Macromol. Symp.* **1991**, *42/43*, 1) with the experimental finding (refs 61 and 75) that no linear "high polymer" is formed until the monomer concentration exceeded 0.21 M. See ref 78.
(84) Schrock, R. R.; Yap, K. B.; Yang, D. C.; Sitzmann, H.; Sita, L. R.; Bazan, G. C. *Macromolecules* **1989**, *22*, 3191–3200.
(85) Thorn-Csanyi, E.; Ruhland, K. *Macromol. Chem. Phys.* **1999**, *200*, 2606–2611.
(86) Ast, W.; Rheinwald, G.; Kerber, R. *Makromol. Chem.* **1976**, *177*, 1341–1348.
(87) Marsella, M. J.; Maynard, H. D.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1101–1103.
(88) Hodge, P.; Kamau, S. D. *Angew. Chem., Int. Ed.* **2003**, *42*, 2412–2414.

Downloaded by UNIV MAASTRICHT on August 28, 2009 | http://pubs.acs.org
Publication Date (Web): June 19, 2009 | doi: 10.1021/cr800541y

(89) Tastard, C. Y.; Hodge, P.; Ben-Haida, A.; Dobinson, M. *React. Funct. Polym.* **2006**, *66*, 93–107.
(90) Kamau, S. D.; Hodge, P.; Hall, A. J.; Dad, S.; Ben-Haida, A. *Polymer* **2007**, *48*, 6808–6822.
(91) Kang, S.; Berkshire, B. M.; Xue, Z.; Gupta, M.; Layode, C.; May, P. A.; Mayer, M. F. *J. Am. Chem. Soc.* **2008**, *130*, 15246–15247.
(92) Bielawski, C. W.; Benitez, D.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 8424–8425.
(93) Thorn-Csanyi, E.; Hammer, J.; Pflug, K. P.; Zilles, U. *Macromol. Chem. Phys.* **1995**, *196*, 1043–1050.
(94) Korshak, Y. V.; Tlenkopachev, M. A.; Dolgoplosk, B. A.; Avdeikina, E. G.; Kutepov, D. F. *J. Mol. Catal.* **1982**, *15*, 207–218.
(95) Hall, A. J.; Hodge, P.; Kamau, S. D.; Ben-Haida, A. *J. Organomet. Chem.* **2006**, *691*, 5431–5437.
(96) Thorn-Csanyi, E.; Hammer, J.; Zilles, J. U. *Macromol. Rapid Commun.* **1994**, *15*, 797–800.
(97) Thorn-Csanyi, E. *NATO ASI Ser., Ser. C* **1998**, *506*, 117–137.
(98) Tlenkopatchev, M. A.; Barcenas, A.; Fomine, S. *Macromol. Theory Simul.* **2001**, *10*, 441–446.
(99) Tlenkopatchev, M. A.; Barcenas, A.; Fomine, S. *Macromol. Theory Simul.* **1999**, *8*, 581–585.
(100) Bielawski, C. W.; Benitez, D.; Grubbs, R. H. *Science* **2002**, *297*, 2041–2044.
(101) Ercolani, G.; Di Stefano, S. *J. Phys. Chem. B* **2008**, *112*, 4662–4665.
(102) Boydston, A. J.; Xia, Y.; Kornfield, J. A.; Gorodetskaya, I. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2008**, *130*, 12775–12782.
(103) By "elevated temperatures" we mean temperatures above ambient, including that attainable in refluxing CH_2Cl_2 (ca. 40 °C), one of the most common solvent/temperature combinations used for RCM reactions.
(104) Forbes, M. D. E.; Patton, J. T.; Myers, T. L.; Maynard, H. D.; Smith, D. W., Jr.; Schulz, G. R.; Wagener, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 10978–10980.
(105) Conrad, J. C.; Eelman, M. D.; Duarte Silva, J. A.; Monfette, S.; Parnas, H. H.; Snelgrove, J. L.; Fogg, D. E. *J. Am. Chem. Soc.* **2007**, *129*, 1024–1025.
(106) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95–102.
(107) (a) Ercolani, G.; Mandolini, L.; Mencareli, P.; Roelens, S. *J. Am. Chem. Soc.* **1993**, *115*, 3901–3908. (b) Dalla Cort, A.; Mandolini, L.; Masci, B. *J. Org. Chem.* **1980**, *45*, 3923–3925.
(108) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183–278.
