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The Influence of Structure on Reactivity in Alkene Metathesis

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Contents

Abstract

Alkene metathesis has grown from a niche technique to a common component of the synthetic organic chemistry toolbox, driven in part by the development of more active catalyst systems, or those optimized for particular purposes. While the range of synthetic chemistry achieved has been exciting, the effects of structure on reactivity have not always been particularly clear, and rarely quantified. Understanding these relationships is important when designing new catalysts, reactions, and syntheses. Here, we examine what is known about the effect of structure on reactivity from two perspectives: the catalyst, and the substrate. The initiation of the pre-catalyst determines the rate at which active catalyst enters the catalytic cycle; the rate and selectivity of the alkene metathesis reaction is dependent on how the substrate and active catalyst interact. The tools deployed in modern studies of mechanism and structure/activity relationships in alkene metathesis are discussed.

1. Introduction

During the past two decades, the alkene metathesis reaction has developed from its early applications in large-scale processes with heterogeneous and ill-defined catalyst systems,[1] to a standard technique in synthetic chemistry and polymer laboratories.[2] The development of well-defined and often bench-stable pre-catalysts[3,4] has been key to the widespread use of alkene metathesis in modern target synthesis projects. The impact of this useful reaction was recognized in 2005 by the award of the Nobel Prize in Chemistry to Yves Chauvin, Robert Grubbs and Richard Schrock.[5-7] Astruc has published an excellent article on the early history of the alkene metathesis reaction,[8] which covers the determination of the mechanism and the rejection of alternative hypotheses, so this early history will not be discussed here.

In its simplest form, alkene metathesis is the transfer of groups between alkenes and metal carbenes, which proceeds *via* the formation of metallocyclobutane (MCB) species which form by [2+2]cycloaddition; retro-[2+2]cycloaddition follows to yield different species (**Scheme 1 (a)**).[9] Through this sequence of steps, new alkene and alkylidene species can be formed. Several types of metathesis reaction have been employed in various branches of chemistry (**Scheme 1 (b)**); the most common reactions are cross-metathesis (CM), ring-closing metathesis (RCM) (in target synthesis), ring-opening metathesis polymerization (ROMP) and acyclic diene metathesis (ADMET) (in polymer chemistry), although other variations and combinations of these processes are known. A recent review documents some of the studies of various processes that occur during metathesis reactions.[10]

[Please insert scheme1_color or scheme1_bw here]

Scheme 1. (a) The basic alkene metathesis mechanism; and (b) alkene metathesis reactions.

Various metal carbene complexes are known to catalyze this reaction, including those based on metals such as rhenium, molybdenum, tungsten, tantalum, titanium and ruthenium (**Figure 1**).[11] A limited selection of these is discussed here. Well-defined and very active molybdenum catalysts such as **Mo1** and **Mo2** are known, but require careful handling in a glove-box.[12] Fürstner has developed a

protocol for trapping and storage of the active species as the bi-pyridine adduct which can be released by reaction with $ZnCl_2$ in hot toluene,[13] but the active catalysts are often intolerant of common functional groups in organic chemistry, particularly those that are protic. Recently, Hoveyda *et al.* prepared well-defined and air-stable tungsten metallacycle pre-catalyst **W1**.[14]

The largest class of well-defined metathesis pre-catalysts feature a ruthenium center, which typically bears phosphine and/or *N*-heterocyclic carbene (NHC) ligands. The two most common types of ruthenium-based metathesis pre-catalyst are phosphine-bound 'Grubbs-type' species such as **G1**[15] and **G2**,[16] and chelated alkoxystyrene 'Hoveyda-type' species such as **GH1**,[17] **GH2**[18] and **Grela**.[19] Pyridine-ligated pre-catalysts such as **G2-3BrPy** have also been reported,[20] while several researchers have focused on the development of indenylidene-bearing complexes such as $\mathbf{M_1}$ and $\mathbf{M_2}$.[21] As a result of their activity, stability, relatively low cost, and ease of handling, the most commonly used pre-catalysts in target synthesis, where very diverse functional groups are often involved, are ruthenium carbene complexes.

[Please insert Figure01]

Figure 1. Selected examples of alkene metathesis (pre-)catalysts; see **Figure 2** for the structure of **SIMes**.

Ruthenium-based complexes can be divided broadly into first- and second-generation species. The former typically bear a non-dissociating phosphine ligand, while in the latter the non-dissociating ligand is an *N*-heterocyclic carbene (NHC) (selected examples used in metathesis are shown in **Figure 2**). Second-generation complexes are typically the most active complexes for metathesis reactions, with the exception of some very simple, straightforward examples.[22] Bis(NHC) complexes are rarely deployed due to their poor activity compared to heteroleptic NHC/phosphine complexes.[23]

[Please insert Figure02]

Figure 2. Selected examples of NHC ligands used for ruthenium-based alkene metathesis pre-catalysts.

A more detailed reaction mechanism for ruthenium-catalyzed RCM and CM is shown in **Scheme 2**. The CM pathway is still accessible for the metathesis of dienes, with the partitioning between RCM and CM being dependent on a number of factors (*vide infra*). This consists of an initiation mechanism, where the (typically 16e$^-$) pre-catalyst is transformed into a (typically 14e$^-$) active species *via* reaction with one alkene (or diene terminus) to form an intermediate alkylidene, which binds a second alkene (or terminus). This then reacts to yield the product (cyclo)alkene and a methylidene intermediate (for terminal alkenes), which in turn reacts with subsequent substrate molecules. For terminal alkenes, ethene is produced during the first metathesis step of the second and subsequent turnovers. It is important to note that while expedient ethene egress is often said to 'drive' metathesis reactions, it is only this initial step that is favored by ethene removal. Each step in the catalytic cycle has been drawn as reversible, although the degree of reversibility is determined by the substrate/pre-catalyst combination (*vide infra*). Second generation complexes, being more active, especially with product alkenes, typically operate in the thermodynamic regime, while reactions catalyzed by first generation complexes are typically under kinetic control.

[Please insert Scheme02_color or Scheme02_bw]

Scheme 2. The mechanism of ruthenium-catalyzed RCM and CM.

This Chapter will focus almost exclusively on alkene metathesis catalyzed by well-defined homogeneous ruthenium catalyst systems, and is divided into three sections: (i) a discussion of how pre-catalyst structure affects the rate and mechanism of initiation in two key series of metathesis pre-catalysts; (ii) a discussion of how substrate structure, both close to and remote from the alkene termini, affects the rate and selectivity of alkene metathesis in synthetic chemistry; and (iii) the tools that have been used by experimental and theoretical chemists to study alkene metathesis reactions. In each case, the discussion will be focused on the specific topics; interested readers are referred to a recent article which covers a wider range of the mechanistic aspects of alkene metathesis with ruthenium complexes, albeit in less depth.[10]

2. Initiation of Metathesis Pre-catalysts

2.1 How Do Metathesis Pre-catalysts Initiate?

Typical alkene metathesis pre-catalysts take the form displayed in **Figure 3**, consisting of a ruthenium(II) center, a carbene with substituent R, two anionic ligands X (typically chloride), a non-dissociating ligand L (typically a trialkylphosphine or *N*-heterocyclic carbene), and a dissociating ligand L' which is most often either a phosphine or a chelating alkoxyarene. While the nature of X, L, L', and R all influence the initiation rate and mechanism, it is the nature of L and X that determine the catalytic activity of the active species itself; complexes **G2**, **M$_2$** and **GH2** all produce the *same* active species, albeit *via* different mechanisms and at different rates.

[Please insert Figure03_color or Figure03_bw]

Figure 3. Components of a typical ruthenium-based metathesis pre-catalyst.

A thorough understanding of the initiation mechanism and rate is important, as this determines the rate at which active catalyst is released into the reaction. Faster initiators do not always perform best in metathesis reactions,[24] presumably due to the much lower stability of intermediate species compared to the pre-catalyst complexes. Polymer chemists often make use of 'latent' pre-catalysts, which are designed to initiate very slowly at room temperature, or only upon specific stimuli such as acid or a specific wavelength of light;[25] these allow for the convenient handling of pre-catalyst/monomer mixtures before the polymerization reaction is begun. Straightforward reactions to form five- and six-membered rings without difficult substitution patterns are often conducted in a straightforward manner with rapid initiators, while more thermally-stable slower-initiating pre-catalysts have been found to perform best for the preparation of challenging tetrasubstituted alkenes (*vide infra*).[22]

Early work had suggested mechanisms for metathesis reactions catalyzed by **G1** in which the alkene might co-ordinate first, followed by phosphine dissociation, or where both phosphine ligands remain co-ordinated throughout the catalytic cycle. However, it was later established that

intermediates in the catalytic cycle were monophosphine ruthenium complexes, and not bisphosphine species; Lloyd-Jones has previously discussed and summarized some of these early studies.[26]

One can envision three potential mechanisms for initiation reactions of these species: associative, dissociative and interchange (**Scheme 3**); these can even be considered as a spectrum between two extremes (associative and dissociative). In the associative mechanism, the alkene substrate co-ordinates to the metal center to form an $18e^-$ intermediate, followed by dissociation of L' and rearrangement to the $16e^-$ η^2-complex. In the dissociative mechanism, the order of the steps is reversed; L' first dissociates to yield a $14e^-$ intermediate which then binds alkene. In the interchange mechanism, binding of the substrate and release of the L' group occurs simultaneously, *via* a single transition state.

[Please insert Scheme03_color or Scheme03_bw]

Scheme 3. Potential mechanisms for metathesis pre-catalyst initiation: (a) associative, (b) dissociative, and (c) interchange.

Differences in experimental behavior would be expected between the three mechanisms. For the dissociative mechanisms, the initiation rate should be essentially independent of the concentration and nature of the alkene substrate, once the association of the substrate proceeded at a rate higher than that of the dissociation step (i.e. saturation behavior). It has been shown that association of the alkene to a 14e ruthenium carbene complex is essentially barrierless.[27] A positive enthalpy of activation would be expected, as the Ru-L' bond is cleaved, along with a positive entropy of activation, the magnitude of which would depend on whether (and how) R and L' are tethered, with larger values for untethered L'. The rate of initiation would be expected to be reduced in the presence of alternative ligands such as excess L'. The associative and interchange mechanisms would proceed at rates dependent on the concentration and nature of the alkene substrate, being favored in the presence of high concentrations of small, electron-rich alkenes, the best ligands requiring the least energetically expensive rearrangement of ligands around the metal center. Both would be expected to have a smaller, yet still positive, enthalpy of activation as the R-L' bond is weakened and the ligands must

move closer together to accommodate the incoming substrate. The entropy of activation would be expected to be large and negative, accounting for most of the rotational and translational entropy of the substrate molecule being lost in the associative mechanism, and a significant proportion of it in the interchange mechanism.

The mechanisms in operation for some important classes of alkene metathesis catalyst have been studied; DFT studies have also provided useful insights into reaction mechanisms. In particular, the initiation mechanisms of ‘Grubbs-type’ and ‘Hoveyda-type’ complexes have been explored. In each case, insights into the effects of structure on initiation rate have been achieved.

2.2 Well-characterized systems

2.2.1 Complexes Bearing a Dissociating Phosphorus-Based Ligand

The initiation mechanisms of four classes of complex are considered. These classes are: 'Grubbs-type' where the alkylidene is a benzylidene and L' is a phosphine; indenylidene complexes where the alkylidene is 3-phenylindenylidene and L' is a phosphine; 'Cazin-type' where L' is a phosphite; and methylidene complexes (**Figure 4**). Grubbs-type and indenylidene complexes are known in both bis(phosphine) (such as **G1**, where L = L' = PCy_3) and NHC/phosphine forms (such as **G2**, where L = **SIMes** and L' = PCy_3), while only heteroleptic NHC/phosphite Cazin-type complexes have been disclosed in the peer-reviewed literature. Notably, methylidene complexes are key intermediates in *all* metathesis reactions involving terminal alkenes and so it is important to understand how these might re-enter the catalytic cycle.

[Please insert Figure04]

Figure 4. The classes of complex considered in this section.

2.2.1.1 Grubbs-type Complexes

Grubbs-type benzylidene complexes[15,16] are one of the most common categories of metathesis pre-catalyst that are employed in target synthesis, predominantly due to their wide availability and their long-term stability if relatively straightforward precautions are taken.

A watershed moment in the understanding of the initiation mechanism of these complexes was the study conducted by Grubbs and co-workers in 2001.[28,29] By this point, it was known that second generation systems were typically far more active in metathesis transformations that their first-generation counterparts.[16] In the initial communication, the authors set out to distinguish between the associative and dissociative mechanisms. The degenerate exchange between free and bound phosphine was explored using ^{31}P magnetization transfer experiments; the resonance for the free phosphine was selectively inverted, and the peak heights of free and bound phosphine were measured after different mixing times (**Scheme 4**). This data then allowed the *rate* of degenerate phosphine

exchange to be measured, which surprisingly revealed that the more active **G2** complex underwent initiation *ca.* 100-fold *slower* than **G1** (k_{obs} = 0.13 ± 0.01 s^{-1} *versus* 9.6 ± 0.2 s^{-1} at 80 °C in toluene. This rate constant was independent of the concentration of excess PCy_3 present in solution, as would be expected for a dissociative process. In addition, the activation parameters determined from variable temperature experiments for **G1** ($\Delta H^{\ddagger}$ = 23.6 ± 0.5 kcal mol^{-1}; $\Delta S^{\ddagger}$ = 12 ± 2 cal K^{-1} mol^{-1}) and **G2** ($\Delta H^{\ddagger}$ = 27 ± 2 kcal mol^{-1}; $\Delta S^{\ddagger}$ = 13 ± 6 cal K^{-1} mol^{-1}) are indicative of a dissociative mechanism due to the quite large and positive enthalpy and entropy values.

[Please insert Scheme04_color or Scheme04_bw]

Scheme 4. Magnetization transfer experiments to explore phosphine exchange rates in **G1** and **G2**.[29]

Subsequent experiments probed the reaction of these species with vinyl ether compounds, which irreversibly yield catalytically-inactive Fischer carbene complexes (the Fischer carbene is far more thermodynamically favorable than the benzylidene complex)[30,31] (**Scheme 5**).[32] The initiation rate constant for **1** was dependent on ethyl vinyl ether (EVE) concentration until *ca.* 10^3 equiv. were employed, while **2** reached saturation with only 5 equiv. present. In each case, initiation rates from reactions with EVE (under saturation conditions) were consistent with those obtained from ^{31}P NMR magnetization transfer experiments, showing that the rate-determining step was phosphine dissociation.

[Please insert Scheme05]

Scheme 5. Reaction of **G1** and **G2** with EVE to form catalytically-inactive Fischer carbene complexes.[29,32]

An expression for the dependence of $1/k_{obs}$ on the $[PCy_3]/[EVE]$ ratio could be derived (**Equation 1**) from application of the steady-state approximation to intermediate carbene complex **1** (**Equation 2**). Experiments performed at a number of $[PCy_3]/[EVE]$ ratios allowed the k_{-1}/k_2 ratio to be determined for **G1** and **G2** (**Figure 5**). The ratios determined were 1.5 x 10^4 and 1.25, respectively;

therefore, while **G1** initiates much faster than **G2**, it preferentially binds phosphine, while **G2** is approximately equally selective for phosphine and alkene.

$$1/k_{obs} = (k_{-1}/k_1k_2)\cdot([PCy_3]/[EVE]) + 1/k_1 \quad (\mathbf{1})$$

$$k_1[\text{pre-catalyst}] = k_{-1}[\mathbf{1}][PCy_3] + k_2[\mathbf{1}][EVE] \quad (\mathbf{2})$$

[Please insert Figure05]

Figure 5. $1/k_{obs}$ *versus* $[PCy_3]/[EVE]$ for **G1** (closed points, solid line) and **G2** (open points, dashed line).[29]

With this mechanism established, subsequent studies have assessed the effects of structure on reactivity. A subsequent full paper explored a wider range of complexes;[29] this included methylidene complexes, but these are discussed in a subsequent section. Initiation rates and activation parameters were determined for most complexes (**Table 1**). In each case, $\Delta H^{\ddagger}$ was large and positive (*ca.* 19 – 27 kcal mol^{-1}). While $\Delta S^{\ddagger}$ was always positive, in a couple of examples (complexes **9** and **11**) the large error in the measurement means that the possible range of values encompasses zero. The data show that there are clear links between structure and reactivity: larger, softer halides increase the initiation rate significantly, but also adversely affect k_{-1}/k_2. The use of PPh_3 in place of PCy_3 in **G2** leads to an increased initiation rate, and only a slight increase in k_{-1}/k_2, while PBn_3 only provokes a small increase in each. The use of unsaturated NHC **IMes** in place of **SIMes**,[33] which is known to lead to a less active catalyst,[24] resulted in a decrease in initiation rate.

Table 1. Initiation rate constants and activation parameters for a range of pre-catalysts.[29]

[Please insert Table01_header]

	k_1 (s^{-1})[a]	k_1 (rel. to G2)	k_{-1}/k_2 [b]	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (cal K^{-1} mol^{-1})	$\Delta G^{\ddagger}$ (kcal mol^{-1})
G1	9.6(2)	74	1.3×10^4	23.6(5)	12(2)	19.9

2	30(2)	231	8.2×10^4	23.1(3)	13(1)	19.1
3	(1660(220))	1.3×10^4	2.6×10^6	19.0(5)	10(2)	16.1
4	19.4(8)	149		24.3(6)	16(2)	19.6(1)
5	0.33(2)	2.5		24(1)	8(3)	22.0(2)
6	1.42(6)	11		24(1)	11(3)	21.1(1)
G2	0.13(1)	1.0	1.25	27(2)	13(6)	23.0(4)
7	0.52(2)	4.0		27(2)	15(6)	22.0(4)
8	29(3)	223	3.3×10^2	23(4)	12(11)	19.0(5)
9	(7.5(5))	58	(2.3)	21(3)	5(9)	19.6(3)
10	0.165	1.3	2.2	27(1)	13(4)	22.7(3)
11	0.03	0.23		25(4)	6(11)	24(1)

[a] At 80 °C in toluene; values in brackets are extrapolated from other temperature ranges. [b] At 50 °C in toluene, except for **9** at 25 °C.