(109) Galli, C.; Mandolini, L. *Eur. J. Org. Chem.* **2000**, 3117–3125.
(110) Mandolini, L. *Adv. Phys. Org. Chem.* **1986**, *22*, 1–111.
(111) Ercolani, G. *Struct. Bonding (Berlin)* **2006**, *121*, 167–215.
(112) Ercolani, G. *J. Phys. Chem. B* **2003**, *107*, 5052–5057.
(113) Corbett, P. T.; Leclaire, J.; Vial, L.; West, K. R.; Wietor, J.-L.; Sanders, J. K. M.; Otto, S. *Chem. Rev.* **2006**, *106*, 3652–3711.
(114) Cacciapaglia, R.; Di Stefano, S.; Mandolini, L. *J. Am. Chem. Soc.* **2005**, *127*, 13666–13671.
(115) Mulder, A.; Huskens, J.; Reinhoudt, D. N. *Org. Biomol. Chem.* **2004**, *2*, 3409–3424.
(116) Li, X.; Liu, D. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 4848–4870.
(117) Huskens, J.; Mulder, A.; Auletta, T.; Nijhuis, C. A.; Ludden, M. J. W.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **2004**, *126*, 6784–6797.
(118) Cacciapaglia, R.; Di Stefano, S.; Mandolini, L. *Acc. Chem. Res.* **2004**, *37*, 113–122.
(119) Flory, P. J. *Statistical Mechanics of Chain Molecules*; Wiley Interscience: New York, 1969.
(120) Page, M. I.; Jencks, W. P. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 1678–1683.
(121) Casadei, M. A.; Galli, C.; Mandolini, L. *J. Am. Chem. Soc.* **1984**, *106*, 1051–1056.
(122) Hubbard, P. A.; Brittain, W. J.; Mattice, W. L.; Brunelle, D. J. *Macromolecules* **1998**, *31*, 1518–1522.
(123) Mitchell, L.; Parkinson, J. A.; Percy, J. M.; Singh, K. *J. Org. Chem.* **2008**, *73*, 2389–2395.
(124) Farina, V.; Shu, C.; Zeng, X.; Wei, X.; Han, Z.; Yee, N. K.; Senanayake, C. H. *Org. Process Res. Dev.* **2009**, *13*, 250–254.
(125) Lee, L.-S.; Ou, H.-J.; Hsu, H.-L. *Fluid Phase Equilib.* **2005**, *231*, 221–230.
(126) Representative data for ethylene solubility in toluene under 1 atm of the gas (ref 125): at 20 °C, 46 mM; at 40 °C, 5 mM. The Diver group has used NMR methods to assess ethylene concentrations in CD_2Cl_2 at ambient temperatures, again under 1 atm of C_2H_4: 32 mM. Temperature effects were not reported. See: Smulik, J. A.; Diver, S. T. *J. Org. Chem.* **2000**, *65*, 1788–1792.
(127) Lysenko, Z.; Maughon, B. R.; Mokhtar-Zadeh, T.; Tulchinsky, M. L. *J. Organomet. Chem.* **2006**, *691*, 5197–5203.
(128) van der Eide, E. F.; Romero, P. E.; Piers, W. E. *J. Am. Chem. Soc.* **2008**, *130*, 4485–4491.
(129) Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 7202–7207.
(130) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543–6554.
(131) Goldring, W. P. D.; Hodder, A. S.; Weiler, L. *Tetrahedron Lett.* **1998**, *39*, 4955–4958.
(132) Nosse, B.; Schall, A.; Jeong, W. B.; Reiser, O. *Adv. Synth. Catal.* **2005**, *347*, 1869–1874.
(133) Sieck, S. R.; McReynolds, M. D.; Schroeder, C. E.; Hanson, P. R. *J. Organomet. Chem.* **2006**, *691*, 5307–5311.
(134) Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082–6083.
(135) Giessert, A. J.; Brazis, N. J.; Diver, S. T. *Org. Lett.* **2003**, *5*, 3819–3822.
(136) Lloyd-Jones, G. C.; Margue, R. G.; de Vries, J. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 7442–7447.
(137) Stephen, H.; Stephen, T. *Solubilities of Inorganic and Organic Compounds*; Pergamon: New York, 1963; Vol. 1, pp 1177−1183.
(138) Xu, Z.; Johannes, C. W.; Houri, A. F.; La, D. S.; Cogan, D. A.; Hofilena, G. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 10302–10316.
(139) Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310–7318.
(140) Fürstner, A.; Thiel, O. R.; Ackermann, L. *Org. Lett.* **2001**, *3*, 449–451.
(141) Lemarchand, A.; Bach, T. *Tetrahedron* **2004**, *60*, 9659–9673.
(142) Rivkin, A.; Biswas, K.; Chou, T.-C.; Danishefsky, S. J. *Org. Lett.* **2002**, *4*, 4081–4084.
(143) Yamamoto, K.; Biswas, K.; Gaul, C.; Danishefsky, S. J. *Tetrahedron Lett.* **2003**, *44*, 3297–3299.
(144) Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973–9976.
(145) Renaud, J.; Ouellet, S. G. *J. Am. Chem. Soc.* **1998**, *120*, 7995–7996.
(146) Lloyd-Jones, G. C.; Murray, M.; Stentiford, R. A.; Worthington, P. A. *Eur. J. Org. Chem.* **2000**, 975–985.
(147) Marco-Contelles, J.; de Opazo, E. *J. Org. Chem.* **2002**, *67*, 3705–3717.
(148) Creighton, C. J.; Leo, G. C.; Du, Y.; Reitz, A. B. *Bioorg. Med. Chem.* **2004**, *12*, 4375–4385.
(149) Crimmins, M. T.; Brown, B. H. *J. Am. Chem. Soc.* **2004**, *126*, 10264–10266.
(150) Marhold, M.; Buer, A.; Hiemstra, H.; van Maarseveen, J. H.; Haufe, G. *Tetrahedron Lett.* **2004**, *45*, 57–60.
(151) Briggs, T. F.; Dudley, G. B. *Tetrahedron Lett.* **2005**, *46*, 7793–7796.
(152) El-azizi, Y.; Schmitzer, A.; Collins, S. K. *Angew. Chem., Int. Ed.* **2006**, *45*, 968–973.
(153) Lee, C. W.; Grubbs, R. H. *J. Org. Chem.* **2001**, *66*, 7155–7158.
(154) Tezuka, Y.; Komiya, R. *Macromolecules* **2002**, *35*, 8667–8669.
(155) Ulman, M.; Grubbs, R. H. *Organometallics* **1998**, *17*, 2484–2489.
(156) Williams, J. E.; Harner, M. J.; Sponsler, M. B. *Organometallics* **2005**, *24*, 2013–2015.
(157) Bielawski, C. W.; Benitez, D.; Morita, T.; Grubbs, R. H. *Macromolecules* **2001**, *34*, 8610–8618.
(158) Berlin, J. M.; Campbell, K.; Ritter, T.; Funk, T. W.; Chlenov, A.; Grubbs, R. H. *Org. Lett.* **2007**, *9*, 1339–1342.
(159) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751–1753.
(160) Monfette, S.; Fogg, D. E. *Book of Abstracts*, 17th International Symposium on Olefin Metathesis (ISOM-17), Pasadena, CA, July 29−Aug 3, 2007.
(161) Conrad, J. C.; Parnas, H. H.; Snelgrove, J. L.; Fogg, D. E. *J. Am. Chem. Soc.* **2005**, *127*, 11882–11883.
(162) Tzur, E.; Ben-Asuly, A.; Diesendruck, C. E.; Goldberg, I.; Lemcoff, N. G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6422–6425.
(163) Craig, S. W.; Manzer, J. A.; Coughlin, E. B. *Macromolecules* **2001**, *34*, 7929–7931.
(164) Hong, S. H.; Wenzel, A. G.; Salguero, T. T.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2007**, *129*, 7961–7968.
(165) Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2004**, *126*, 7414–7415.
(166) Amoroso, D.; Snelgrove, J. L.; Conrad, J. C.; Drouin, S. D.; Yap, G. P. A.; Fogg, D. E. *Adv. Synth. Catal.* **2002**, *344*, 757–763.
(167) Amoroso, D.; Yap, G. P. A.; Fogg, D. E. *Organometallics* **2002**, *21*, 3335–3343.
(168) Haigh, D. M.; Kenwright, A. M.; Khosravi, E. *Tetrahedron* **2004**, *60*, 7217–7224.
(169) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130–9136.
(170) Yang, Q.; Xiao, W.-J.; Yu, Z. *Org. Lett.* **2005**, *7*, 871–874.