As the dissociation of the phosphine ligand forms a key step, changing the electronic and steric properties of this ligand can tune the rate of its dissociation from the ruthenium center. The steric properties of phosphine ligands can be measured using the Tolman Cone Angle, which is the solid angle formed when the metal center is present at the vertex and the outermost atoms of the *P*-substituents at the perimeter of the cone.[34] The electronic properties of phosphines can be measured using the Tolman Electronic Parameter (TEP), which is based on the ability of a metal center bearing the ligand to donate electron density into the carbonyl π*-orbital.[34] Love *et al.* prepared a series of analogues of **G2** which bore a series of trialkyl and triarylphosphines and measured their initiation rate constants, typically using ^{31}P magnetization transfer experiments (**Table 2**). These were compared to values for metrics including the cone angle (for the trialkylphosphines) and Hammett Substituent Constants (for the *para*-substituted triarylphosphines). TEP values are included here, for reference. It can be seen that bulky, less electron-rich phosphines lead to faster initiation; a good correlation was observed between $\log(k_I(\mathrm{X}))$ and σ_P. Interestingly, there was no correlation between

the properties of the phosphines and the k_{-1}/k_2 ratio, which describes the selectivity for phosphine over alkene.

Table 2. Analogues of **G2** and their initiation rate constants.[35]

[Please insert Table02_header]

PR_3	**X**	**k_1 (s^{-1})[a]**		**k_1 (rel. to G2)**	**k_{-1}/k_2**	**Θ [b]**	**TEP (cm^{-1}) [b]**	**σ_P [c]**
PCy_3 (**G2**)	-	0.13	± 0.01	1.0	1.25	170 °	2056.4	
P^nBu_3	-	(8.1	± 0.1) x 10^{-4} [d]	0.006		132 °	2060.3	
$PPh_2(OMe)$	-	1.7	± 0.4	13		132 °	2072.0	
PAr_3	CF_3	48	± 2	369	7.3			0.53
	Cl	17.9	± 0.4	138	45		2072.8	0.23
	F	8.5	± 0.2	65	7.9		2071.3	0.06
	H	7.5	± 0.6	58	2.3	145 °	2068.9	0
	Me	4.1	± 0.2	32	2.8		2066.7	-0.17
	OMe	1.8	± 0.1	14	7.5		2066.1	-0.27

[a] At 80 °C in toluene. [b] Tolman Cone Angle and Electronic Parameter, see reference.[34] [c] Hammett Substituent Constant, see reference.[36] [d] Determined using stoichiometric experiments with EVE.

The effect of solvent choice on initiation rate has also been explored. Sanford *et al.* suggested a tentative link between dielectric constant and initiation rate for **G1** and **G2**, based on a small set of initiation rate data (**Table 3**, Entries 1 to 8). However, a later study by Percy and Nelson with a wider set of solvents established that no such link exists for **G2** (**Table 3**, Entries 9-17).[37] In addition, the initiation rate constants cover a relatively small range. Notably, initiation is slowest in hexafluorobenzene, which is interesting given reports of its accelerating effects on alkene metathesis reactions, even as part of a solvent mixture.[38,39]

Table 3. Solvent effects on the initiation rate of **G1** and **G2**.[29,37]

Entry	Solvent	Complex	ε [a]	k_I (s^{-1}) [b]	T
1 [29]	pentane	**G1**	1.84	0.013(1)	20 °C
2 [29]	toluene	**G1**	2.43	0.016(1)	20 °C
3 [29]	diethyl ether	**G1**	4.42	0.022(4)	20 °C
4 [29]	DCM	**G1**	9.02	0.021(1)	20 °C
5 [29]	THF	**G1**	7.47	0.032(4)	20 °C
6 [29]	Toluene-d_8	**G2**	2.43	4.6(4) x 10^{-4}	35 °C
7 [29]	DCM-d_2	**G2**	9.02	6.1(2) x 10^{-4}	35 °C
8 [29]	THF-d_8	**G2**	7.47	1.0(1) x 10^{-3}	35 °C
9 [37]	benzene-d_6	**G2**	2.27	1.0 x 10^{-4}	25 °C
10 [37]	chloroform-*d*	**G2**	4.89	4.5 x 10^{-5}	25 °C
11 [37]	DCM-d_2	**G2**	9.02	1.4 x 10^{-4}	25 °C
12 [37]	1,2-difluorobenzene [c]	**G2**	2.26	1.4 x 10^{-4}	25 °C
13 [37]	dimethyl carbonate [c]	**G2**	3.17	1.5 x 10^{-4}	25 °C
14 [37]	hexafluorobenzene [c]	**G2**	2.05	3.3 x 10^{-5}	25 °C
15 [37]	MTBE [c]	**G2**		1.3 x 10^{-4}	25 °C
16 [37]	toluene-d_8	**G2**	2.43	9.2 x 10^{-5}	25 °C
17 [37]	trifluorotoluene [c]	**G2**	9.40	1.3 x 10^{-4}	25 °C

[a] Dielectric constant, from reference.[40] [b] Determined by UV/visible spectroscopy for **G1** (0.77 mmol L^{-1} **G1** and 0.58 mol L^{-1} EVE) and NMR spectroscopy for **G2** (5 - 17 mmol L^{-1} **G2**, depending on solubility, and 0.5 mol L^{-1} EVE). [c] 10% w/w chloroform-*d* was present for the deuterium lock.

Various attempts were made to correlate single parameters to initiation rate data, without success. The only approach that yielded a good correlation between properties and initiation rate was a multiparameter approach, previously used by Adjiman *et al.*.[41] The initiation rate could then be linked to five solvent properties (α, hydrogen bonding acidity; β, hydrogen bonding basicity; π*, a

measure of van der Waals interactions; δ, polarizability correction factor; δ_H, Hildebrand solubility parameter) (**Equation 3**). This correlation may have some predictive value, although the quite narrow spread of initiation rate constants suggests that initiation rates should be sufficient to enable metathesis in most solvents that are tolerated by the catalyst.

$$\log_{10}(k_1) = A\alpha + B\beta + C\pi^* + D\delta + E(\delta_H)^2 + F \quad (3)$$

where A = -0.924(66), B = 0.990(73), C = 1.88(04), D = -0.170(028), E = -1.26(12), F = -4.59(05)

2.2.1.2 Indenylidene Complexes

Indenylidene complexes have been employed by a number of researchers.[21] A key intermediate complex in the synthesis of almost all indenylidene complexes is complex **M_{10}**, which is prepared in one step from the reaction of $[RuCl_2(PPh_3)_3]$ with 1,1-diphenylprop-2-yn-1-ol under acidic conditions (**Scheme 6**).[42] While **M_{10}** is itself not active for alkene metathesis, subsequent ligand exchange with phosphines, NHCs or other ligands can furnish a range of metathesis pre-catalysts.

[Please insert Scheme06]

Scheme 6. Synthesis of complex **M_{10}**.[42]

Recently, Urbina Blanco *et al.* investigated the initiation mechanism of a series of these species.[43] 1D [^{31}P, ^{31}P] EXSY NMR experiments were conducted to probe the rate of degenerate phosphine exchange; control experiments established that this approach gave results consistent with those reported by Grubbs. Data was collected for a number of indenylidene complexes, including **M_{10}** (**Table 4**). Several interesting results arose from these data. Complex **M_{10}**, while metathesis inactive, exhibited the highest initiation rate (i.e. rate of phosphine dissociation) of the complexes studied. Complex **M_2**, a close analogue of **G2**, initiated so slowly that a rate constant could not be measured for this exchange. Thirdly, complex **M_{20}** clearly exhibited a *negative* entropy of activation, which is inconsistent with a dissociative mechanism for phosphine exchange.

Table 4. Initiation rate data and activation parameters for **G2** and selected indenylidene complexes.[43]

Complex	k_1 (s^{-1}) [a]	k_1 (rel. to G2)	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (cal K^{-1} mol^{-1})	$\Delta G^{\ddagger}$ (kcal mol^{-1})
G2	0.12	1.0	27(4)	12(10)	23(5)
$\mathbf{M_1}$	1.72	14	23(1)	8(4)	21(2)
$\mathbf{M_{10}}$	236 [b]	1967	26(5)	26(18)	18(8)
$\mathbf{M_2}$	<0.01	<0.08	nd [c]	nd [c]	nd [c]
$\mathbf{M_{20}}$	0.19	1.6	17(3)	-13(8)	21(4)
$\mathbf{M_{23}}$	4.29	36	27(1)	21(4)	21(2)

[a] Determined at 80 °C in toluene-d_8 with 40 mmol L^{-1} complex and 1.5 equiv. phosphine. [b] Extrapolated from experiments at lower temperature. [c] Not determined.

Of these results, the latter is the most intriguing, especially given that all benzylidene complexes and all other indenylidene complexes initiate *via* a dissociative mechanism. Further experiments showed that the initiation rate of $\mathbf{M_{20}}$ (and analogues bearing tri(*para*-trifluoromethylphenyl)phosphine and tri(*para*-methylphenyl)phosphine ligands) was dependent on the phosphine concentration. Reactions with butyl vinyl ether (BVE) indicated a dependence of k_{obs} on [BVE] for $\mathbf{M_2}$ but not $\mathbf{M_{23}}$; again, a negative entropy of activation was suggestive of an associative or interchange mechanism ($\Delta S^{\ddagger}$ = -12(9) cal K^{-1} mol^{-1}). This is to date the only phosphine-bearing complex to initiate *via* a non-dissociative pathway. Supporting DFT calculations indicated that the energetics of the dissociative and interchange pathways were very similar for most complexes; with the exception of $\mathbf{M_{23}}$, $\Delta\Delta G^{\ddagger}$ is < 5 kcal mol^{-1}.

While the behavior of $\mathbf{M_{20}}$ is interesting, it appears to be the exception rather than the rule, with the use of a bulkier NHC (SIPr) or phosphine (PCy_3) shifting the balance back towards the dissociative mechanism. The indenylidene ligand is proposed to play a key role; while the 14e species derived from dissociation of tricyclohexylphosphane from **G2** can benefit from an agostic interaction

with a closely located aromatic C-H bond (Ru-H distance of 2.81 Å), that derived from $\mathbf{M_{20}}$ cannot (**Figure 6**).

[Please insert Figure06a_color and Figure06b_color, or Figure06a_bw and Figure06b_bw]

Figure 6. (a) Stabilizing Ru-H interaction for **G2**-derived **1b** and (b) its absence in the $\mathbf{M_{20}}$-derived complex **12**; most H atoms are excluded for clarity.

2.2.1.3 Cazin-type Complexes

In 2010, Cazin introduced a new family of ruthenium-indenylidene metathesis pre-catalysts which bore phosphite ligands in place of phosphine ligands;[44] this was followed in 2011 by the disclosure of the corresponding benzylidene variants (from the reaction of **G2**-derived bis(pyridine) complex **G2py**)[45] and subsequent full papers in 2012 and 2013 where a range of indenylidene species were reported.[46,47]

The synthesis of the indenylidene complexes was accomplished by addition of phosphite to the corresponding pyridine complexes; however, in some cases a mixture of *cis*-dichloride and *trans*-dichloride complexes was obtained (**Scheme 7**).

[Please insert Scheme07]

Scheme 7. Synthesis of mixed NHC/phosphite indenylidene complexes.[44,46,47]

SIMes-bearing complexes are therefore most often isolated as the *cis*-dichloride isomer, while complexes bearing the bulkier SIPr ligand are typically isolated as the *trans*-dichloride isomer. The activation parameters for *trans-cis* isomerization have been determined ($\Delta H^{\ddagger}$ = 22.6 kcal mol^{-1}; $\Delta S^{\ddagger}$ = -4.2 cal K^{-1} mol^{-1});~~,~~ ~~which~~ the small entropy term suggests that phosphite dissociation is not involved in the *trans-cis* isomerization~~;~~. ~~I~~In addition, the presence of excess phosphite does not affect the isomerization rate. The ~~*geometry of these cis-*~~complexes ~~often necessitates a~~must undergo *cis-trans* isomerization before phosphite dissociation, which adds the thermodynamic advantage of the more stable isomer to the energetic barrier for initiation and renders these complexes poorly active at low

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temperatures. ~~While the barrier for *cis*-*trans* isomerization has not been determined experimentally, given the thermodynamic preference for the *cis* isomer and the activation parameters for *trans*-*cis* isomerization, the barrier can be estimated at ≥ *ca*. 26 kcal mol^{-1}, followed by a barrier for phosphite dissociation.~~ At elevated temperatures, these complexes are highly active, especially for challenging metathesis transformations that benefit from high temperatures.

Commented [NW1]: Not completely clear to me what the key point is here. If the isomerisation is rate limiting, this looks a sensible estimate. If phosphite dissociation is rate limiting, then it is only the thermodynamic preference for cis that is added to that barrier.

2.2.1.4 Methylidene Complexes

While methylidene complexes are intermediates in metathesis reactions, and rarely used as pre-catalysts, their involvement in many metathesis reactions means that their initiation behavior deserves discussion. It is worth reiterating explicitly at this point that pre-catalysts that differ only in the nature of the carbene and/or dissociating ligand L' will form the *same active species* during the metathesis reaction. Where the metathesis of terminal alkenes is considered, this active species will be a ruthenium methylidene complex.

Grubbs attempted to study the initiation of methylidene complexes **14a** and **14b** bearing tricyclohexylphosphane ligands (**Figure 7**);[29] these are formed in metathesis reactions catalyzed by **G1** and **G2**, respectively, and were prepared by reaction of **G1** or **G2** with ethene. Fogg later published an improved synthesis of **14b**, based on ligand exchange in **G1**-derived **14a**, as the **G2**/ethene route is tedious and low-yielding.[48]

[Please insert Figure07]

Figure 7. Methylidene complexes **14a** and **14b**, derived from pre-catalysts **G1** and **G2**, respectively.

It was discovered that the initiation rate could not be measured; at the temperatures required to effect initiation, the complexes decomposed in solution.[29] Later studies probed the decomposition of this complex in detail.[49,50] It follows that capture of these methylidenes by phosphine removes active catalyst from the cycle and necessitates the recruitment of more 14e species *via* pre-catalyst initiation.

2.2.2 Complexes Bearing a Chelating Alkoxystyrene Ligand

2.2.2.1 Initiation of Hoveyda-Type Complexes

The second of the two most popular classes of metathesis pre-catalysts is the so-called 'Hoveyda-type' complexes that bear a chelating alkoxystyrene ligand, which were discovered serendipitously during metathesis reactions of 2-alkoxystyrene compounds.[17,18]

Much effort has been expended recently to understand how Hoveyda-type pre-catalysts initiate. Originally, it was simply assumed that the initiation mechanism was dissociative, and data to support this was published by Love *et al.*, in which no dependence of the initiation rate of **GH2** on substrate concentration was observed.[35] No entropy change was required to reach the transition state ($\Delta H^{\ddagger}$ = 19.9(5) kcal mol^{-1} and $\Delta S^{\ddagger}$ = 1(2) cal K^{-1} mol^{-1} for the initiation of **GH2** with EVE in toluene). However, activation parameters collected during a later study, also by the Grubbs group, suggested a non-dissociative mechanism, due to the *negative* entropy of activation ($\Delta H^{\ddagger}$ = 15.2(8) kcal mol^{-1} and $\Delta S^{\ddagger}$ = -19(3) cal K^{-1} mol^{-1} for the initiation of **GH2** with butyl vinyl ether (BVE) in benzene or toluene).[51] No detailed mechanistic analysis of the latter result was presented, but clearly the entropy of activation is consistent with either an associative or an interchange mechanism.

Plenio and co-workers published a detailed exploration of the mechanism of initiation of **GH2** and the analogous Grela catalyst **Gr2** (which bears an electron-withdrawing nitro-group which accelerates initiation);[19,52] most kinetic data were obtained using UV/visible spectroscopy. It was found that the rate of initiation of these complexes in the presence of ethyl vinyl ether (EVE) or diethyl diallylmalonate (DEDAM) depended linearly on the concentration of substrate (see **Figure 8**). The rate of initiation (k_{init}) was determined from a plot of k_{obs} versus substrate concentration, where the substrate was always present in excess (see **Equation 4**). Due to the sterically hindered nature of the metal center, an associative mechanism was ruled out, and an interchange mechanism was proposed.

$$d[Ru]/dt = -k_{init}[Ru][substrate] = -k_{obs}[Ru]; \text{ where } k_{obs} = k_{init}[substrate] \quad (4)$$

[Please insert Figure08]

Figure 8. Initiation rate, with EVE, of **GH2** (k_{init} = 0.0691(2) L mol^{-1} s^{-1}; black line; *c.f.* 0.0238(32) with DEDAM) and **Gr2** (k_{init} = 0.192(3) L mol^{-1} s^{-1}; grey line; *c.f.* 0.0764(20) with DEDAM) in toluene at 40 °C, determined by Plenio *et al.*.[52]

Following this, Percy and Hillier published a combined theoretical and experimental study of the initiation of **GH2**. UV/visible kinetic studies (in DCM) were conducted at a range of temperatures to reveal activation parameters for the initiation step with EVE ($\Delta H^{\ddagger}$ = 14.1(1.2) kcal mol^{-1}, $\Delta S^{\ddagger}$ = -18.5(5.0) cal K^{-1} mol^{-1}, $\Delta G^{\ddagger}$ (298 K) = 19.6(2.0) kcal mol^{-1}). These activation parameters are consistent with either an associative or an interchange mechanism. DFT calculations (using the M06-L functional) were used to investigate which of the associative, dissociative and interchange mechanisms were favored with a model alkene (ethene). The lowest energy pathway was found to be the interchange mechanism, with the associative and dissociative pathways presenting barriers that were higher by *ca*. 3 – 6 kcal mol^{-1}. It should be noted, however, that the modelling of intermolecular reactions by DFT calculations is difficult due to the issues involved in treating entropy. The approach of Percy and Hillier, where a 'pre-complex' is considered, will underestimate the entropic penalty of such processes (i.e. the interchange and associative pathways), and therefore *underestimate* the free energy barrier. The alternative approach, favored by researchers such as Solans-Monfort, will *overestimate* the free energy barrier for intermolecular processes, due to an overestimate of the magnitude of the (negative) entropy of activation.[53] The issues involved in studying these processes by DFT methods are discussed in more detail in a subsequent section.

A subsequent study by Plenio considered the initiation of an extensive range of complexes, a number of which were novel.[54] The substitution pattern of the aryl ring was varied at the 4- and 5-positions, and methyl and *iso*propyl ethers were both considered (**Figure 9**).