(171) McNaughton, B. R.; Bucholtz, K. M.; Camaano-Moure, A.; Miller, B. L. *Org. Lett.* **2005**, *7*, 733–736.
(172) Nevalainen, M.; Koskinen, A. M. P. *Angew. Chem., Int. Ed.* **2001**, *40*, 4060–4062.
(173) Fürstner, A.; Thiel, O. R.; Lehmann, C. W. *Organometallics* **2002**, *21*, 331–335.
(174) Czelusniak, I.; Heywood, J. D.; Kenwright, A. M.; Khosravi, E. *J. Mol. Catal. A* **2008**, *280*, 29–34.
(175) Haigh, D. M.; Kenwright, A. M.; Khosravi, E. *Macromolecules* **2005**, *38*, 7571–7579.

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(176) Fürstner, A.; Gastner, T.; Weintritt, H. *J. Org. Chem.* **1999**, *64*, 2361–2366.
(177) Young, D. G. J.; Burlison, J. A.; Peters, U. *J. Org. Chem.* **2003**, *68*, 3494–3497.
(178) Sheddan, N. A.; Arion, V. B.; Mulzer, J. *Tetrahedron Lett.* **2006**, *47*, 6689–6693.
(179) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856–9857.
(180) Ulman, M.; Belderrain, T. R.; Grubbs, R. H. *Tetrahedron Lett.* **2000**, *41*, 4689–4693.
(181) Chen, X.; Wiemer, D. F. *J. Org. Chem.* **2003**, *68*, 6597–6604.
(182) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204–2207.
(183) Selvakumar, N.; Kumar, P. K.; Reddy, K. C. S.; Chary, B. C. *Tetrahedron Lett.* **2007**, *48*, 2021–2024.
(184) Louie, J.; Grubbs, R. H. *Organometallics* **2002**, *21*, 2153–2164.
(185) Colacino, E.; Martinez, J.; Lamaty, F. *Coord. Chem. Rev.* **2007**, *251*, 726–764.
(186) MacNaughtan, M. L.; Johnson, M. J. A.; Kampf, J. W. *Organometallics* **2007**, *26*, 780–782.
(187) MacNaughtan, M. L.; Johnson, M. J. A.; Kampf, J. W. *J. Am. Chem. Soc.* **2007**, *129*, 7708–7709.
(188) Alcaide, B.; Almendros, P. *Chem.—Eur. J.* **2003**, *9*, 1259–1262.
(189) Hoye, T. R.; Promo, M. A. *Tetrahedron Lett.* **1999**, *40*, 1429–1432.
(190) Bourgeois, D.; Pancrazi, A.; Nolan, S. P.; Prunet, J. *J. Organomet. Chem.* **2002**, *643−644*, 247–252.
(191) van Gerven, P. C. M.; Elemans, J. A. A. W.; Gerritsen, J. W.; Speller, S.; Nolte, R. J. M.; Rowan, A. E. *Chem. Commun.* **2005**, 3535–3537.
(192) Courchay, F. C.; Sworen, J. C.; Wagener, K. B. *Macromolecules* **2003**, *36*, 8231–8239.
(193) Lehman, S. E., Jr.; Wagener, K. B. *Organometallics* **2005**, *24*, 1477–1482.
(194) Petkovska, V. I.; Hopkins, T. E.; Powell, D. H.; Wagener, K. B. *Macromolecules* **2005**, *38*, 5878–5885.
(195) Courchay, F. C.; Sworen, J. C.; Ghiviriga, I.; Abboud, K. A.; Wagener, K. B. *Organometallics* **2006**, *25*, 6074–6086.
(196) Petkovska, V. I.; Hopkins, T. E.; Powell, D. H.; Wagener, K. B. *Anal. Chem.* **2006**, *78*, 3624–3631.
(197) Joe, D.; Overman, L. E. *Tetrahedron Lett.* **1997**, *38*, 8635–8638.
(198) Chuchuryukin, A. V.; Chase, P. A.; Dijkstra, H. P.; Suijkerbuijk, B.; Mills, A. M.; Spek, A. L.; van Klink, G. P. M.; van Koten, G. *Adv. Synth. Catal.* **2005**, *347*, 447–462.
(199) Thorn-Csanyi, E.; Dehmel, J.; Luginsland, H.-D.; Zilles, J. U. *J. Mol. Catal. A* **1997**, *115*, 29–35.
(200) Arakawa, K.; Eguchi, T.; Kakinuma, K. *J. Org. Chem.* **1998**, *63*, 4741–4745.
(201) Michrowska, A.; Wawrzyniak, P.; Grela, K. *Eur. J. Org. Chem.* **2004**, 2053–2056.
(202) Cottier, L.; Descotes, G. R.; Soro, Y. *Synth. Commun.* **2003**, *33*, 4285–4295.
(203) Albrecht, M.; Yeni, *Synthesis* **2008**, 2451–2461.
(204) Boyer, F.-D.; Hanna, I. *Eur. J. Org. Chem.* **2006**, 471–482.
(205) Austin, K. A. B.; Banwell, M. G.; Loong, D. T. J.; Rae, A. D.; Willis, A. C. *Org. Biomol. Chem.* **2005**, *3*, 1081–1088.
(206) Christoffers, J.; Oertling, H.; Fischer, P.; Frey, W. *Tetrahedron* **2003**, *59*, 3769–3778.
(207) Kidd, T. J.; Leigh, D. A.; Wilson, A. J. *J. Am. Chem. Soc.* **1999**, *121*, 1599–1600.
(208) Jarosz, S.; Listkowski, A. *Can. J. Chem.* **2006**, *84*, 492–496.
(209) Tae, J.; Yang, Y.-K. *Org. Lett.* **2003**, *5*, 741–744.
(210) Hamilton, D. G.; Feeder, N.; Teat, S. J.; Sanders, J. K. M. *New J. Chem.* **1998**, *22*, 1019–1021.
(211) Srikrishna, A.; Dethe, D. H. *Tetrahedron Lett.* **2005**, *46*, 3381–3383.
(212) Lee, C. W.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 2145–2147.
(213) An exception is **84**, the structure of which follows the precedents of section 3.1.4.
(214) Clark, J. S.; Kettle, J. G. *Tetrahedron* **1999**, *55*, 8231–8248.
(215) Kotha, S.; Khedkar, P.; Ghosh, A. K. *Eur. J. Org. Chem.* **2005**, 3581–3585.
(216) Arisawa, M.; Kato, C.; Kaneko, H.; Nishida, A.; Nakagawa, M. *Perkin 1* **2000**, 1873–1876.
(217) Irie, O.; Samizu, K.; Henry, J. R.; Weinreb, S. M. *J. Org. Chem.* **1999**, *64*, 587–595.
(218) Sivaramakrishna, A.; Su, H.; Moss, J. R. *Angew. Chem., Int. Ed.* **2007**, *46*, 3541–3543.
(219) Maughon, B. R.; Grubbs, R. H. *Macromolecules* **1997**, *30*, 3459–3469.
(220) Constable, D. J. C.; Jimenez-Gonzalez, C.; Henderson, R. K. *Org. Process Res. Dev.* **2007**, *11*, 133–137.
(221) Shu, C.; Zeng, X.; Hao, M.-H.; Wei, X.; Yee, N. K.; Busacca, C. A.; Han, Z.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2008**, *10*, 1303–1306.
(222) Monfette, S.; Fogg, D. E. In *Ring-Closing Metathesis in the Synthesis of Medium and Large Rings: Challenges and Implications for Sustainable Synthesis*; Dragutan, V., Finkelshtein, E., Eds.; Green Metathesis Chemistry, NATO Science Series II; Springer Verlag: 2009.
(223) Bach, T.; Lemarchand, A. *Synlett* **2002**, 1302–1304.
(224) Fürstner, A.; Ackermann, L.; Beck, K.; Hori, H.; Koch, D.; Langemann, K.; Liebl, M.; Six, C.; Leitner, W. *J. Am. Chem. Soc.* **2001**, *123*, 9000–9006.
(225) Fürstner, A.; Koch, D.; Langemann, K.; Leitner, W.; Six, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2466–2469.
(226) Smith, A. B., III; Basu, K.; Bosanac, T. *J. Am. Chem. Soc.* **2007**, *129*, 14872–14874.
(227) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791–799.
(228) Grela, K.; Harutyunyan, S.; Michrowska, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4038–4040.
(229) Fogg, D. E.; Foucault, H. M. In *Ring-Opening Metathesis Polymerization*; Crabtree, R. H., Mingos, M. P., Eds.; Comprehensive Organometallic Chemistry III; Elsevier: Oxford, 2007; Vol. 11, pp 623−652.