[Please insert Figure09]

Figure 9. Complexes studied by Plenio *et al.*.[54]

Cyclic voltammetry experiments were used to quantify the oxidation potentials of these species (Ru^{II} to Ru^{III}), showing that the substitution pattern of the alkoxystyrene ligand had an effect on the electron density at the metal center. This effect was communicated *via* the ruthenium carbene moiety, as shown by a good Hammett correlation when the carbene moiety was connected to the *ipso* carbon of the aromatic ring, and a poor correlation when the alkoxy-substitutent was connected to the *ipso* position. Plots of k_{obs} *versus* [substrate] exhibited curvature (e.g. **Figure 10**), which was attributed to a contribution from a (substrate-independent) dissociative pathway and a contribution from a (substrate and substrate concentration dependent) interchange pathway (**Equation 5** and **Scheme 8**).

$$d[Ru]/dt = k_{obs}[Ru]$$

$$\text{where } k_{obs} = ((K_D \cdot k_{assoc}) \cdot [\text{substrate}]/(1 + k_{assoc}/k_{-D}) \cdot [\text{substrate}]) + k_I \cdot [\text{substrate}] \quad (\mathbf{5})$$

[Please insert Figure10]

Figure 10. Rate constants k_{obs} for the reaction of **GH2** (closed points) and **Gr2** (open points) with (a) diethyl diallylmalonate and (b) styrene in toluene at 303 K.[54]

[Please insert Scheme08]

Scheme 8. Plenio's mechanistic scheme for the initiation of Hoveyda-type complexes (L = SIMes).[54]

Diverse behavior was exhibited by the set of pre-catalysts considered, and with different substrates. Initiation rates for pre-catalysts with electron-withdrawing substituents were insensitive to changes in substrate, while substrate structure was found to alter the relative contributions to the initiation rate from the dissociative and interchange pathways (**Table 5**). While many of the error bars are rather large, several trends are evident: faster initiators are less sensitive to substrate structure and show more interchange character (entries 13 and 14 are essentially the same). Electron-withdrawing groups tend to increase the initiation rate. It would be expected that k_D should be substrate independent, but this appears not to be the case for complex **18** (compare entries 5 and 6).

Table 5. Influence of substrate and pre-catalyst structure on initiation rate of a series of Hoveyda-type complexes (NB: entries 3 and 4 are **GH2**, while 10 is **Gr2**).[54]

Entry	Substrate	R	R^1	R^2	$k_D \cdot 10^3$ (s^{-1})	$k_{assoc} \cdot K_D \cdot 10^3$ (L mol^{-1} s^{-1})	$k_I \cdot 10^3$ (L mol^{-1} s^{-1})
1	BVE	^{i}Pr	H	NEt_2	17.5(1.3)	109(18)	18.0(7)
2	BVE	^{i}Pr	H	O^{i}Pr	45(4)	107(18)	25.1(1.4)
3	BVE	^{i}Pr	H	H	22(2)	43(9)	24.5(8)
4	Hex-1-ene	^{i}Pr	H	H	25(8)	105(76)	21(4)
5	BVE	^{i}Pr	H	NO_2	59(19)	84(51)	63(6)
6	Hex-1-ene	^{i}Pr	H	NO_2	110(27)	210(100)	43(9)
7	BVE	^{i}Pr	NEt_2	H	33(3)	113(22)	39.8(1.5)
8	BVE	^{i}Pr	O^{i}Pr	H	54(8)	155(48)	55.5(3.5)
9	BVE	^{i}Pr	F	H	24(3)	109(34)	49.6(2.0)
10	BVE	^{i}Pr	NO_2	H	25(9)	102(75)	56(5)
11	BVE	Me	H	H	21(18)	61(10)	151(9)
12	Hex-1-ene	Me	H	H	- [a]	- [a]	102(4)
13	BVE	Me	NO_2	H	- [a]	- [a]	402(4)
14	Hex-1-ene	Me	NO_2	H	- [a]	- [a]	431(69)

[a] Fitted a linear expression ($k_I \cdot$ [substrate]).

Further studies have been predominantly theoretical in nature. Solans-Monfort has compared the initiation processes of some Hoveyda-type complexes, considering not only the initial step but the subsequent steps required to generate the new alkylidene (i.e. that bearing the substrate molecule) using the B3LYP-D density functional.[53] Interestingly, the dissociation of the alkoxystyrene ligand to yield a 14e species presented a significant (*ca.* 10 kcal mol^{-1}) barrier. The energy difference between dissociative and interchange mechanisms was small, such that the mechanism in operation could not

be firmly established. Percy and Hillier have also carried out further DFT studies with some prototypical substrates including EVE, ethene, propene, and 1-hexene.[31] It was also shown through experiment that while exposure of **GH2** to EVE leads to complete conversion to the Fischer carbene, reaction with ethene is far slower, due to the much less favorable methylidene product (*versus* the Fischer carbene that results from reaction with EVE).[32] The barrier to the metallacyclobutanation event was found to be similar to that for the initial interchange or dissociation step; both are highly dependent on the substrate structure.

Further studies by Percy (including one in collaboration with Mauduit) have provided initiation rates (k_I) for a number of commercially-available Hoveyda-type complexes that are used in synthetic projects (**Table 6**). [55-57] In each case, a plot of k_{obs} *versus* [EVE] yielded a linear plot, from which k_I could be determined; no curvature was exhibited; it should be noted that the concentrations used were in the typical range used for synthetic metathesis experiments, rather than the high (up to 2 mol L^{-1}) concentrations that Plenio used, and so are more likely to exhibit 'ideal' behavior. The initiation rate changes with the electronic nature of the substituent, as is known from Plenio's study. In addition, the replacement of SIMes with SIPr significantly decreases the initiation rate. This trend is opposite to that observed for indenylidene complexes, where SIPr-bearing complexes initiate more rapidly;[43] this can be explained by the different mechanisms that operate in each case (interchange *versus* dissociative), where a bulkier NHC would hinder the approach of the substrate molecule to the ruthenium center. SIPr-bearing complexes are often more active for the synthesis of relatively unhindered alkenes by metathesis,[24] despite their slower initiation rate.

Table 6. Initiation rates for Hoveyda-type complexes (at 298 K in DCM), as determined by UV/visible studies with EVE as substrate (25 – 200 mmol L^{-1}).[55-57]

Complex	**L = SIMes**	k_I **(L mol^{-1} s^{-1})**	**L = SIPr**	k_I **(L mol^{-1} s^{-1})**
[Please insert Table06_l1]	**GH2** [55]	0.0264	**25** [56]	0.00296
[Please insert	**Gr2** [56]	0.317	**26** [56]	0.0368

Table06_l2]				
[Please insert Table06_l3]	**27** [57]	0.132		
[Please insert Table06_l4]	**28** [56]	3.40	**29** [56]	0.668
[Please insert Table06_l5]			**30** [56]	0.571

Solvent effects on the initiation rate of **GH2** have also been probed by Percy and Nelson.[37] As was found for **G2**, the identity of the solvent did not have a serious impact on the initiation rate of the pre-catalyst (**Table 7**). Initiation rates spanned a range from 0.0231 – 0.0592 L mol^{-1} s^{-1} (at 25 °C), with rates higher in aromatic solvents than in chlorinated solvents. The initiation rate was shown to be highest in methyl *tert*-butyl ether.

Table 7. Solvent effects on the initiation rate of **GH2**.[37]

Entry	**Solvent**	**ε** [a]	k_I **(L mol^{-1} s^{-1})** [b]	k_I **(rel. to DCM)**	**T**
1 [37]	benzene	2.27	0.0460	1.74	25 °C
2 [37]	chloroform	4.89	0.0231	0.88	25 °C
3 [37]	DCM	9.02	0.0264	1.00	25 °C
4 [37]	1,2-difluorobenzene	2.26	0.0390	1.48	25 °C
5 [37]	dimethyl carbonate	3.17	0.0411	1.56	25 °C
6 [37]	hexafluorobenzene	2.05	0.0515	1.95	25 °C
7 [37]	MTBE		0.0592	2.24	25 °C
8 [37]	toluene	2.43	0.0509	1.93	25 °C
9 [37]	trifluorotoluene	9.40	0.0446	1.69	25 °C

[a] Dielectric constant, from reference.[40] [b] Determined by UV/visible spectroscopy (0.1 mmol L^{-1} **GH2** and 25 - 200 mol L^{-1} EVE).

Again, attempts were made to correlate initiation rates to physical properties; while a weak correlation with $E_T(30)$ was obtained (**Figure 11**), the best correlation was observed with a multiparameter approach (**Equation 6**). Comparison with the data for **G2** suggests that differences in behavior result from different dependencies on β and π*; **G2** depends strongly on both of these factors, while for **GH2** the error bars encompass zero (or close to it).

[Please insert Figure11]

Figure 11. Initiation rate of **GH2** *versus* solvent $E_T(30)$.[37]

$$\log_{10}(k_I) = A\alpha + B\beta + C\pi^* + D\delta + E(\delta_H)^2 + F \qquad (\mathbf{6})$$

where A = -0.793(145), B = 0.106(161), C = 0.0993(899), D = 0.0487(614), E = -1.13(26), F = -1.04(11)

2.2.2.2 Is Initiation Reversible? The 'Boomerang' Mechanism

At around the same time that the initiation mechanism of Hoveyda-type complexes was probed in detail, doubt was cast on another aspect of their behavior. When these species were first reported, they were billed as 'recyclable' metathesis catalysts;[17,18] the authors of the original manuscript successfully recovered material that they claimed to be regenerated pre-catalyst, formed *via* re-capture of the alkoxystyrene ligand. This has been termed the 'boomerang' or 'release-return' mechanism (**Scheme 9**).

[Please insert Scheme09]

Scheme 9. The 'boomerang' or 'release-return' mechanism for Hoveyda-type complexes.

Blechert has shown that added alkoxystyrene reduces the rate of metathesis,[58] while Grela has provided experimental evidence to support the uptake of alkoxystyrene by the active species.[22] In the latter study, the reaction of substrate **31** catalyzed by 5 mol% **GH2**-d_7 or **Gr2**-d_7 (where the *iso*-propyl

moiety is perdeuterated) in the presence of 5 mol% of the appropriate d_0-styrene led to incorporation of the unlabeled styrene into the pre-catalyst that was recovered after complete conversion of the substrate (59%D in 85% recovered **GH2** after 60 min; 63%D in 67% recovered **Gr2** after 15 min) (**Scheme 10**).

[Please insert Scheme10]

Scheme 10. Grela's experiments to probe styrene crossover.[22]

In 2010, Plenio published a study of the behavior of two model catalysts (**22** and **34**) (**Figure 12**); **22** bore a fluorine substituent, and **34** was functionalized with a fluorescent tag. Reactions with complex **34** resulted in the appearance of fluorescence at a rate that was dependent on the identity and concentration of the substrate; the fluorescence did not decrease after the metathesis reaction was complete, suggesting that the styrene unit had not returned to the metal center. Similar experiments with fluorine-labelled complex **22** yielded the same result; the signals for free and bound styrene appeared at different chemical shifts. The authors proposed that the recovered pre-catalyst was simply a consequence of incomplete initiation. Solans-Monfort reached a similar conclusion through DFT studies, where the barriers to pre-catalyst regeneration and reaction with the product alkene were found to be similar.[59] In the presence of a large excess of product alkene (i.e. under catalytic conditions), pre-catalyst regeneration is unlikely to be competitive.

[Please insert Figure12]

Figure 12. GH2 analogues bearing reporter groups.[60]

However, a more recent study by Fogg and co-workers has provided convincing evidence that the pre-catalyst *does* re-form.[61] Even very small quantities of added alkoxystyrene were found to compete effectively with substrates, while ethene was found to increase the rate of catalyst decomposition and decrease the rate of uptake of alkoxystyrene. Crossover experiments were conducted with added ^{13}C-labelled 2-*iso*propoxystyrene (at the same loading as the pre-catalyst),

which cannot undergo label scrambling unlike deuterated compounds for which H/D exchange can be ruthenium-catalyzed. NMR analyses of metathesis reaction mixtures revealed gradual incorporation of the ^{13}C-labelled styrene into the reservoir of unreacted **GH2**, reaching approximately equilibrium populations (43-47%, *versus* <10% in the absence of substrate). The authors suggested that the results of Plenio are relevant only to **GH2** analogues bearing electron-withdrawing substituents, which initiate more rapidly and would be expected to undergo cross-metathesis with the active species more slowly; they also noted that ethene resulting from metathesis would accumulate in the vessels used for the studies, potentially inhibiting the reaction with the alkoxystyrene ligand (see Section 4.1.1.2).

2.3 Summary

In this section, the initiation mechanisms of some common metathesis pre-catalysts have been discussed. Benzylidene, indenylidene and Hoveyda-type complexes are the most widely used classes of metathesis pre-catalyst, and therefore the understanding of their properties is highly important.

Phosphine- and phosphite-bearing complexes almost always initiate *via* a dissociative mechanism in which the release of a ligand precedes the binding of the substrate. Only one exception is known, as discussed above. Less electron-rich phosphine ligands have been shown to increase the rate of pre-catalyst initiation, as do bulkier NHC ligands (such as SIPr). A significant drawback to the use of these types of pre-catalyst is the potential for the phosphine ligand to capture the methylidene intermediate, yielding a species which will decompose more readily than enter the catalytic cycle.

In contrast, Hoveyda-type complexes initiate *via* a mechanism with a varying degree of interchange character; these catalysts therefore initiate at a rate that is acutely dependent on the nature of the substrate and its concentration, with small and electron-rich substrates allowing for faster initiation. Electron-withdrawing substituents on the chelating alkoxystyrene ligand also accelerate pre-catalyst initiation. The exact role of the alkoxystyrene ligand after initiation is still a subject of investigation, although there is evidence that this returns to the metal center during the course of the reaction.

3. The Effects of Substrate Structure on Reactivity

As alkene metathesis has become a staple technique in organic synthesis, it has occurred within a very large number of reaction systems bearing a diverse range of functional groups, particularly in total synthesis,[62-64] forming rings of many different sizes. This section comprises a summary of some functional groups and structural features that can influence the outcome of metathesis reactions, with selected examples from the literature. It should be noted that in some cases the effect that structure has on reactivity is dependent on the structure of the metathesis catalyst also; for example, first generation systems are more reluctant to react with tri- and tetra-substituted alkenes, and generally lead to lower *E*/*Z* ratios.[22,24] As the volume of synthetic chemistry that has been performed is far larger than that of the corresponding mechanistic work, the synthetic literature is the primary source of how structure and reactivity are related. As synthetic studies are usually focused on obtaining the highest possible yield of the pure compound of interest, information is generally reported as a purified yield after work-up, and typically only at one time point. This limitation should be kept in mind by the reader.

3.1 Functional Group Effects

3.1.1 Alkene Substitution Pattern

3.1.1.1 Alkenes *versus* Allenes and Alkynes

Alkene metathesis catalysts are also capable of undergoing reaction with allene and alkyne functionality, which can lead to the synthesis of polyene compounds. For example, Diver has explored the use of alkene/alkyne cross metathesis, which leads to 2-substituted 1,3-dienes (**Scheme 11**).[65] Prunet has recently disclosed an elegant metathesis cascade sequence towards the synthesis of Taxol, involving two alkenes and one alkyne functional group (**Scheme 12**);[66] the desired product was accompanied by small quantities of a side product that resulted from metathesis of the two alkenes.

[Please insert Scheme11]

Scheme 11. Cross ene-yne metathesis.[65]

[Please insert Scheme12]

Scheme 12. Metathesis cascade leading to the polycyclic core of Taxol.[66]

This breadth of reactivity necessitates understanding and control of selectivity. To this end, Sohn and Ihee have conducted fluorescence resonance energy transfer (FRET) experiments with a range of catalysts, with specially designed alkenes, allenes and alkynes that are tethered to a dye (**Figure 12**). When the ruthenium complex co-ordinates the alkene/allene/alkyne, the fluorescence is quenched. Catalysts studied included **Mo1**, **G1**, **G2**, **GH1** and **GH2**; rate constants and thermodynamic parameters were obtained in each case (**Table 8**). These experiments showed that catalyst systems react differently with different substrates. Rate differences were typically not significant, with the exception of the reactions of **G1** with allene and **GH2** with alkyne. **Mo1** was found to be poorly selective, with the reaction with alkyne being slightly (three-fold) faster and (four-fold) more thermodynamically favorable than reaction with alkene or allene. In terms of equilibrium constant, **G1** reacted more favorably with allene than alkene, which was preferred over alkyne; *K* covered a 300-fold range. **GH1** showed the same order of thermodynamic stability, with a much smaller range of *K* (*ca.* ten-fold). **G2** reacted most favorably with alkyne than allene, and allene than alkene (100-fold range of *K*); here, the trends in k_{rel} and *K* diverged (in terms of magnitude). **GH2** showed the same order of reactivity, but the equilibrium constant was 10,000-fold larger with alkyne than alkene. Understanding this order of reactivity can be used to plan the order of events at the metal during target synthesis projects though it must be pointed out that all these motifs are terminal and simpler than those found in natural product precursors.

[Please insert Figure13]

Figure 13. Use of FRET studies to probe the binding of metathesis catalysts to functional groups.[67,68]

Table 8. Rates of reaction of dye-functionalized alkenes, alkynes and allenes with various metathesis (pre-)catalysts.[67,68]

	Alkene			Alkyne			Allene		
	$k \cdot 10^{-2}$ (L mol^{-1} s^{-1})	k_{rel}	K_{rel}	$k \cdot 10^{-2}$ (L mol^{-1} s^{-1})	k_{rel}	K_{rel}	$k \cdot 10^{-2}$ (L mol^{-1} s^{-1})	k_{rel}	K_{rel}
Mo1 [a]	6.54(2.51)	1	1	18.1(6.7)	2.77	3.80	6.07(87)	0.93	0.90
G1 [b]	37.1(1.3)	1	1	2.60(9)	0.07	0.15	525(53)	14.2	34.4
G2 [b]	1.19(33)	1	1	2.98(34)	2.50	93.8	1.63(27)	1.37	9.70
GH1 [b]	0.434(529)	1	1	0.255(262)	0.59	0.72	1.19(29)	2.60	15.2
GH2 [b]	1.10(53)	1	1	8.63(42)	7.85	9670	4.98(87)	4.53	5.05

[a] Reaction with functionalized coumarin dyes. [b] Reaction with functionalized dapoxyl dyes.

3.1.1.2 Substitution at the Alkene Termini

The RCM rate depends critically on the alkene substitution pattern during two steps in the reaction; the influence this exerts will depend considerably on the pre-catalyst employed. The catalyst reacts with one alkene terminus first, to yield the propagating carbene. This intermediate carbene complex then reacts with the alkene at the other end of the chain, or with a second alkene substrate, to yield the product.

Ulman and Grubbs have measured the rates of reaction of **G1** with a series of alkenes (**Table 9**). Methylation at the allylic position led to a reduction in reaction rate of *ca.* two orders of magnitude, while methylation at the homoallylic position made little difference to the reaction rate. The reaction with *neo*-hexene did not occur at all, nor did the reaction with 2-methylpent-1-ene, showing that steric bulk in the wrong place can have a dramatic effect on the reaction rate. While this study explores the reactivity of a relatively old metathesis pre-catalyst that has largely been superseded by second generation alternatives, it still serves to highlight that reactions with more substituted alkene termini will proceed more slowly; in functionalized molecules, the ruthenium carbene is therefore most likely to react with the less substituted terminus first.