(230) Yee, N. K.; Farina, V.; Houpis, I. N.; Haddad, N.; Frutos, R. P.; Gallou, F.; Wang, X.-J.; Wei, X.; Simpson, R. D.; Feng, X.; Fuchs, V.; Xu, Y.; Tan, J.; Zhang, L.; Xu, J.; Smith-Keenan, L. L.; Vitous, J.; Ridges, M. D.; Spinelli, E. M.; Johnson, M.; Donsbach, K.; Nicola, T.; Brenner, M.; Winter, E.; Kreye, P.; Samstag, W. *J. Org. Chem.* **2006**, *71*, 7133–7145.
(231) Galan, B. R.; Gembicky, M.; Dominiak, P. M.; Keister, J. B.; Diver, S. T. *J. Am. Chem. Soc.* **2005**, *127*, 15702–15703.
(232) Blacquiere, J. M.; Jurca, T.; Weiss, J.; Fogg, D. E. *Adv. Synth. Catal.* **2008**, *350*, 2849–2855.
(233) P'Pool, S. J.; Schanz, H.-J. *J. Am. Chem. Soc.* **2007**, *129*, 14200–14212.
(234) Stark, A.; Ajam, M.; Green, M.; Raubenheimer, H. G.; Ranwell, A.; Ondruschka, B. *Adv. Synth. Catal.* **2006**, *348*, 1934–1941.
(235) Slugovc, C.; Demel, S.; Stelzer, F. *Chem. Commun.* **2002**, 2572–2573.
(236) Maynard, H. D.; Okada, S. Y.; Grubbs, R. H. *Macromolecules* **2000**, *33*, 6239–6248.
(237) Wu, Z.; Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1995**, *117*, 5503–5511.
(238) Arisawa, M.; Terada, Y.; Takahashi, K.; Nakagawa, M.; Nishida, A. *J. Org. Chem.* **2006**, *71*, 4255–4261.
(239) Fürstner, A.; Thiel, O. R.; Kindler, N.; Bartkowska, B. *J. Org. Chem.* **2000**, *65*, 7990–7995.
(240) Smith, A. B., III; Kozmin, S. A.; Adams, C. M.; Paone, D. V. *J. Am. Chem. Soc.* **2000**, *122*, 4984–4985.
(241) Smith, A. B., III; Adams, C. M.; Kozmin, S. A. *J. Am. Chem. Soc.* **2001**, *123*, 990–991.
(242) Smith, A. B., III; Adams, C. M.; Kozmin, S. A.; Paone, D. V. *J. Am. Chem. Soc.* **2001**, *123*, 5925–5937.
(243) Michaut, A.; Rodriguez, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 5740–5750.
(244) Blankenstein, J.; Zhu, J. P. *Eur. J. Org. Chem.* **2005**, 1949–1964.
(245) Cheung, L. L.; Marumoto, S.; Anderson, C. D.; Rychnovsky, S. D. *Org. Lett.* **2008**, *10*, 3101–3104.
(246) Akine, S.; Kagiyama, S.; Nabeshima, T. *Inorg. Chem.* **2007**, *46*, 9525–9527.
(247) Shima, T.; Hampel, F.; Gladysz, J. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5537–5540.
(248) Nawara, A. J.; Shima, T.; Hampel, F.; Gladysz, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 4962–4963.
(249) de Quadras, L.; Hampel, F.; Gladysz, J. A. *Dalton Trans.* **2006**, 2929–2933.
(250) Skopek, K.; Barbasiewicz, M.; Hampel, F.; Gladysz, J. A. *Inorg. Chem.* **2008**, *47*, 3474–3476.
(251) Dietrich-Buchecker, C.; Jimenez-Molero, M. C.; Sartor, V.; Sauvage, J.-P. *Pure Appl. Chem.* **2003**, *75*, 1383–1393.
(252) Frey, J.; Kraus, T.; Heitz, V.; Sauvage, J.-P. *Chem. Commun.* **2005**, 5310–5312.
(253) Frey, J.; Kraus, T.; Heitz, V.; Sauvage, J.-P. *Chem.—Eur. J.* **2007**, *13*, 7584–7594.
(254) Chuchuryukin, A. V.; Dijkstra, H. P.; Suijkerbuijk, B. M. J. M.; Klein Gebbink, R. J. M.; van Klink, G. P. M.; Mills, A. M.; Spek, A. L.; van Koten, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 228–230.
(255) Song, K. H.; Kang, S. O.; Ko, J. *Chem.—Eur. J.* **2007**, *13*, 5129–5134.
(256) Kilbinger, A. F. M.; Cantrill, S. J.; Waltman, A. W.; Day, M. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 3281–3285.
(257) Hou, H.; Leung, K. C. F.; Lanari, D.; Nelson, A.; Stoddart, J. F.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 15358–15359.
(258) Youm, K.-T.; Nguyen, S. B. T.; Hupp, J. T. *Chem. Commun.* **2008**, 3375–3377.

(259) Wakabayashi, R.; Kubo, Y.; Hirata, O.; Takeuchi, M.; Shinkai, S. *Chem. Commun.* **2005**, 5742–5744.
(260) Rudzevich, Y.; Cao, Y.; Rudzevich, V.; Bohmer, V. *Chem.—Eur. J.* **2008**, *14*, 3346–3354.
(261) Lankshear, M. D.; Evans, N. H.; Bayly, S. R.; Beer, P. D. *Chem.—Eur. J.* **2007**, *13*, 3861–3870.
(262) Muthusamy, S.; Gnanaprakasam, B.; Suresh, E. *J. Org. Chem.* **2007**, *72*, 1495–1498.
(263) Weck, M.; Mohr, B.; Sauvage, J.-P.; Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 5463–5471.
(264) Mohr, B.; Weck, M.; Sauvage, J.-P.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1308–1310.
(265) Rapenne, G.; Dietrich-Buchecker, C.; Sauvage, J.-P. *J. Am. Chem. Soc.* **1999**, *121*, 994–1001.
(266) Mobian, P.; Kern, J.-M.; Sauvage, J.-P. *J. Am. Chem. Soc.* **2003**, *125*, 2016–2017.
(267) Arico, F.; Mobian, P.; Kern, J.-M.; Sauvage, J.-P. *Org. Lett.* **2003**, *5*, 1887–1890.
(268) Dietrich-Buchecker, C.; Rapenne, G.; Sauvage, J.-P. *Chem. Commun.* **1997**, 2053–2054.
(269) Shima, T.; Bauer, E. B.; Hampel, F.; Gladysz, J. A. *Dalton Trans.* **2004**, 1012–1028.
(270) Bauer, E. B.; Ruwwe, J.; Hampel, F. A.; Szafert, S.; Gladysz, J. A.; Martin-Alvarez, J. M.; Peters, T. B.; Bohling, J. C.; Lis, T. *Chem. Commun.* **2000**, 2261–2262.
(271) Bauer, E. B.; Hampel, F.; Gladysz, J. A. *Organometallics* **2003**, *22*, 5567–5580.
(272) Lewanzik, N.; Oeser, T.; Bluemel, J.; Gladysz, J. A. *J. Mol. Catal. A: Chem.* **2006**, *254*, 20–28.
(273) Horn, C. R.; Martin-Alvarez, J. M.; Gladysz, J. A. *Organometallics* **2002**, *21*, 5386–5393.
(274) Stahl, J.; Bohling, J. C.; Bauer, E. B.; Peters, T. B.; Mohr, W.; Martin-Alvarez, J. M.; Hampel, F.; Gladysz, J. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1871–1876.
(275) Horn, C. R.; Gladysz, J. A. *Eur. J. Inorg. Chem.* **2003**, 2211–2218.
(276) Wang, L.; Shima, T.; Hampel, F.; Gladysz, J. A. *Chem. Commun.* **2006**, 4075–4077.
(277) Wang, L.; Hampel, F.; Gladysz, J. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4372–4375.
(278) Ruwwe, J.; Martin-Alvarez, J. M.; Horn, C. R.; Bauer, E. B.; Szafert, S.; Lis, T.; Hampel, F.; Cagle, P. C.; Gladysz, J. A. *Chem.—Eur. J.* **2001**, *7*, 3931–3950.
(279) Chase, P. A.; Lutz, M.; Spek, A. L.; van Klink, G. P. M.; van Koten, G. *J. Mol. Catal. A* **2006**, *254*, 2–19.
(280) Li, Y.; Zhang, T.; Li, Y.-L. *Tetrahedron Lett.* **2007**, *48*, 1503–1505.
(281) Pentzer, E. B.; Gadzikwa, T.; Nguyen, S. T. *Org. Lett.* **2008**, *10*, 5613–5615.

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