Table 9. Rates of reaction of **G1** with various alkenes (31 equiv.).[69]

Substrate	Temperature	k (L mol^{-1} sec^{-1})
[Please insert Table09_l1]	7 °C	1.3(4) x 10^{-3}
[Please insert Table09_l2]	7 °C	2.15(1) x 10^{-3}
[Please insert Table09_l3+4]	7 °C	1.48(4) x 10^{-3}
[Please insert Table09_l3+4]	35 °C	*ca.* 10^{-2}
[Please insert Table09_l5]	7 °C	1.02(6) x 10^{-3}
[Please insert Table09_l6]	35 °C	2.5(2) x 10^{-4}
[Please insert Table09_l7]	35 °C	- [a]
[Please insert Table09_l8]	35 °C	- [b]
[Please insert Table09_l9]	35 °C	- [b]
[Please insert Table09_l10]	35 °C	3.0(4) x 10^{-4}
[Please insert Table09_l11]	35 °C	7.6(8) x 10^{-4}

[a] Too slow to quantify; minor degree of reaction in 4 d. [b] No reaction.

For reactions with very hindered termini, Hoye has developed the 'relay ring-closing metathesis' (RRCM) approach, where a specially designed triene is used as the precursor (e.g.

Scheme 13).[70] The initial RCM step yields an intermediate carbene in which the ruthenium catalyst has been delivered to a hindered site by virtue of the intramolecular nature of the reaction; this carbene then performs the desired RCM reaction. The 'throw-away' fragment is typically a volatile unit, such as dihydrofuran or cyclopentene, although diethyl diallylmalonate-type units have also been utilized.[71]

[Please insert Scheme13_color or Scheme13_bw]

Scheme 13. An example of the application of RRCM.[70]

Grubbs and co-workers have conveniently classified various alkene termini according to their metathesis activity, taking into account the dependence of such classifications on the catalyst system employed.[72] The four classifications for alkenes are:

- Type 1: Rapidly homodimerises, but reversibly. Alkenes that are typically sterically unhindered and/or electron rich, rendering them the most reactive. Homodimers form during metathesis reactions, but the homodimers will also undergo metathesis.
- Type 2: Homodimerises slowly; homodimers are only sparingly consumable. Alkenes that are less reactive than Type I alkenes, due to steric and/or electronic effects. Homodimers do not form as quickly, and those that form undergo metathesis slowly.
- Type 3: Alkene does not homodimerise. Alkenes that are less reactive again, and will not homodimerise in metathesis reactions.
- Type 4: Alkene is inert to metathesis but will not deactivate the catalyst.

Using these classifications, the outcome of a cross-metathesis reaction can be anticipated by referring to **Table 10**. Four outcomes can result: no CM, where no metathesis reaction occurs; non-selective CM where a mixture of homodimers and the desired cross-metathesis product will be obtained; statistical CM where the yield of the desired cross-metathesis product will depend on the relative concentrations of each alkene that were added at the start of the reaction; and selective CM where the desired product is obtained selectively. Cross-metathesis outcomes are therefore dependent on the rate

of secondary metathesis processes; for example, in the reaction of a Type I with a Type II (or III) alkene, dimerization of the Type I alkene will occur but the dimers are consumable, while dimerization of the Type II (or III) alkene will be much slower (**Scheme 14**). In this case, productive metathesis to yield the desired product should dominate.

Table 10. Expected cross-metathesis outcomes as a function of the classifications of the alkenes employed.[72]

	Type I	**Type II**	**Type III**	**Type IV**
Type I	Statistical CM	Selective CM	Selective CM	No CM
Type II	Selective CM	Non-selective CM	Selective CM	No CM
Type III	Selective CM	Selective CM	Non-selective CM	No CM
Type IV	No CM	No CM	No CM	No CM

[Please insert Scheme14]

Scheme 14. Understanding of the relative rates of reaction of different alkenes, in order to rationalize and predict reaction outcomes.

This system of classification is quite broad, and does not describe *quantitative* differences in the reaction rates of different alkene substitution patterns. The reactivity of alkenes covers a continuum from the very reactive to the unreactive, but the classifications described by Grubbs are a convenient way in which to describe alkene substrates. In addition, the cross-metathesis focus of the study means that the effects on the cyclisation step (i.e. second metathesis step) have not been elucidated. Examples of alkenes of each type can be found in **Table 11**, based on a literature survey by Grubbs and co-workers. These classifications demonstrate the superior reactivity of the second-generation pre-catalysts; substrates that react slowly with **G1**, such as 1,1-disubstituted alkenes, will often undergo metathesis mediated by **G2**, for example.

Table 11. Examples of Type I, II, III and IV alkenes, with respect to **G1** and **G2**.[72]

Alkene	**G1**	**G2**

Type I	Terminal alkenes, allyl silanes, primary allylic alcohols, ethers, esters, allyl boronate esters, allyl halides	Terminal alkenes, primary allylic alcohols, esters, allyl boronate esters, allyl halides, styrenes (without large *ortho*-substituents), allyl phosphonates, allyl silanes, allyl phosphane oxides, allyl sulfides, protected allyl amines
Type II	styrene, secondary allylic alcohols, vinyl dioxolanes, vinyl boronates	styrenes (with large *ortho*-substituents), acrylates, acrylamides, acrylic acid, acrolein, vinyl ketones, unprotected tertiary allylic alcohols, vinyl epoxides, secondary allylic alcohols, perfluoroalkyl alkenes
Type III	vinyl siloxanes	1,1-disubstituted alkenes, non-bulky trisubstituted alkenes, vinyl phosphonates, phenyl vinyl sulfone, tertiary allylic carbons (all alkyl substituents), protected tertiary allylic alcohols
Type IV	1,1-disubstituted alkenes, disubstituted α,β-unsaturated carbonyls, tertiary allylic carbon-containing alkenes, perfluoroalkyl alkenes, protected tertiary allylamines	vinyl nitro alkenes, protected trisubstituted allyl alcohols

However, this difference in reactivity has been used to enforce selectivity in some reactions. For example, Fürstner has utilized bulky silyl groups to disfavor competing side reactions in the metathesis of trienes (**Scheme 15**).[73] In the absence of a silyl group, considerable quantities of the smaller ring product were obtained.

[Please insert Scheme15]

Scheme 15. Use of bulky silyl groups to direct metathesis.[73]

Metathesis to form tri- and tetra-substituted alkenes has been one of the key aims of modern metathesis pre-catalyst development; as discussed above, first generation systems such as **G1** are reluctant to react with more heavily-substituted alkenes, while second generation complexes are more reactive with these substrates, even in cross-metathesis applications.[74] Mioskowski and co-workers have compared the reactivity of **G1** to [$RuCl_2$(IMes)(PCy_3)(=CHPh)] **11** in some prototypical reactions, showing that the latter outperformed the former, particularly in the synthesis of tri- and tetra-substituted alkenes.[75] Ritter has explored the ring-closing reactions of some prototypical dienes **35-37** bearing varying degrees of substitution;[24] concentration/time profiles were collected for **35** and

36 under relatively mild conditions (**Figure 14 (a)** and **(b)**) ; **G2** and **11** clearly outperform **G1** by a greater extent as alkene substitution is increased and the reaction is rendered more challenging. For the most challenging example **37**, 5 mol% pre-catalyst was used, leading to no conversion for **G1** after 4 days, yet 17% and 31% for **G2** and **11**, respectively. Notably, as reaction with the least hindered alkene is fastest, substrate **36** is likely to undergo initial cross metathesis at the same rate as **35**, but with slower cyclisation, while compound **37** impedes both the initial cross-metathesis step *and* ring-closing.

[Please insert Figure14a]

[Please insert Figure14b]

Figure 14. (a) Substrates considered. (b) Concentration/time profiles for the RCM of **35** (open points) and **36** (filled points) with **G1** (circles), **G2** (diamonds) and **11** (triangles) (conditions: 0.1 mol L^{-1} in DCM-d_2, 30 °C, with 1 mol% catalyst).

Appropriate modification of the NHC has been shown to generate catalysts for which heavy substitution of the alkene termini is less challenging. For example, complexes **38** and **39** bear *ortho*-tolyl groups in place of the mesityl groups present in the SIMes ligand (**Figure 15**);[76-78] as a result, these complexes are far more efficient for RCM reactions to form tetrasubstituted alkenes, although these still remain among the most challenging substrates for alkene metathesis. Complex **38** has been used in Stoltz's syntheses of Elatol and related natural products, in a key step where a tetrasubstituted cyclohexene ring is formed (**Scheme 16**).[79,80]

[Please insert Figure15]

Figure 15. Metathesis pre-catalysts bearing less sterically-demanding NHCs.[76,77]

[Please insert Scheme16]

Scheme 16. Metathesis as a key step in Stoltz's synthesis of Elatol.[80]

3.1.1.3 Substitution at the Allylic and Homoallylic Positions

Allylic functionality is suitably close to the alkene termini to exert a considerable effect on the outcomes of metathesis reactions. Much of the study of allylic functionality has focused on allylic chalcogen substituents[81] (particularly hydroxyl groups), although it can be seen from the examples of Ulman above that allylic methylation can disfavor metathesis.[69]

It is generally accepted that an allylic hydroxyl group accelerates the rate of metathesis.[82] This effect was discussed by Hoye, who monitored a series of binary competition reactions between dienes **40**-**44** which differed only in their allylic substitution pattern. The alternative alkene terminus was trisubstituted in order to ensure that reaction proceeded via initial cross-metathesis at the desired terminus. The reactions of these substrates should then have proceeded as per **Scheme 17**, with the allylic substitution pattern influencing primarily the rate of initial cross-metathesis. Relative rates for the RCM of **40**-**44** were determined from their relative conversions once the most reactive substrate had achieved *ca.* 50 to 100% conversion (**Table 12**). The quality of the data was unclear (only one dataset was reported, and that graphically only), and relative reactivities are not based on actual rate or rate constant comparisons, making these values estimates at best. While these results demonstrated that **41** underwent RCM faster than **42**, the relative rate was modest (*ca.* 1.5-fold). Crucially, a key experiment (R = R' = H) was not conducted; therefore, while an allylic hydroxyl group resulted in faster metathesis than the analogous substrate with an allylic methyl group, it is not possible to infer the rate difference between the simplest systems. The data obtained were still valuable, showing that allylic methyl and methoxy functionality are both detrimental to metathesis rate.

[Please insert Scheme17]

Scheme 17. RCM of a series of dienes conducted by Hoye and co-workers.[82]

Table 12. Relative rates for a series of RCM substrates that differ only in the allylic substitution pattern.[82]

Substrate	R	R'	Relative RCM rate
40	H	OH	60

41	Me	OH	12
42	Me	H	8
43	H	OMe	1
44	Me	OMe	~0

Percy and co-workers have studied the RCM of a series of difluorinated cyclooctenones, which bore different protecting groups at the allylic hydroxyl , *en route* to conformationally locked sugar mimics (**Scheme 18**).[83,84] The rates and effective molarities[85,86] of the ring-closing reactions were measured; the effective molarity (EM) is the ratio of the rate of intra- *versus* intermolecular reaction and provides a measure of the kinetic preference for ring closing over oligomerisation (**Equation 7**). A related quantity is the thermodynamic effective molarity (EM_T) which represents the relative equilibrium constants for cyclisation *versus* oligomerisation, and therefore the thermodynamic cyclisation efficiency (**Equation 8**); these metrics are discussed in more detail in a subsequent section. The presence of a protecting group reduced the *rate* of reaction *versus* the unprotected alcohol (R' = H > Bz > Bn) as determined using kinetic experiments followed by GC (**Figure 16**), but led to an increased preference for the desired cyclic product (R' = Bz > Bn > H). Notably, as the protecting group is not present in the final product, the use of protecting groups to control selectivity in this way will have no effect on the structure of the final target molecule. An increase in EM of tenfold allows the reaction to be conducted at concentrations ten times higher, reducing the cost and environmental impact of the process. While an accelerating effect might be identified here, this is relative to the protected alcohol; the corresponding *des*-hydroxy compound has not been studied. The *gem*-dimethylated compound **46** underwent RCM much faster and with a much higher EM than analogue **45**; *gem*-disubstitution and its effects on RCM are discussed later.

[Please insert Scheme18]

Scheme 18. RCM reactions to form cyclooctenones studied by Percy.[83]

$$EM = k_{intra}/k_{inter} \quad (7)$$

$$EM_T = K_{intra}/K_{inter} \quad (8)$$

[Please insert Figure16]

Figure 16. Concentration/time data for the production of products **52** (R = H, circles), **50** (R = Bz, diamonds) and **51** (R = Bn, triangles) from the three diene RCM reaction of **48**, **45** and **47**, with 30 mol% $Ti(O^iPr)_4$ and 6 mol% **G2** in DCM at reflux.[83]

The origin of the allylic hydroxyl effect could potentially be the co-ordination of the hydroxyl group to the chloride ligand, directing it to the alkene terminus. This explanation was invoked to explain the diastereoselectivity of the cross-metathesis reaction between enantiomerically enriched 3-phenylprop-1-en-3-ol and 2-methyl-2-phenylcyclopropene conducted by Hoveyda and co-workers;[87] hydrogen bonding of the alcohol to the chloride ligand present on the metathesis catalyst was proposed to induce diastereoselectivity, as the cyclopropene substrate would be expected to co-ordinate the ruthenium center placing the largest ligand towards the bottom (**Scheme 19**). The evidence for such an intermediate is limited to some simple DFT calculations, however. The topic of the allylic hydroxyl effect clearly requires further investigation.

[Please insert Scheme19]

Scheme 19. Stereocontrol *via* hydrogen bonding, proposed by Hoveyda and co-workers.[87]

Wagener and co-workers have investigated the effects of allylic methylation with pre-catalysts **G1** and **G2**.[88] Each pre-catalyst was in turn exposed to *ca.* 3 equivalents of 3-methylpent-1-ene in benzene-d_6 at 318 K. The ^{1}H NMR spectra were checked periodically, showing clearly the pre-catalyst, methylidene **14**, ethylidene **53** (for G2 only) and phosphane-bound carbene **54**. The presence of methylidene indicated that at least two turnovers had been completed, while propagating carbene was formed from the reaction of methylidene or benzylidene with the alkene substrate. The metathesis reaction was very slow, which was attributed to the steric bulk of the substrate. This was believed to lead to the substrate partitioning in favor of MCBs that result in non-productive metathesis, rather

than those that favor productive metathesis (**Scheme 20**). Ulman observed no reaction of **G1** with the same substrate,[69] presumably due to the pre-catalyst being far more thermodynamically favorable, and similar issues in progressing through productive MCBs in which two substituents sterically impede each other.

[Please insert Scheme20]

Scheme 20. Reactions with substrates bearing allylic methyl groups.[88]

Bulky allylic substituents have been used to direct metal carbene movement during a metathesis reaction. For example, Schmidt and co-workers used a bulky trityl (triphenylmethyl) protecting group to promote selectivity for a specific ring size in the RCM of **55** (**Scheme 21**).[89] Use of the trityl group yielded 20:1 selectivity for the five-membered ring with **G1** (L = PCy_3), 12:1 with a benzyl group instead, or 1:1 with no protecting group. This presumably occurred due to steric interaction between the trityl group and the MCB, disfavoring formation of the six-membered ring. Lower (or no) selectivity was obtained with **G2** (3:1 and 1:1 for trityl and benzyl respectively), due to the fact that steric control is a kinetic effect, and that **G2** operates in the thermodynamic regime.

[Please insert Scheme21]

Scheme 21. Directing carbene movement *via* the use of bulky protecting groups.[89]

Schore and co-workers have explored the reaction of **G1** with a variety of alkenes, and quantified equilibrium constants for these reactions (**Table 13**). For **G1**, the reaction is favorable with ethene and propene (K_{eq} = 8.7 and 1.8 respectively), while the equilibrium constant tends to *ca.* 0.3 for longer 1-alkenes. The equilibrium constant with bulkier alkenes is much lower, with the presence of an allylic methyl or bulkier groups at the homoallylic position disfavoring the reaction. These data reflect how favorable the initial cross-metathesis step is.

Table 13. Equilibrium constants and free energies for the reactions between pre-catalyst **G1** and various model alkene substrates, as measured by NMR integration (typically the average of 10 measurements).[90]

Substrate	K_{eq}	$\Delta G°$ (kcal mol^{-1})	Substrate	K_{eq}	$\Delta G°$ (kcal mol^{-1})
[Please insert Table13_l1a]	8.66(25)	-1.251(17)	[Please insert Table13_l1b]	0.00188(11)	3.677(33)
[Please insert Table13_l2a]	1.76(11)	-0.326(37)	[Please insert Table13_l2b]	0.128(8)	1.208(33)
[Please insert Table13_l3a]	0.34(21)	0.624(36)	[Please insert Table13_l3b]	0.0148(4)	2.469(14)
[Please insert Table13_l4a]	0.286(6)	0.729(12)	[Please insert Table13_l4b]	0.0364(22)	1.932(36)
[Please insert Table13_l5a]	0.323(12)	0.660(21)	[Please insert Table13_l5b]	0.172(4)	1.026(13)
[Please insert Table13_l6a]	0.304(8)	0.694(15)	[Please insert Table13_l6b]	0.00455(33)	3.143(42)
[Please insert Table13_l7a]	0.304(11)	0.695(21)	[Please insert Table13_l7b]	0.00210(12)	3.596(33)
[Please insert Table13_l8a]	0.304(6)	0.694(12)	[Please insert Table13_l8b]	0.00186(14)	3.787(42)

3.1.1.4 Coordinating Functional Groups

Various functional groups have been proposed to co-ordinate the metal center in intermediates on metathesis pathways. Beneficial and detrimental effects have been proposed in different studies in the literature to result from the coordinating effects of Lewis basic functionality. Typically, this functional group is positioned such that a 1,5- or 1,6-chelate is formed (e.g. **Figure 17**).

[Please insert Figure17]

Figure 17. Potential chelate formation in metathesis reactions, referred to here as 1,5-chelate formation and 1,6-chelate formation.

Various stable chelates of this type have been isolated and characterized,[91] in some cases spawning entire new series of pre-catalysts (e.g. Hoveyda-type complexes, which bear a 2-alkoxystyrene ligand).[17,18] The use of more strongly-bound chelates based on sulfur- and nitrogen-containing functional groups has led to the isolation and characterization of highly stable latent pre-catalysts that can be handled in the presence of substrates, but do not undergo metathesis until activated by, for example, high temperatures.[25,92]

Davis has explored the use of allyl sulfides and selenides in metathesis reactions, and homologues thereof.[93] Allyl sulfides were found to be suitable CM partners, but longer chain homologues (homoallyl, etc.) were found to be much poorer (**Scheme 22 (a)**). The authors proposed that the Lewis basic sulfur interacted with the 14e ruthenium carbene, promoting the reaction. CM was then utilized to functionalize cysteine residues on proteins[94] with groups including alcohols, poly(ethylene glycol) and carbohydrates, *via* allylation followed by cross-metathesis. In a subsequent study, allyl selenides were found to be even better metathesis substrates.[95] Selenium and sulfur are good ligands for late transition metals, but an interaction between the heteroatom and the ruthenium center is not favorable when a four membered chelate complex would be involved. However, five- and six-membered chelates would most likely be stable (**Scheme 22 (b)**). A possible explanation is therefore that placement of the heteroatom in the appropriate position of the alkene substrate *prevents* chelation to the ruthenium center, which would be expected to interfere with the metathesis reaction. Chelating sulfides are commonly structural features of latent alkene metathesis pre-catalysts that require high temperatures or other stimuli to effect catalytic activity.[92]

[Please insert Scheme22]

Scheme 22. (a) Cross-metathesis with sulfide substrates and (b) potential chelation of the ruthenium center.[93]

Researchers at Boehringer-Ingelheim studied the effects of amide protecting group on the RCM reactions of **56-59** (**Figure 18**).[96] Exposure of **56-59** to 30 mol% **G1** in DCM-d_2 allowed the

relative proportions of carbene at each terminus to be evaluated by ^{1}H NMR. The catalyst underwent metathesis with the unprotected amide **56** or *N*-benzylated amide (**58**) at terminus A preferentially, while BOC protection (**57**) or *N*-acylation (**59**) favored initiation at terminus B. The latter terminus is remote from the modification, and so serves as a 'control' terminus. Protection of the amide was proposed to disrupt 1,6-chelation of the metal center by the ester through $A_{1,3}$ strain.

[Please insert Figure18_color or Figure18_bw]

Figure 18. Probing the selectivity of the initial cross-metathesis event.[96]

Quinn et al. proposed that co-ordination of the metal center promotes metathesis at sites that possess coordinating functionality in the allylic position (**Scheme 23**).[97] However, this selectivity could be explained by the larger size of the benzyl ether group, which is a steric reason for preferential reaction at the site bearing the allylic ester.

[Please insert Scheme23]

Scheme 23. Selectivity for allylic acetate.[97]

The effects of allylic chalcogens are not necessarily always positive, however. Cossy and co-workers proposed that co-ordination of an allylic acetate group effectively protected one terminus from reaction and allowed chemoselective cross-metathesis at the other (**Scheme 24 (a)**);[98] the proposed mechanism suggested that the ester group chelated the MCB that would be formed if reaction occurred at the terminus closest to this group, preventing it from forming a ruthenium carbene here. In contrast, a ruthenium carbene at the alternative terminus would be able to undergo cross metathesis unimpeded. However, the explanation presented in the original paper would require the reaction of a molecule of diene with two molecules of active catalyst; diene is present in 20-fold excess over pre-catalyst so the presence of two ruthenium centers on a single molecule of diene seems unlikely. Another explanation might be that **GH2** reacts with acrolein first, as it is present in three-fold excess over the diene; the reactivity of the intermediate species **60** might then influence

selectivity (**Scheme 24 (b)**). The ester is much bulkier than the alcohol and so may promote cross-metathesis at the less hindered end of the molecule. Alternatively, the cross-metathesis reaction at the position bearing an allylic ester may simply be slower than at the less hindered end.

Neither of these explanations is satisfying; clearly the effects of potential chelating groups and how they affect selectivity are poorly understood, and in need of further exploration.

[Please insert Scheme24]

Scheme 24. Cross metathesis reactions studied by Cossy and co-workers.[98]

3.1.1.5 Substitution of the Substrate Backbone

Substitution elsewhere on the substrate can also exert an effect on both the rate and efficiency of RCM, generally by affecting the relative energies of the different conformations of the substrate; in some conformations, the termini will be closer together than in others. This reduction of the entropic or enthalpic penalty of cyclisation is often referred to in the literature as 'pre-organization'.

Gem-disubstitution of the alkene backbone can aid cyclisation, either *via* the Thorpe-Ingold effect[99,100] or the reactive rotamer effect.[101] The former effect is a change of angle Θ between the reacting termini due to a corresponding change in the angle between the two substituents R (**Figure 19**, left); for bulky substituents R, it is proposed that Θ is reduced, bringing the two termini closer together in space. An alternative explanation is the reactive rotamer effect, whereby bulky R substituents reduce the energy difference between the *gauche* and *anti* forms, effectively lowering the relative energy of the rotamer where the reacting groups are closer in space (**Figure 19**, right). The latter effect has been shown to predominate in some intramolecular Diels-Alder reactions where backbone substitution patterns with similar steric impact but different angle Θ were found to cyclize faster than the parent dihydro compound; if angle compression were the only factor that determined reaction rate, then the cyclobutane-substituted substrate would be expected to react more slowly than the corresponding dihydro compound, yet it reacted significantly faster (k_{rel} = 208).[102]

[Please insert Figure19_color or Figure19_bw]

Figure 19. Thorpe-Ingold *versus* reactive rotamer effects.

Wagener and co-workers reported the considerable effect of bis-*gem*-dimethylation of 1,8-nonadiene-5-one on the metathesis outcome (**Scheme 25**);[103] the heavily-alkylated substrate most likely undergoes significant relief of strain upon cyclisation. Calculations (M06-L/6-311G*) by Percy and Hillier revealed a 3.6 kcal mol^{-1} difference in favor of oligomerisation for the non-alkylated example, and a 3.7 kcal mol^{-1} difference in favor of RCM for the alkylated substrate. This corresponds to a *ca.* 10^5-fold difference in effective molarity.

[Please insert Scheme25]

Scheme 25. Bis-*gem*-dimethylation to promote ring closure.[103]

The beneficial effect of *gem*-diester substitution on the efficiency of RCM has led to substrates such as diethyl diallylmalonate (**35**) being used as model substrates for the testing of catalysts[24] and conditions.[41] This substrate can undergo RCM at high concentrations without oligomerisation, while 1,6-heptadiene has an EM of *ca.* 0.5 mol L^{-1}, meaning that for selectivity for cycloalkene over oligomer, reactions must be run at millimolar concentrations.[104] Notably, the *rate* of RCM is not enhanced by this *gem*-disubstitution, with diethyl diallylmalonate undergoing RCM at approximately *half* the rate of 1,6-heptadiene (**Figure 20**).[105]

[Please insert Figure20]

Figure 20. Concentration/time profiles for the products of RCM of diethyl diallylmalonate (**35**) (open points) and 1,6-heptadiene (filled points) (10 mmol L^{-1} in DCM-d_2, 25°C, 1 mol% **G2**).[105]

As discussed above, Percy and co-workers published a study in which *gem*-dimethylation of the backbone was found to increase the rate *and* EM of the cyclisation (see **Scheme 18** above). In this case, the target was an eight-membered ring and the substituents were methyl groups rather than bulky esters, which may avoid steric clashes with a bulky catalyst coordinated to a terminus.

O'Hagan and Nolan have studied the effect of *gem*-difluorination on the ring-closing reactions of some simple 1,8-nonadiene substrates (**61**-**65**, to yield the corresponding cycloheptenes (**Scheme 26**).[106] Reactions were only studied under one set of conditions, so effective molarity data is not available, but the reactions could be divided into two groups: one yielded predominantly oligomeric material and less than 20% conversion to cycloalkene, while the other group yielded >70% conversion to cycloalkene (**Figure 21**). While the study is billed as the disclosure of a *rate* acceleration, the primary difference manifests in the degree of conversion to cycloalkene *versus* oligomer, which is a thermodynamic effect when second-generation catalysts are employed.[104] The effect of *gem*-difluorination therefore appears to yield the same outcome as the presence of much bulkier *gem*-diester substitution. A search for structural data showed that the F-F angle was typically *ca.* 104 °, *versus ca.* 105° for the ketal, 109° for dimethyl and 108° for diester; the corresponding C-C angle should therefore be *larger* for the *gem*-difluorinated substrate **63** (from the Cambridge Structural Database: 117° *versus* 112°, 109° or 108°), which is at odds with the experimental data. Exploration of the relative energies of the *anti* and *gauche* rotamers did not fully explain the trend. However, isodesmic calculations showed that ΔH was considerably lower for the RCM to form the *gem*-difluoro, *gem*-diester and ketal-bearing products. This is therefore a thermodynamic effect, proposed to arise from *trans*-axial hyperconjugative $\sigma_{CH}/\sigma_{CF^*}$ stabilizing interactions. The use of metathesis to prepare fluorinated products, as well as the use of fluorine-bearing pre-catalysts and solvents, has been reviewed recently.[107]

[Please insert Scheme26]

Scheme 26. RCM of model 1,8-nonadiene compounds with different backbone substitution.[106]

[Please insert Figure21]

Figure 21. Concentration/time profiles for the RCM of dienes **61**-**65** (0.25 mol L^{-1} in toluene-d_8 at 15 °C with 2 mol% $\mathbf{M_{20}}$): **61** (H, H; open squares), **62** (H, F; open diamonds), **63** (F,F; filled squares), **64** (*gem*-diester, filled diamonds) and **65** (ketal, filled triangles).

The conformation of the acyclic form is important, and can be influenced by the substitution pattern. Crimmins and co-workers have prepared seven-, eight- and nine-membered oxacycles **66**-**68** in excellent yields (**Scheme 27**).[108] In these examples, the substitution pattern favored a *gauche* arrangement between C4 and C5, allowing donation of electron density from the σ_{CH} orbital into the σ^*_{CO} orbital, and thereby reducing the rotational freedom around the C4-C5 bond (**Figure 22**). The *gauche* conformation favors cyclisation more than the *anti* conformation, so a substitution pattern that favors the *gauche* conformation will reduce both the entropic and enthalpic penalties of cyclisation. The successful synthesis of a cyclononene compound in this fashion is particularly noteworthy, given the reluctance of cyclononene itself to form by RCM, even at sub-millimole per litre concentrations.

[Please insert Scheme27]

Scheme 27. Synthesis of medium rings by Crimmins (5 – 7 mol% **G1** with a substrate concentration of 3 mmol L^{-1} in refluxing DCM).

[Please insert Figure22]

Figure 22. Electron donation from the σ_{CH} orbital to the σ^*_{CO} orbital stabilizes a C4-C5 *gauche* arrangement, restricting rotation and reducing the entropic penalty to cyclisation.

Amides and esters can promote or disfavor RCM, depending on how they affect the conformation of the diene substrate. For example, amide **69** undergoes relatively straightforward RCM, despite the (often challenging) formation of a seven-membered ring (**Scheme 28**); the N-C bond of the amide is a restricted rotor, due to the donation of the nitrogen lone pair into the carbonyl π^* orbital, which will reduce the entropic penalty of cyclisation to a value approaching that of a six-membered ring.

[Please insert Scheme28]

Scheme 28. Formation of a seven-membered ring bearing an amide.[109]

In contrast, substrate **71** does not undergo successful RCM, potentially due (at least partly) to the difference in energy between the *s-cis* and *s-trans* conformations of the ester. As the *s-cis* is lower in energy, yet the product cycloalkene must feature the *s-trans* conformation, there is an additional enthalpic penalty which disfavors RCM (**Scheme 29**).[110]

[Please insert Scheme29]

Scheme 29. Conformational preference in ester **71**.[110]

Annelative strategies have also enabled RCM of otherwise difficult substrates. Some of the earliest examples of medium-ring formation feature annelative syntheses which reduce the entropic penalty of ring closing. For example, RCM of a 1,9-decadiene motif requires seven rotors to be frozen, while if one rotor is already fixed the entropic penalty of cyclisation is decreased. As a useful guideline, the EM is increased by *ca.* 7-fold for every rotor that is fixed.[111] Compounds **72**-**74** successfully undergo RCM, although with varying degrees of success (**Scheme 30**);[110] while a rotor is fixed in each example, the stereochemistry of **74** presumably introduces additional strain into the product ring which will disfavor cyclisation over oligomerisation at any given concentration.

[Please insert Scheme30]

Scheme 30. Annelative syntheses of eight-membered rings.[110]

3.1.2 Detrimental Functionality

Certain compounds can interfere with metathesis reactions by bringing about catalyst decomposition, either by 'poisoning' the catalyst or by generating an intermediate species that is far less metathesis active. Thermal decomposition and modes of decomposition by compounds other than those likely to be incorporated into metathesis substrates have been discussed in a recent review.[10]

3.1.2.1 Functional Groups That Generate Inactive Complexes

Carbenium species **75** and phosphonium alkylidene **76** were obtained from the reaction mixture rather than the expected species when **G2** was exposed to vinyl chlorides in benzene at room temperature, **77** (**Scheme 31**).[112]

[Please insert Scheme31]

Scheme 31. Decomposition *via* reaction with vinyl chlorides.[112]

The metathesis of vinyl halides is possible but does not always proceed smoothly due to the potential for the formation of by-products from the intermediate carbene species. Vinyl chloride substrates that have been known to undergo metathesis smoothly, include an intermediate from Stoltz's synthesis of Elatol (see **Scheme 16**), but in this case the formation of a vinyl chloride can be avoided if the catalyst first reacts with the alternative terminus.[80] Similarly, Dorta has shown that the RCM of vinyl bromides can be achieved, but only with a specific substitution pattern (**Scheme 32**).[113] Appropriate substitution of the terminus bearing the bromide presumably disfavors the initial cross metathesis reaction at that site.

[Please insert Scheme32]

Scheme 32. RCM of alkenyl bromides, studied by Dorta.[113]

3.1.2.2 Functional Groups That Generate Less Active Complexes

While some substrates will disable the catalyst outright, there are several functional groups that will generate less active complexes as reaction intermediates.

One such substrate is acrylonitrile, which can be a problematic substrate due to the formation of **83**, which is a stable intermediate that results from the capture of the intermediate $14e^-$ compound by phosphine (**Scheme 33**). This can be avoided by the use of phosphine-free catalysts, such as **GH2** and **G2py**.[20]

[Please insert Scheme 33]

Scheme 33. Formation of less active carbenes by reaction with acrylonitrile.

Similarly, reaction with vinyl ethers generates less active Fischer carbene species. Grubbs and co-workers have prepared and characterized a series of these complexes, *via* metathesis of the corresponding alkene with **G1** or **G2** (e.g. **Scheme 34**).[32] While these species can still perform metathesis, they are poorly active, and require high temperatures at which there are competing decomposition reactions to yield hydridocarbonyl complexes.

[Please insert Scheme34]

Scheme 34. Synthesis of Fischer carbene complexes *via* metathesis.[32]

1,6-Hexadiene motifs have been found to lead to sequestration of the catalyst in some reactions. Snapper isolated η^2-complex **86** from the ring-opening reaction of cyclobutene **87** with **G1** as well as from the metathesis of 1,6-hexadiene **88** (**Scheme 35**).[114] The stability of this product was such that it could be isolated and crystallized, so this represents an extreme case. In a later study, Percy and co-workers showed that even the simplest parent molecule,1,6-hexadiene, reduced the rate of RCM reactions of 1,6-heptadiene and 1,7-octadiene,[115] suggesting that the formation of such η^2-complexes impedes RCM reactions *via* catalyst sequestration.

[Please insert Scheme35]

Scheme 35. Isolation of an η^2-complex from metathesis reactions.[114]

A number of structural motifs are therefore potentially detrimental to the performance of metathesis reactions; some of these appear innocent, and can be hard to identify in densely-functionalized molecules. Processes that can lead to ruthenium hydride complexes are particularly problematic, as these ruthenium hydride species can bring about unwanted alkene isomerization in substrates and/or products.

3.2 Selectivity in Ring-Closing Metathesis Reactions

Selective reactions are crucial for a number of reasons, specifically to enable the most economical use of starting materials and to avoid time-consuming and expensive purification steps to separate the desired product from the by-product(s). Selective reactions enable the number of purification and processing steps to be minimized, and therefore lead to more cost-effective and convenient chemical processes. Two key types of selectivity are considered here: *E*/*Z* selectivity and ring/chain selectivity. The former topic is discussed only briefly, as this is predominantly determined by the catalyst, rather than the substrate. The latter selectivity is dependent on substrate structure, predominantly the size of the target cycloalkene, and concerns the competition between intramolecular metathesis (RCM) to form cycloalkenes and intermolecular metathesis (cross metathesis) to form dimers, and potentially longer chains.

3.2.1 *E*/*Z* Selectivity

The alkene stereoselectivity can be determined by either the substrate or the catalyst. In terms of substrate control, the key factors are the degree of alkene substitution and whether the product is acyclic or cyclic, and if the latter, the target ring size. For catalyst control, traditional metathesis pre-catalysts (e.g. Grubbs- and Hoveyda-types) the degree of thermodynamic control is key, with second generation catalysts often leading to excellent *E*-selectivity, as this is typically the thermodynamic product. However, new *Z*-selective catalysts have recently emerged, which enforce kinetic *Z*-selectivity by favoring side-bound intermediates.[116]

E/*Z* selectivity in cross-metathesis is typically very high with second-generation metathesis pre-catalysts, and >20:1 *E*/*Z* selectivities can often be attained in cross-metathesis reactions with relatively unhindered substrates.[117] However, for more substituted substrates, lower *E*/*Z* ratios are typically obtained.[74]

For RCM, the target ring size influences the configuration of the product alkene; for common and medium rings (5-10 members), the *Z*-cycloalkenes are less strained than the *E*-cycloalkenes by up to 9 kcal mol^{-1}[118] and so rings of these sizes are isolated solely as the *Z*-diastereoisomers. There are

exceptions, such as the highly functionalized example reported by Prunet and co-workers in which an *E*-cyclooctene product was obtained (**Scheme 36**).[119] The densely functionalized and doubly annelated scaffold must render the corresponding *Z*-isomer too strained to form in an equilibrium mixture. For larger rings such as macrocycles, the difference in strain energy between *E*- and *Z*-isomers is reduced, and both isomers can form from RCM reactions.

[Please insert Scheme36]

Scheme 36. Formation of an *E*-cyclooctene product by RCM.[119]

The choice of catalyst influences the *E*/*Z*-selectivity in cross-metathesis reactions. First and second generation complexes differ in their reactivity with substituted alkenes. First generation complexes are typically slow to form tri- or tetrasubstituted alkenes, and react slowly with disubstituted alkenes. In contrast, second generation complexes are more reactive with more substituted alkenes, which allows them to 'edit' the stereochemistry of alkenes by reacting with the products. The net result is that second generation complexes operate in the thermodynamic regime. This can be detrimental if kinetic control is preferred; for example, in the initial synthesis of BILN 2061, a first generation complex yielded better selectivity for ring over oligomer.[120,121] However, if higher *E*/*Z* ratios are desired, second generation complexes are the better choice. An illustration of the difference in *E*/*Z* ratios, and particularly their evolution with time, was provided by Grubbs and co-workers (**Scheme 37** and **Figure 23**). As can be seen from the graph, **G1** leads to approximately 5:1 *E*/*Z* throughout the reaction. In contrast, **G2** initially yields lower *E*/*Z* ratios of *ca.* 2:1, which then rise to *ca.* 9:1 over the course of the reaction. Modifications of the pre-catalyst structure such as alteration of the NHC ligand and phosphine ligand can also affect *E*/*Z* selectivity, with a bulkier NHC and more labile phosphine ligand appearing to be the optimal combination.[122,123]

[Please insert Scheme37]

Scheme 37. Model cross metathesis reaction.[24]

[Please insert Figure23]

Figure 23. Extent of conversion (filled points) and *E*/*Z* product ratio (open points) over time for the reaction in **Scheme 37** catalyzed by **G1** (top) and **G2** (bottom).[24]

More recently, ranges of pre-catalysts that are *Z*-selective have been disclosed. These include cyclometalated complexes such as **89** and **90**,[124,125] and anion-exchanged species such as **91** and **92** (**Figure 24**).[126,127] These species are typically far less active in traditional test reactions, but are capable of enforcing *Z*-selectivity in applications where the substrate does not determine *E*- or *Z*-selectivity. This has been shown to be due to the reaction proceeding *via* side-bound MCBs, rather than the bottom-bound MCBs that are prevalent in metathesis reactions catalyzed by traditional catalysts such as **G1**, **G2** and **GH2**;[116,128] in these side-bound MCBs, the alkene substituents are *both* directed away from the bulky NHC ligand, rendering the most energetically favorable MCB the one which leads to the *Z*-alkene. This area is a current focal point for metathesis pre-catalyst development, and has been reviewed recently.[129]

[Please insert Figure24]

Figure 24. *Z*-selective metathesis pre-catalysts.

3.2.2 Intra- *versus* Intermolecular Metathesis

One of the most common outcomes when an RCM reaction fails is the competing cross-metathesis of the substrate to form linear or cyclic dimers, or potentially oligomers or even polymers. The competition between RCM and CM in the metathesis of dienes will depend on a number of factors, predominantly related to the structure of the target cycloalkene. The strain introduced (ΔH; composed of angle strain, transannular strain, and torsional strain) will depend on the substitution pattern of the diene, while the loss of entropy (ΔS) will depend on the number of rotors frozen in the product that were otherwise free to rotate in the substrate. The formation of macrocycles will predominantly be influenced by ΔS, as rings greater than *ca* 12 members in size typically suffer relatively little strain.[111]

Macrocycle formation is not considered in detail here, but has been reviewed recently;[130] this section will focus on rings of 5 – 10 members.

3.2.2.1 The Influence of Ring Size on Reaction Outcome

A key determinant of ring-closing metathesis outcome is the target ring size. A brief survey of the literature, with selected examples, quickly establishes which ring sizes can be formed in a straightforward manner, and which are still challenging targets. As discussed previously, yield measurements do not describe the efficiency of metathesis reactions well, and it is important to take into account the concentration regime required to obtain practical yields. The concentration at which a cyclisation *via* RCM is conducted can be a good indicator of the magnitude of the effective molarity (see the subsequent section for a discussion on quantitative measurements of cyclisation efficiency).

Syntheses of five- and six-membered rings by RCM are typically straightforward, with most early studies of ruthenium-catalyzed ring-closing metathesis reporting the syntheses of primarily five- and six-membered products using early pre-catalysts such as **G1** at relatively high concentrations (*ca.* 10^{-1} mol L^{-1}).[109,131] Even substrates with more challenging substitution patterns (*vide infra*) undergo cyclisation catalyzed by 5 mol% **G1** in moderate to excellent yields in 24 h at room temperature (**Scheme 38**).[132]

[Please insert Scheme38]

Scheme 38. Synthesis of tetrasubstituted cycloalkenes with **G1**.[132]

The typically very efficient synthesis of five- and six-membered rings has allowed a number of solvent-free syntheses to be conducted. Vo Thanh and co-workers reported the solvent-free microwave-heated RCM reactions of **93** and **94**, with high to excellent conversion for all of the five- and six-membered ring syntheses studied; [133] excellent isolated yields of **95** and **96** were reported (**Scheme 39**).

[Please insert Scheme39]

Scheme 39. Solvent-free syntheses of cycloalkenes under microwave irradiation.[133]

Cyclisation of Linalool **97** to yield 2-methylcyclopenten-2-ol has also been achieved under solvent-free conditions (with **GH2**), yielding isobutene as a by-product (**Scheme 40**).[134] Both metathesis products were then converted to useful fuel compounds.

[Please insert Scheme40]

Scheme 40. Solvent-free RCM of Linalool **97**.[134]

Five-membered ring formation typically drives RRCM, which allows the synthetic chemist to control the locus of reaction (*vide supra*).[70] RRCM has been used to overcome the problematic RCM of sterically hindered substrates. RRCM tethers based on bis-allyl ether, 1,6-heptadiene[135] and diethyl diallylmalonate[71] motifs have also been reported.

The synthesis of seven-membered rings is more difficult, with early examples of seven-membered heterocycle formation proceeding in up to *ca.* 70% yield, but few reports of the formation of simple cycloheptenes. Wagener reported the RCM of a 1,8-nonadiene derivative (see **Scheme 25**) but this is an exceptional example where tetramethylation of the backbone drives the cyclisation.[103] The preparation of seven-membered cyclic amides such as **69** has been reported; in this example, the conformational restriction afforded by the amide functional group probably aids cyclisation by reducing the entropic penalty, and therefore facilitates cyclisation at a relatively high reaction concentration (**Scheme 28**, above).[109]

Cycloheptenes have been prepared by RCM, with a challenging 1,2-dimethylated cycloheptene product **98** prepared *via* RCM of the corresponding α,ω-diene in 71% yield using pre-catalyst **99** (**Scheme 41**).[136]

[Please insert Scheme41]

Scheme 41. Synthesis of **98** by RCM.[136]

Schmidt and co-workers have studied ring size selectivity using a series of functionalized substrates.[137] Compound **100** can undergo metathesis to yield products **101**-**104**, which feature one or more five- or six-membered rings (**Scheme 42 (a)**). In this case, the choice of reaction conditions was found to influence the outcome; under conditions where kinetic control was established (with first-generation pre-catalysts), the bis(dihydrofuran) product **101** was favored. When thermodynamic control was established by using second-generation catalyst systems and providing ethene to facilitate ring-opening, higher proportions of the bis(dihydropyran) product **102** were obtained. However, the formation of the bis(dihydropyran) product requires the formation of a fused ring system, and therefore is not the best test of five- *versus* six-membered ring synthesis. When triene **105** was exposed to different catalysts, first-generation **G1** resulted in no selectivity, while use of second-generation **G2** favored the six-membered ring by 3:1 (**Scheme 42 (b)**).

[Please insert Scheme42]

Scheme 42. Five- *versus* six-membered ring formation in functionalized substrates.[137]

Percy and co-workers have examined the rate of cyclisation to form five-, six- and seven-membered rings, *via* ^{1}H NMR kinetic experiments (10 mmol L^{-1} in $CDCl_3$ and CD_2Cl_2 at 298K with 1 mol% **G2**).[115] The use of 1,6-heptadiene, 1,7-octadiene and 1,8-nonadiene avoided biasing of the reaction results by the functional group substitution pattern. There was a slight rate difference in favor of the six-membered ring product, while RCM to form cycloheptene was slow and incomplete, yielding a cyclic dimer by-product even at low concentration. The order of reactivity was confirmed by a competition experiment in which all three substrates were present (**Figure 25**).

[Please insert Figure25]

Figure 25. Competition experiment between 1,6-heptadiene, 1,7-octadiene and 1,8-nonadiene, to form cyclopentene (triangles), cyclohexene (circles) and cycloheptene (diamonds) respectively.[115]

Syntheses of seven-membered rings are therefore achievable *via* RCM but present more of a challenge than five- or six-membered ring syntheses, requiring higher reaction temperatures and lower substrate concentrations, and typically result in lower yields.[132]

Eight-membered rings are less commonly prepared by annulative RCM, with a number of reports of failure. Medium ring synthesis by RCM is often challenging, and has been the topic of a number of reviews.[138,139] Grubbs reported the failure of dienes **108** and **109** to undergo RCM when conducted at an initial substrate concentration of 10 mmol L^{-1} (**Scheme 43**);[132] the *gem*-diester functionality is therefore not sufficient to achieve selective cyclisation at this reaction concentration. Instead, dimeric species **110** and **111** were isolated and characterized, indicating that the effective molarity was very low; the EM is likely to be below 1 mmol L^{-1} as the desired cyclooctene products were not detected in the reaction mixture. This is in stark contrast to the five-, six- and seven-membered ring analogues, which underwent RCM smoothly, in some cases under neat conditions.

[Please insert Scheme43]

Scheme 43. Unsuccessful synthesis of some eight-membered rings by RCM.[132]

Hammer and Undheim reported the RCM of **112**-**116** in yields from 53 – 99%, but could not prepare the cyclooctene analogue from **117** (**Scheme 44**). Yield differences were obtained between different isomers which cyclize to form the same ring size. Substrates in which a diene terminus was only three bonds from the dihydropyrazine nitrogen atom required more forcing conditions to achieve cyclisation. Reactions were typically conducted at *ca.* 50 mmol L^{-1}. The ease of RCM of **115**, even at 40 mmol L^{-1}, suggests that the formation of the spirocycle aids cyclisation, either through restricting rotation of the sidechains, or by reducing the angle between the two alkene tethers.

[Please insert Scheme44]

Scheme 44. Synthesis of spirocycles by RCM.[140]

The outcomes of eight-membered ring syntheses by RCM are often very sensitive to the substitution pattern. Grubbs and co-workers were unable to cyclize dienes **71** and **118** using pre-catalyst **70** (**Figure 26**).[110] The bulky disubstitution of **118** did not provide enough of a driving force for cyclisation, while **71** is likely to adopt a conformation that hinders cyclisation (*vide supra*).

[Please insert Figure26]

Figure 26. Substrates that failed to undergo cyclisation.[110]

Linderman used trialkylstannyl-substitution to drive the cyclisation of dienes that would not otherwise undergo RCM.[141] Substrate **119** did not undergo RCM with **G1** in 12 hours, yet trialkylstannyl-substituted substrate **120** gave the desired product in 74% yield (**Scheme 45**). The effective steric bulk of the tributyltin group (i.e. that which might affect the CH_2-CH(R)-O angle or the CH_2-CH(R)-O-CH_2 dihedral angle) is unlikely to be significantly more than a *tert*-butyl group, and therefore there must also be a contribution from the interactions of the oxygen atom with the C-Sn molecular orbitals. The trialkylstannyl group could be elaborated further *via* tin-lithium exchange and reaction with electrophiles, so provided a useful functional group for further elaboration of the product as well as a cyclisation aid. Calculations by Percy and Hillier showed that this difference in substitution had a small (ca. 1 kcal mol^{-1}) effect on the difference in energy difference between RCM and oligomerisation, consistent with an estimated 10-fold increase in effective molarity.

[Please insert Scheme45]

Scheme 45. Cyclisation promoted by stannane substituents.[141]

More recent examples of cyclooctene formation have been reported where cyclisation was achieved without the need for annelation. For example, Percy has reported the syntheses of difluorinated cyclooctenones *en route* to conformationally-locked sugar mimics (**Scheme 46**).[84] These cyclizations were aided by a judicious choice of protecting group (*vide supra*); RCM of benzyl-protected **47** proceeded at 2.2 mmol L^{-1} in 46% yield, while the benzoyl-protected substrate **45**

underwent RCM at 10 mmol L^{-1} in 75% yield. Collectively, these results illustrate that synthesis of cyclooctenes can be challenging, and that the outcome of such reactions can acutely depend on substrate structure.

[Please insert Scheme46]

Scheme 46. Synthesis of cyclooctenone compounds *en route* to conformationally-locked sugar mimics.[84]

Reports of cyclononene syntheses by RCM are less common. Cyclononene itself is the most strained unsubstituted *Z*-cycloalkene.[118] In addition, up to eight rotors must be fixed to form cyclononene by annulation, which carries a high entropic cost, which can be estimated (see Section 3.2.2.2). Banfi and co-workers reported the synthesis of **121** and **122** from substrates **123** and **124** (**Scheme 47**).[142] However, 20 mol% pre-catalyst loadings and long reaction times (2 – 3 days) were required to obtain yields of 26 – 69% (thus TON ≈ 1 – 2.5). This reaction was likely to be aided by *gem*-substitution of the backbone (*vide supra*).

[Please insert Scheme47]

Scheme 47. Synthesis of a cyclononene by RCM.[142]

Gesson and co-workers prepared **125** from **126** *via* RCM (**Scheme 48**).[143] The pre-catalyst loading was high (10 – 20%), and only 58% conversion was achieved after three days in toluene at room temperature. However, this represents one of the few successful non-annelative cyclononene syntheses by RCM in the literature. Other examples of nine-membered ring synthesis have typically involved annelation rather than annulation.[144,145]

Commented [NW2]: The scheme says 126 from 125, and 49%.

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[Please insert Scheme48]

Scheme 48. Synthesis of a cyclononene by Gesson and co-workers.[143]

Crimmins and co-workers have prepared seven-, eight- and nine-membered oxacycles in excellent yields (**Scheme 27** above). In these examples, the substitution pattern favored a *gauche* arrangement that facilitated RCM.

Cyclodecene synthesis by RCM is rare, and typically requires high dilution conditions. Rychnovsky and co-workers have prepared cyclodecene **127** by exposing a 1 mmol L^{-1} solution of **128** to 20 mol% **G2** (**Scheme 49**).[146] This cyclisation will be assisted by the bulky *gem*-diester substitution pattern, although high dilution conditions (1 mmol L^{-1}; 822 mg in 1.6 L) were necessary to avoid competing cross-metathesis. If it is assumed that, in the worst case, the remaining *ca.* 10% of material is oligomer, the effective molarity would be at least *ca.* 10 mmol L^{-1}. Similarly, Koskinen and co-workers achieved RCM of **129** under high dilution conditions, isolating a mixture of the *E*- and *Z*-isomers (**Scheme 50**).[147]

[Please insert Scheme49]

Scheme 49. Synthesis of a ten-membered ring by Rychnovasky.[146]

[Please insert Scheme50]

Scheme 50. Synthesis of a ten-membered ring by Koskinen.[147]

This brief summary of the literature serves to highlight the relative ease with which different target cycloalkenes can be prepared by RCM. While five- and six-membered rings can often be prepared smoothly under very concentrated (or solvent-free) conditions by RCM, seven-membered rings are less straightforward to prepare. Eight-membered ring synthesis poses a bigger challenge, and is acutely sensitive to the substitution pattern of the substrate. Nine- and ten-membered rings are rarely prepared, with most literature examples requiring very high dilution and proceeding with often very modest yield and TON. The ring size not only affects RCM but also ROMP behavior,[148] as ROMP releases ring-strain and allows the rotation of bonds that are otherwise restricted, although the topic of ROMP is beyond the scope of this manuscript.[149] While the substitution pattern clearly exerts

an effect, as seen in some examples in this section and in previous sections, the target ring size is a critical factor in the success or failure of a metathesis reaction.

3.2.2.2 Quantitative Insights into Cyclisation Efficiency

There are relatively few quantitative studies of cyclisation efficiency using RCM, most of which have been conducted by Percy and co-workers. In these studies, the concepts of effective molarity and thermodynamic effective molarity (see **Equations 7** and **8** above)[85] have been used to provide a simple, understandable way to quantitatively describe how efficient RCM is compared to cross metathesis. This information is important, as it allows the degree of cyclisation *versus* cross metathesis to be quantified at different concentrations, and therefore allows the synthetic chemist to identify the most appropriate reaction concentration (see **Equations 9** and **10**).

$$[\text{cycloalkene}]/[\text{oligomer}] = EM/[\text{substrate}]_0 \quad \text{(kinetic control)} \quad (\mathbf{9})$$

$$[\text{cycloalkene}]/[\text{oligomer}] = EM_T/[\text{substrate}] \quad \text{(thermodynamic control)} \quad (\mathbf{10})$$

Notably, the actual chemical reaction is factored out, as the same bonds are broken and formed in both the intra- and intermolecular reactions. The effective molarity has units of mol L^{-1}, and is not always a physically attainable concentration. However, for most RCM reactions, the attainment of high reaction concentrations does not represent a problem; most are far less efficient. The EM represents the reaction concentration at which a 1:1 mixture of cycloalkene and oligomer would be expected; i.e. the concentration at which the intra- and intermolecular reactions occur at the same rate (for EM) or with the same equilibrium constant (for EM_T). Therefore, in order to avoid deleterious oligomerisation processes, metathesis reactions should be conducted at a concentration of *ca.* a tenth to a hundredth of EM (or EM_T).

The various contributions to EM have been discussed in detail in the literature. In an in depth analysis of the effects of ring strain on cyclisation efficiency, Galli and Mandolini separated EM (and EM_T) into enthalpic and entropic contributions (**Equations 11** and **12**); for EM, these can be further

broken down into $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ (where these represent the differences in the activation parameters for intra *versus* intermolecular reaction), while for EM_T the relevant quantities are $\Delta\Delta H$ and $\Delta\Delta S$.

$$EM = EM_S \cdot EM_H = \exp[-(\Delta H^{\ddagger}_{intra} - \Delta H^{\ddagger}_{inter})/RT] \cdot \exp[(\Delta S^{\ddagger}_{intra} - \Delta S^{\ddagger}_{inter})/R] \quad (\mathbf{11})$$

$$EM_T = EM_{S,T} \cdot EM_{H,T} = \exp[-(\Delta H_{intra} - \Delta H_{inter})/RT] \cdot \exp[(\Delta S_{intra} - \Delta S_{inter})/R] \quad (\mathbf{12})$$

Intramolecularity can accelerate chemical reactions by bringing the reacting groups together. The entropic cost of an intramolecular reaction should be considerably less than that of the corresponding intermolecular reaction; if the loss of rotational entropy for the (otherwise free to rotate) bonds frozen is less than the translational and rotational entropy of a molecule of substrate, the intramolecular reaction is entropically favorable. For most cyclizations, this will be the case. The enthalpic demands of cyclisation can be acceptable (if strain in the acyclic compound is relieved) or unfavorable (if strain is introduced). The advantage of intramolecularity therefore depends on the entropic and enthalpic costs of cyclisation *versus* oligomerisation. Through empirical studies, Mandolini and co-workers have shown that EM_T can be estimated in a relatively straightforward manner from the strain energy of the product cycloalkene (the enthalpic consequences, **Equation 13**) and the number of rotors frozen (r) (the entropic consequences, **Equation 14**).[111] In rings comprising *ca.* 3 – 10 members the entropy of rotation of the bonds is lost (*ca.* 4 cal K^{-1} mol^{-1} per rotor, as determined by averaging over a large number of systems);[150] for larger, more flexible rings, this penalty is less. For comparison, the estimated loss of entropy for a bimolecular reaction (e.g. oligomerisation) is *ca.* 30 – 50 cal K^{-1} mol^{1}.

$$\Delta\Delta H = -(\Delta H_{intra} - \Delta H_{inter}) \approx H_{strain} \quad (\mathbf{13})$$

$$\Delta\Delta S = (30 - 4r) \text{ cal } K^{-1} \text{ mol}^{-1} \quad (\mathbf{14})$$

There are very few measured EMs for RCM reactions. Percy and co-workers quantified EM for the RCM of substrates **45**-**48** to form cyclooctenones **49**-**52** using a series of synthetic experiments, in which the RCM reactions of several substrates were conducted at a range of initial

substrate concentrations for a fixed period of time (**Scheme 18**, above).[83] Kinetic EMs were quantified from the ratio of cyclic product to cross-metathesis product over a range of concentrations of these reactions (i.e. the rate at which cyclisation occurs with respect to cross-metathesis). Two key conditions were met; firstly, the reactions were shown to be effectively irreversible, as exposing the eight-membered ring products to the pre-catalyst at higher concentration did not result in ring-opening to form oligomeric material. Secondly, it is known that all steps up to propagating carbene formation are common to both the cyclisation and oligomerisation pathways (see **Schemes 2** and **51**) and so the reaction of the propagating carbene is product-determining, although two different propagating carbenes can form which may have different reactivity. The ratio of intra- to intermolecular product yields an expression which can be rearranged to allow EM to be determined from a linear plot of [cycloalkene]/[oligomer] versus the reciprocal of initial diene concentration (**Equation 13**; [**130**] = [**130a**] + [**130b**] and **Figure 27**).

[Please insert Scheme51]

Scheme 51. Determination of EM for an RCM reaction; L = SIMes.[83]

$$[\text{cycloalkene}]/[\text{oligomer}] = k_{intra}\cdot[\mathbf{130}]/k_{inter}\cdot[\mathbf{130}][\text{diene}] = k_{intra}/(k_{inter}\cdot[\text{diene}]) = \text{EM} / [\text{diene}] \qquad (\mathbf{13})$$

[Please insert Figure27]

Figure 27. Determination of EM for **49** (R' = Bz; triangles), **51** (R' = Bn; diamonds) and **52** (R' = H; circles) (R = H for all three) by conducting reactions at a range of concentrations.[83]

EM has also been determined for a related system, in which cyclisation was achieved using an RRCM strategy (**Scheme 52**).[135] Competing intermolecular reaction of the intermediate carbene stripped the RRCM fragment, yielding **131** as a by-product. The EM was measured at 0.14 mmol L^{-1}, three orders of magnitude lower than for formation of the analogous disubstituted cyclooctenone.

[Please insert Scheme52]

Scheme 52. Determination of EM for RCM to form a trisubstituted alkene.[135]

This treatment of data is not universally applicable, as it requires that the observed product ratio is the kinetic ratio of products, not the thermodynamic ratio; if there is inter-conversion between reaction products then the observed product distribution does not reflect $k_{intra}/(k_{inter}$[diene]) and the treatment does not hold. For reactions that are under thermodynamic control, alternative approaches must be used. Chemists at Boehringer-Ingelheim have prepared HCV protease inhibitor using an RCM reaction as a key step (**Scheme 53**).[96,120,121,151] The first generation process involved RCM of substrate **132** (at *ca.* 14 mmol L^{-1}) using 3 mol% **GH1** in toluene at 353 K,[120,121] but the high dilution rendered this process difficult to scale up. The EM of analogous substrate **56** was quantified using the method of Percy described above, and was found to be 46 mmol L^{-1} (at 313 K in DCM).[151] Quantification was achieved by analysis of the crude reaction mixture after work-up, but the results were sufficient to establish that reaction conditions well below 50 mmol L^{-1} were needed to obtain the desired macrocyclic product **134** selectively.

[Please insert Scheme53]

Scheme 53. Synthesis of a macrocycle *en route* to a HCV protease inhibitor.[120,121,151]

Changes to the metathesis step could not be assessed by quantifying the kinetic EM using the established method, as the pre-catalyst was changed to **Gr2**, which operates in the thermodynamic regime rather than the kinetic regime; under such conditions, the product ratio does not necessarily reflect the relative *rates* of cyclisation and oligomerisation, as these products can interconvert. Instead, the ~~*modified* *Modified* *thermodynamic* *e*~~*Effective* ~~*molarity*~~ *Molarity* (MEM_T) was quantified; ~~which~~ this quantity is the square of EM_T, divided by EM_T of the cyclic dimer.[152] ~~represents the thermodynamic effective molarity of the cycloalkene *versus* that of its dimer,~~[152] ~~was quantified, providing a~~This quantit~~ative~~y was used as a metric for cyclisation efficiency but it cannot be compared with other efficiency metrics from the literature. The cyclisation of **56** proceeded in toluene at 333 K (with 3 mol% **GH1**) with MEM_T of 0.096 mol L^{-1}. Substrate **57**, in which the

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cyclopropylamide functionality was protected as the corresponding *tert*-butyl carbamate (BOC), underwent RCM (0.2 mol L^{-1} in toluene at 60°C with 0.1 mol% **Gr2)** to form **135**; MEM_T was found to be 1.85 mol L^{-1}. A further increase in the reaction temperature (to 383 K) increased MEM_T to 2.56 mol L^{-1}. The considerable difference in MEM_T between substrates was attributed to the calculated reduced strain energy of the BOC-protected product, with respect to the diene;[96] i.e. protection of the nitrogen decreases H_{strain} and therefore increases the MEM_T of the desired product.

As MEM_T lacks a clear practical meaning for synthetic chemists, ~~and therefore~~ the use of EM_T is preferable as this indicates the necessary concentration regime. Few MEM_T values have been measured, making it difficult to put these measured values into any context. A method for determining EM_T from reactions under thermodynamic control has been developed by Mandolini and co-workers during their studies of cyclophane synthesis.[153] Conducting a reaction with various initial effective monomer concentrations and plotting the concentration of each size of product ring yields curves which reach a maximum at EM_T, so a parabolic function can be used to estimate this value.

Percy has used this method to quantify the EM_T of the cyclizations of two prototypical dienes by RCM (**Scheme 54**).[104] Reactions were conducted over a range of concentrations and the relative proportions of the products were quantified by ^1H NMR spectroscopy. In two cases (1,6-hepadiene and 1,8-nonadiene to cyclopentene and cycloheptene, respectively), EM_T could be obtained using this method. In the latter case, isomerization-RCM processes removed material from the equilibrium due to the formation of cyclohexene, which does not undergo ring-opening in metathesis reactions.[154] Therefore, a plot of [cyclopentene] versus $[1,6\text{-heptadiene}]_0$ yielded EM_T (cyclopentene) = 538 mmol L^{-1}, while a plot of [cycloheptene] versus ($[1,8\text{-nonadiene}]_0$ – [cyclohexene]) yielded EM_T (cycloheptene) = 53 mmol L^{-1} (**Figure 28**). This method for quantifying EM_T therefore has potential benefits in metathesis chemistry: if a series of RCM reactions are carried out at different concentrations, the maximum practical reaction concentration can be identified; if a synthetic preparation of cyclopentene or cycloheptene was desired, the reaction should be conducted at ca. 5 mmol L^{-1} or 0.5 mmol L^{-1} respectively, to ensure 100:1 selectivity for the cycloalkene over oligomer. For other ring systems, EM_T could be estimated (cyclohexene, >> 4 mol L^{-1}; *cis*-cyclooctene, 0.1 – 1 mmol L^1; *cis*-cyclononene and *cis*-cyclodecene, < 0.1 mmol L^{-1}). Often, during synthetic campaigns,

the reaction concentration is selected by trial and error, rather than being selected from consideration of measured EMs, and multiple parameters may be changed simultaneously. In addition, if EM_T determination (or, at least, estimation) were to become routine in ring-closing metathesis studies, quantitative insight into the effect of different substrate structural features could be accumulated.

[Please insert Scheme54]

Scheme 54. Prototypical diene substrates studied by Percy and co-workers.[104]

[Please insert Figure28]

Figure 28. Concentrations of (a) cyclopentene in the RCM reactions of 1,6-heptadiene (0.025 – 3 mol L^{-1}) and (b) cycloheptene in the RCM reactions of 1,8-nonadiene after 18 hours at 298 K with 3 mol% **G2** in chloroform-*d* (black) or DCM-d_2 (grey).[104]

4. Tools for studying catalytic metathesis

A broad range of techniques have been applied to the study of alkene metathesis reactions. These have been both experimental and theoretical in nature, and include detailed NMR spectroscopic studies, mass spectrometry studies, and quantitative time-resolved studies. The study of metathesis has gained significant benefits from the increasing computational power available to theoretical chemists, which have allowed complete systems to be modelled at appropriate levels of theory that render the results consistent with experiment. However, further challenges exist for the quantitative study of metathesis chemistry.

4.1 Experimental Methods

4.1.1 NMR Spectroscopy

NMR spectroscopy has been used extensively for the study of metathesis reactions. Some selected examples of key techniques and their application are briefly described here. Applications can be divided into three broad categories: (i) NMR for the characterization of reaction products, and most interestingly for the deconvolution of complex mixtures; (ii) NMR for the collection of concentration/time profiles for reactions; and (iii) NMR for the measurement of rates of dynamic processes, typically under cryogenic conditions.

4.1.1.1 NMR Spectroscopy for Characterization

The characterization of the reaction products from metathesis reactions is not always straightforward. While the small molecule products of CM and RCM can typically be identified and characterized using standard NMR techniques (e.g. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectroscopy), and 2D techniques such as [^{1}H, ^{1}H] COSY and [^{1}H, ^{13}C] HSQC),[155] the deconvolution of complex mixtures remains challenging. Metathesis of dienes can yield the RCM product, CM product, linear oligomers or cyclic oligomers, or a mixture of all four plus the starting material. Many of these species will have similar NMR spectra, depending on the structure of the starting material used.

More advanced techniques have been used effectively. Fogg has applied DOSY (diffusion-ordered spectroscopy)[156] to separate the ^{1}H NMR signals for cyclic product and cyclic dimer in model RCM reactions such as that illustrated in **Scheme 55**.[157] ^{1}H DOSY NMR resolves signals based on their diffusion co-efficient; one dimension of the resulting 2D spectra is the ^{1}H NMR spectrum, while the other is the diffusion co-efficient (a time-bound parameter), which is related to molecular weight. Later, Sliwa showed that the same technique could be applied to discriminate between cyclic monomer and dimer products of the RCM reactions of some β-lactam-containing substrates.[158]

[Please insert Scheme55]

Scheme 55. DOSY studies of a model RCM reaction.[157]

However, this approach only works where signals for each component are suitably resolved; for overlapping signals, an *average* of the diffusion coefficients will be obtained. This can in theory be mitigated by the use of so-called 'pure-shift' DOSY, in which the J_{HH} coupling is suppressed;[159,160] in this case, all ^{1}H NMR signals are singlets and the resolution of signals for different products in the mixture might be better resolved. However, we are unaware of this having been deployed to study RCM reactions, at the time of writing. In addition, Morris and co-workers have published a method for estimating molecular weight based on the diffusion coefficient in a number of common solvents, which could potentially be used to identify the size of oligomers in RCM reactions, although this has not yet been achieved.[161]

Percy and co-workers have used 2D [^{1}H, ^{13}C] HSQC-TOCSY and 1D ^{1}H TOCSY experiments to probe the composition of reaction mixtures derived from the metathesis of prototypical diene substrates in which many of the components exhibited overlapping signals (see **Scheme 54** above).[104] The former technique comprises an [^{1}H, ^{13}C] HSQC spectrum in which cross-peaks are observed between all carbons and *J*-coupled protons in that spin system. In the Percy example, species corresponding to diene, linear oligomer (i.e. bearing terminal and internal alkenes) and cyclic oligomer, with internal alkenyl protons only, could be observed (**Figure 29**). Signals at *ca.* 5.0 and 5.85 ppm in the ^{1}H NMR spectrum correspond to terminal alkenyl protons, while signals at *ca.* 5.45 ppm correspond to internal alkenes. Looking down the ordinate at 5.45 ppm clearly shows the presence of products which only contain internal alkenes. Less time-consuming 1D ^{1}H TOCSY experiments also confirmed the presence of these species; selective irradiation of key signals yielded ^{1}H NMR spectra of the component to which that proton belonged. These techniques do not provide any information on the approximate size of these species, however, and simply confirm their presence.

[Please insert Figure29_color or Figure29_bw]

Figure 29. Partial [^{1}H, ^{13}C] HSQC-TOCSY NMR analysis of a reaction mixture derived from the metathesis of 1,7-heptadiene; the ^{1}H NMR spectrum is at the top.

4.1.1.2 NMR Spectroscopy for Kinetic Studies

NMR spectroscopy is the pre-eminent analytical technique for the study of alkene metathesis reactions, due in part to the fact that metathesis pre-catalysts, substrates and products (with the exception of polymer side products) are typically very soluble in NMR solvents such as chloroform-*d*, DCM-d_2, benzene-d_6, toluene-d_8 and THF-d_8. This allows for a degree of speciation and quantification of multiple components that cannot be achieved with techniques such as GC and UV/visible spectroscopy, which are most often best suited to the observation of organic and inorganic components respectively, depending on the structure of the substrate. Organic products can typically be identified and quantified *via* characteristic signals, particularly for the alkene moieties. Alkylidene species can be profiled *via* their signals in the low field region of the NMR spectrum (*ca*. 16 to 22 ppm). At lower temperatures, metallacyclobutane species can be identified and quantified (*vide infra*); to date 14e$^-$ carbene complexes of the form $[RuCl_2(L)(=CR_2)]$ (L = NHC or phosphine) have yet to be identified, with the exception of $[RuCl_2(L)(=CHPR_3][X]$-type complexes prepared by Piers, where the alkylidene moiety bears a bulky phosphonium substituent.[162]

NMR kinetic experiments using ^1H and ^{31}P nuclides have been routinely employed to measure the initiation rate of pre-catalysts bearing phosphine ligands. Pre-catalyst quenching experiments with ethyl vinyl ether can be monitored by ^1H NMR spectroscopy over time, which provides a measure of initiation rate when phosphine dissociation is rate-determining (i.e. second generation complexes) (see section 2 for a fuller discussion of the initiation rate of key metathesis pre-catalysts).

Concentration/time profiles for reactions are usually collected using NMR spectroscopy; a range of participant species can be profiled depending on the shift range selected for the experiment. Such profiles can be used in various ways, from the assessment of catalyst performance[24] to the exploration of the effects of substrate structure on reactivity,[115] all without perturbation of the reaction mixture. In addition, Percy and co-workers have used NMR kinetic experiments to investigate deleterious isomerization side reactions;[57,163] importantly, the concentrations of substrate and products could be monitored at the same time as the concentrations of pre-catalyst, and phosphane-bound methylidene, ethylidene and ruthenium hydride species (*via* characteristic signals in the low field

region, *ca.* 16 – 20 ppm). While these kinetic studies are typically straightforward to conduct, a suitably long interpulse delay (T_1 for alkenes is often 5 – 7 s) and robust internal standardization are usually necessary to ensure accurate quantification and to check for mass balance,[115] with the latter being particularly important where longer chain insoluble oligomers or polymers might form. In addition, the full interpretation and interrogation of the resulting kinetic data remains a key challenge, as data often does not fit to a simple kinetic order.[105]

The presence of ethene in the reaction mixtures presents a serious challenge in the study of metathesis reactions. As metathesis mediated by modern pre-catalysts is under thermodynamic control,[104] the presence of ethene can affect the rate and degree of substrate conversion. While some studies state clearly that the reactions are carried out in closed vessels,[24] the rate of ethene egress may vary considerably depending on the size and shape of the reaction vessel. Even in NMR tubes with pierced caps, the rate of ethene egress is slow, and ethene is found to accumulate in solution to levels where it might reasonably compete with alkene substrates.[115] Fogg has provided evidence that ethene inhibits the reaction of the active methylidene species with the alkoxystyrene ligand in reactions catalyzed by **GH2**, thereby leading to accelerated catalyst decomposition.[61] RCM reactions of diethyl diallylmalonate conducted in sealed tubes led to a marked increase in decomposition with respect to the same reactions carried out where ethene may escape the vessel. Methylidene complexes are considerably more fragile than complexes such as ruthenium benzylidene species.[50] Finding elegant ways in which to treat ethene in kinetic studies are key to the development of the next generation of kinetic studies of metathesis. Its involvement in many processes in reaction mixtures, from formation of low energy MCBs that might protect or sequester the ruthenium catalyst, to its potential to render key steps such as alkylidene transfer reversible, make its role in alkene metathesis very complex. Useful approaches to dealing with ethene in kinetic studies might be, for example, through the expedient removal of ethene from the reaction, as egress is slow even from open vessels. Alternatively, and perhaps more elegantly, accounting for the physical and chemical processes in which it participates would enhance our understanding of the kinetics of alkene metathesis.

4.1.1.3 NMR Spectroscopy for Dynamic Processes

While various NMR techniques have been used for the characterization of reaction products and the profiling of reaction mixtures over time, different techniques have been used to monitor dynamic processes that occur during metathesis reactions. While many intermediate species have not yet been detected by NMR spectroscopy (e.g. 14e$^-$ ruthenium carbenes, as mentioned above), the study of exchange processes can be used to infer their existence.

Grubbs and co-workers, and Nolan and co-workers, have used magnetization transfer experiments (such as ^{31}P EXSY, or the DANTE pulse sequence) to measure the rate at which free phosphine is exchanged with the phosphine bound to the ruthenium center.[29,43] The signal for the free phosphine is selectively irradiated, and spectra are acquired after a range of different mixing times. The relative sizes of the peaks for free and bound phosphine can be used to calculate the rate of exchange. As *ca*. 1.5 equiv. of the former is present in solution, the rate determining step ought to be dissociation of the phosphine from the complex. While the intermediate 14e$^-$ carbene complex (e.g. [$RuCl_2(PCy_3)$(=CHPh)]) is not actually observed due to the free energy difference between 14e$^-$ and 16e$^-$ carbenes, the rate of its formation can be measured using these NMR techniques. Alternative methods of measuring the phosphine dissociation rate typically involve reactions with ethyl vinyl ether, in which the phosphine dissociation event is usually rate-determining, but dynamic techniques are far more straightforward to carry out.

2D [^{1}H, ^{1}H] EXSY and ROESY experiments have been used to explore dynamic processes including the degenerate exchange of ethene or other alkenes in metallacyclobutanes at low temperatures (*ca.* – 50 °C). These processes proceed *via* retro[2+2]cycloaddition, rotation of the η^2-bound alkene, and then [2+2]cycloaddition to form an MCB. Rate constants have been determined for these exchange processes, despite the fact that the intermediate η^2-complexes are unobservable by NMR spectroscopy; in addition, exchange rates can even be measured for reactions that simply re-form the starting material (i.e. degenerate processes). For example, Piers and Grubbs have generated MCBs **137** and **138** from complexes such as **Piers1** and **136**, showing that the NHC structure influences the exchange rate (**Scheme 56 (a)**).[164,165] Later studies explored exchange in more substituted MCBs and in complexes with various unsymmetrical NHCs (**Scheme 56 (b)**).[166,167]

[Please insert Scheme56_color or Scheme56_bw]

Scheme 56. Studies of MCBs using low temperature [^{1}H, ^{1}H] EXSY experiments (in DCM-d_2) (DEP = 2,6-diethylphenyl, DIPP = 2,6-di*iso*propylphenyl).[164-166]

Piers and co-workers have also explored portions of the PES for the metathesis of diethyl diallylmalonate, an ubiquitous model substrate for RCM, using these methods.[168,169] Generation of MCB **139** from the reaction of **Piers2** with the cyclopentene product was achieved at low temperatures, allowing various steps of the reaction to be probed (**Scheme 57**). At these low temperatures, many steps were found to be reversible, despite the cyclisation of this substrate being overwhelmingly thermodynamically favorable (and therefore irreversible) at room temperature. While not all species could be characterized and studied (as discussed, 14e$^-$ carbene complexes are not detected by NMR), a considerable number of MCBs could. In addition, the presence of the intermediate 14e$^-$ species could be inferred by the study of processes that must proceed *via* such complexes. A number of equilibrium constants and rate constants were obtained *via* carefully conducted experiments with these *in situ* generated species. For example, the reaction of **139** with ethene allowed determination of the equilibrium constant (*ca.* 300) and therefore of the energy difference between these two MCBs (*ca.* 2 kcal mol^{-1}). The highest barrier that was encountered was for the reaction of methylidene with the substrate to yield the initial MCB complex (*ca*. 16 kcal mol^{-1}). This study was exciting due to the mapping of a PES for an RCM reaction *experimentally*, at a level of detail that would normally require the use of DFT calculations. The only caveat is that these studies were conducted at very low temperatures (*ca*. 220 K), some 50 – 150 K below the temperatures at which synthetic RCM reactions are carried out; for this reason, the authors warned that extrapolation of these results to higher temperature conditions be approached with caution.

[Please insert Scheme57]

Scheme 57. Mapping the PES for diethyl diallylmalonate RCM using low temperature NMR studies (220 K).

4.1.2 Kinetic Studies by Other Methods

Gas chromatography and UV/visible spectroscopy have been used for the study of metathesis reactions. Although these typically do not allow the same degree of detailed speciation as NMR spectroscopy, and may require perturbation of reaction mixtures, these methods have proven useful for certain applications, and are often more practical over very short and over long timescales.

4.1.2.1 Kinetic Studies using UV/Visible Spectroscopy

UV/visible spectroscopy is useful for the monitoring of organometallic species, but is not useful for monitoring the organic component of typical metathesis reactions. Ruthenium species relevant to alkene metathesis are typically very highly colored (red or green) and have molar absorptivities of *ca.* 10^3 L mol^{-1} cm^{-1}.[54,55] This technique has therefore been heavily used for the study of pre-catalyst initiation, where the decrease in the absorbance for the pre-catalyst can be monitored over time and used to obtain rate constants for pre-catalyst initiation with different complexes, substrates, or in different solvents.

Various researchers have used UV/visible spectroscopy to acquire initiation rate data. Grubbs and co-workers measured initiation rates for **G1** and analogues by following the decrease of the absorbance for the pre-catalyst in the presence of a large excess of EVE (*ca.* 750 equiv.);[29] phosphine dissociation is rapid ($t_{1/2}$ typically *ca.* 30 seconds), rendering this reaction too fast to monitor using NMR spectroscopy. Plenio and co-workers, and Percy and co-workers, have used UV/visible spectroscopy to monitor initiation rates for a range of Hoveyda-type pre-catalysts with different substrates, and in different solvents (*vide supra*).[31,37,52,54-56] In some cases, substrate:pre-catalyst ratios were much greater than 10^5:1, yet UV/visible spectroscopy can reliably and accurately monitor low concentrations of (highly absorbing) pre-catalyst species in the presence of a vast excess of substrate.

4.1.2.2 Kinetic Studies using Gas Chromatography

In contrast to UV/visible spectroscopy, GC is not suited to the analysis of catalyst(-derived) species, but can be used for the accurate detection and quantification of organic molecules such as substrates and products from metathesis reactions. GC is therefore an ideal method for conducting kinetic experiments over a number of hours, by withdrawing and quenching aliquots of reaction mixtures. Researchers including Percy and Fogg have used GC to profile reactions.[83,170] In addition, GC can resolve mixtures that NMR cannot, particularly in the case of series of oligomers (with different boiling points) where signals for the chain and end-groups of oligomers of various sizes overlap.[104]

The need to perturb the reaction mixture is a drawback, however. Samples must be taken from the reaction mixture, which has the potential to introduce air and moisture, or perturb the headspace where a population of ethene may have accumulated. The assumption must also be made that the withdrawn aliquot of the reaction mixture is homogenous; for RCM reactions, one must be sure that no insoluble polymer has formed, by using an internal standard to check for mass balance, for example.

A significant potential pitfall when monitoring metathesis reactions by GC is the potential for misleading results arising from incomplete pre-catalyst quenching. Metathesis pre-catalysts are often rather robust, and special measures must be taken to ensure that the pre-catalyst is entirely disabled before the reaction mixture is concentrated. As concentration is a critical factor in metathesis reactions, concentration of active reaction mixtures can lead to misleading results, with the degree of conversion and oligomerisation exaggerated. Percy and co-workers have demonstrated this by comparing treated and untreated aliquots from a reaction which formed a cyclooctenone product (**Figure 30**). Where the aliquots were not treated to disable the active catalyst, a misleading reaction profile was obtained. Fogg and co-workers have claimed that oligomers are *intermediates* in RCM, on the basis of reaction profiles generated using GC analysis, where the populations of oligomer are found to increase rapidly at the start of the reaction and then decrease as cycloalkene is formed;[170] however, these observations must be treated with caution because the aliquots were not quenched before analysis.

[Please insert Figure30]

Figure 30. Conversion/time profiles for the RCM reaction to form **140** with (solid points) and without (open points) quenching of the pre-catalyst before analysis by GC.

4.1.3 Isotopic Labelling Studies

The isotopic labelling of reaction components can be a useful method for the exploration of mechanistic aspects of catalytic reactions.[171] The field of alkene metathesis has seen some applications of this approach, typically to follow the movement of specific moieties during the reaction. Some selected examples of the use of labelling approaches are discussed here.

As discussed above, Fogg has used ^{13}C-labelling to show that the alkoxystyrene ligand of pre-catalysts such as **GH2** returns to the metal center after the metathesis cycle. The use of ^{13}C labels is preferable (where possible) to avoid interference from ruthenium-catalyzed H/D exchange processes.

Wagener has used deuterium-labelled substrates to probe alkene isomerization processes that occur during metathesis reactions.[172] The observation of a 1,2-deuterium shift as well as a 1,3-deuterium shift provided evidence for a metal hydride addition/elimination process as opposed to a π-allylruthenium hydride mechanism, as the latter would be expected to yield a net 1,3-deuterium shift only (**Scheme 58**). In addition, complete deuteration next to the oxygen suggested that this isomerization was irreversible, otherwise H/D exchange at this position would have been expected.

[Please insert Scheme58]

Scheme 58. Probing deleterious isomerization processes using deuterium labelling.[172]

Few kinetic isotope effects (KIEs) have been reported. Ulman studied the metathesis of styrene-d_5 and styrene-d_8 with **G1**; the rates of reaction were 2.15(1) x 10^{-3} and 1.3(4) x 10^{-3} L mol^{-1} s^{-1}, respectively, indicating a KIE (k_H/k_D) of 1.7. This was proposed to be due to the change of hybridization (sp^3 to sp^2) during retro[2+2]cycloaddition of the MCB (**Scheme 59**).

[Please insert Scheme59_color or Scheme59_bw]

Scheme 59. Deuterium KIE for the reaction of **G1** with deuterated styrenes.[69]

4.1.4 Mass Spectrometric Studies

Mass spectrometry (MS) studies have played a key role in the study of metathesis reactions, particularly in the hands of Chen and co-workers, who have identified intermediates in the catalytic cycle,[173] and probed the energetics of their reactions,[27] using electrospray MS techniques. Species such as 14e$^-$ ruthenium carbene complexes can be detected by mass spectrometry;[173] in the presence of different alkene substrates, the different carbene products (from cross metathesis or ROMP, for example) can be detected. Further, the fragments into which any proposed species can be broken by successively higher lens potentials can be used to check the species' structure. In successive and more advanced studies, interpretation of data from the energy-resolved collision induced dissociation (CID) cross-section measurements allowed the construction of potential energy surfaces for some steps of the metathesis reaction.[27] Metathesis pre-catalysts were typically custom-made species, modified with ionic tags, to facilitate detection by MS.

Metzger has also conducted a number of electrospray MS studies, and has probed the reactions of simple diene substrates with **G1**.[174] In these studies, the use of alkali metal adducts avoided the need to synthesize custom pre-catalyst complexes. Of particular interest were the phosphine-bound complexes **141** and the cyclic η^2-complexes **142** which existed in equilibrium in the reactions (**Scheme 60**). The equilibrium position and the rate at which the cyclic η^2-complexes progressed through the catalytic cycle were found to depend on the chain length (i.e. on *n*); species **142c** (*n* = 4) progressed faster than **142b** (*n* = 3) and **142d** (*n* = 5) which progressed at approximately equal rates. Relative ratios were evaluated for chelated **142** to phosphane-bound **141** for *n* = 3 (1:7), *n* = 4 (1:3) and *n* = 5 (1:5). These (albeit surprisingly modest) differences demonstrated that the species **142c** which goes on to form the six-membered ring product (cyclohexene) was both formed more favorably (*versus* the phosphane-bound alkylidene) and progressed more rapidly. Metzger also found that η^2-complex **142a** derived from 1,5-hexadiene was far more favored than **141a**, more so than for the corresponding complexes derived from 1,6-heptadiene; phosphane-bound complex **141a** was

detected at levels ten-fold lower than the corresponding chelated alkylidene **142a** (**Scheme 60**). The interesting case of 1,5-hexadiene was discussed more fully in Section 3.1.2.2.

[Please insert Scheme60]

Scheme 60. ESI-MS studies by Metzger and co-workers.[174]

Of course, all these studies were conducted in the gas-phase, and so solution-phase reactivity may be different. The ability to detect and manipulate species that are unstable or undetectable in solution is incredibly powerful, and has been used to investigate mechanistic aspects of metathesis chemistry. These techniques show further potential for the investigation of structure/activity relationships in metathesis and other catalytic reactions, as they can isolate and study key intermediates such as the alkylidene complexes **142**.

4.1.5 Deconvolution of Kinetic Data

Simple reaction profiling is relatively straightforward for metathesis reactions. Unfortunately, more in-depth analysis of kinetic data from metathesis reactions is more difficult, with data often not following a simple kinetic order.[24] More complex approaches are therefore necessary to gain quantitative information from reaction kinetic data.

One approach involves the use of software that fits concentration/time data to a series of differential equations, where the initial concentrations and approximate values for the rate constants in the model are supplied. The software then adjusts the values of rate constants to obtain the best possible fit of the simulated reaction profile to the supplied data points. Once rate constants are known, concentration/time data can be simulated and predicted under different reaction conditions.

Adjiman and co-workers attempted to use reaction simulation approach to gain additional insight from data acquired for RCM reactions conducted in different solvents. The concentration/time profiles were fitted to a simple model (**Equations 14**-**18**; simulations are shown in **Figure 31**), which considered the initiation (rate constants k_1 and k_{-1} for the forward and reverse reactions), RCM (k_2 and

k_{-2}), and decomposition steps (k_3), using numerical integration software. Decomposition was modelled according to the mechanism presented by Grubbs and co-workers.[50] The values for the rate constants obtained varied widely, while initiation rate values were inconsistent with those measured previously.[29] In most cases, rapid pre-catalyst initiation was suggested (e.g. k_1 (DCM) = 0.0617 s^{-1}), whereas other experimental measurements of initiation rate under the same conditions yielded very different rate constants (e.g. k_1 (DCM) = 1.4 x 10^{-4} s^{-1}).[37] The simulations also predicted complete phosphane dissociation, inconsistent with published experimental and computational findings.

$$(d/dt)[\mathbf{G2}] = -k_1 \cdot [\mathbf{G2}] + k_{-1} \cdot [14e^- \text{ benzylidene}] \cdot [PCy_3] \quad (\mathbf{14})$$

$$(d/dt)[PCy_3] = k_1 \cdot [\mathbf{G2}] - k_{-1} \cdot [14e^- \text{ benzylidene}] \cdot [PCy_3] - k_3 \cdot [14e^- \text{ benzylidene}]^2 \quad (\mathbf{15})$$

$$(d/dt)[14e^- \text{ benzylidene}] = k_1 \cdot [\mathbf{G2}] - k_{-1} \cdot [14e^- \text{ benzylidene}] \cdot [PCy_3] - 2k_3 \cdot [14e^- \text{ benzylidene}]^2 \quad (\mathbf{16})$$

$$(d/dt)[\text{substrate}] = -k_2 \cdot [\text{substrate}] \cdot [14e^- \text{ benzylidene}] + k_2 \cdot [\text{product}] \cdot [14e^- \text{ benzylidene}] \quad (\mathbf{17})$$

$$(d/dt)[\text{product}] = k_2 \cdot [\text{substrate}] \cdot [14e^- \text{ benzylidene}] - k_2 \cdot [\text{product}] \cdot [14e^- \text{ benzylidene}] \quad (\mathbf{18})$$

[Please insert Figure31]

Figure 31. Simulated concentration/time profiles for the RCM of diethyl diallylmalonate (0.1 mol L^{-1}) with 0.4 mol% **G2** in acetic acid (solid black), cyclohexane (dashed black), acetone (solid dark grey), chlorobenzene (dashed dark grey), toluene (solid light grey) and dichloromethane (dashed dark grey).[41]

However, without the constraint introduced by measuring the absolute value of the initiation rate constant in the model, the fitting is too flexible and will force a fit across a wide range of different initial values for the rate constants. Percy and co-workers made progress towards an improved model[105] by measuring the initiation rate and then fixing it in the model, and by altering the differential equations to render initiation irreversible and "decomposition" simply the capture of $14e^-$ methylidene by phosphine.[29] An improved model enabled the RCM of diethyl diallylmalonate to be described across a limited range of concentrations (50 – 120 mmol L^{-1} and 250 – 500 mmol L^{-1}, using

two different sets of rate constants k_{-1}, k_2 and k_{-2}), showing that even a simple model has predictive value when calibrated appropriately. This model was also used to compare the relative rates of RCM (i.e. relative values of k_2 with the same values of k_1 (initiation) and k_3 (decomposition)) of some prototypical substrates (diethyl diallylmalonate, 1,6-heptadiene, 1,7-octadiene; 0.27: 0.59:1.00). The model does suffer from a number of limitations. Kinetic data could be described over wide concentration ranges (the widest range was 250 mmol L^{-1}), and the model cannot describe reactions where oligomeric material also forms. Ethene is not treated at any point in the model, due to the complexities of modelling both the chemical and physical processes in which it is involved. A more detailed and useful kinetic model for RCM remains to be constructed.

Plenio has developed an alternative way in which to treat concentration/time data from RCM reactions mediated by Hoveyda-type complexes.[175] The authors conducted a series of kinetic experiments (at 303 – 323 K in toluene-d_8) using a range of pre-catalysts, at different concentrations, and with different pre-catalyst loadings. Using a detailed and *a priori* mathematical approach, the authors successfully separated values for rate constants for activation (k_{act}), catalysis (k_{cat}) and decomposition (k_{dec}), showing that each was concentration-independent (**Equation 19**).

$$-((d/dt)[\text{substrate}]) / [\text{substrate}] = k_{cat} \cdot [\text{pre-catalyst}]_0 \cdot (k_{act} / (k_{dec} - k_{act})) \cdot (\exp(-k_{act} \cdot t) - \exp(-k_{dec} \cdot t)) \quad (\mathbf{19})$$

Observed differences in the rate of conversion and the final conversion were rationalized using these rate constants; rapidly-initiating pre-catalysts were typically found to lead to more rapid but less complete conversion of the substrate. The concentrations of active catalyst could be inferred from the data treatment, and the relative rates of RCM of several substrates could be quantified (**Figure 32**). However, this model suffers from some of the same drawbacks as the Percy model, namely that the accumulation of ethene is not accounted for and that reactions that do not smoothly form only cycloalkene cannot be described in this way. In addition, RCM is again considered as a single step, with the assumption that ring-closing is much faster than the initial cross-metathesis reaction with the substrate.

[Please insert Figure32]

Figure 32. Relative rates of RCM of several substrates, as measured by Plenio.[175]

The deconvolution of kinetic data, with the aim of quantifying rate constants for important steps, remains a considerable challenge in the quantitative study of metathesis chemistry. Insights into how the rates of key steps of the metathesis mechanism are affected by catalyst and substrate structure are potentially very valuable, and could contribute to the design of reactions and pre-catalysts.

4.2 Computational Approaches: Successes and Challenges

Metathesis chemistry has benefitted greatly from computational studies by a number of researchers, including Cavallo, Hillier, Houk and Truhlar. While an in-depth discussion of all of these studies is beyond the scope of this manuscript, the area has been reviewed relatively recently.[176,177] The present discussion will be limited to a brief discussion of selected examples of successful studies and ongoing challenges. These discussions are divided into: (i) treatment of Ru-P binding; (ii) treatment of the binding of substrates and (iii) MCB formation.

4.2.1 Ruthenium-Phosphine Binding

The initiation event is a key step in the alkene metathesis mechanism, and considerable effort has been expended in attempts to understand it (*vide supra*). Much of the interest in this step was driven by what was seen as the counterintuitive order of initiation rates for **G1** and **G2**; the NHC present in **G2** would be expected to accelerate dissociation of the phosphine due to the *trans* effect, yet it was found that **G2** initiated orders of magnitude *slower* than **G1**. Calculations with functionals such as BP86 and B3LYP often yield energies for phosphine dissociation that are inconsistent with experiment, typically significantly underestimating the energy required for the ligand dissociation.[178,179] Much of this stems from the way in which these functionals treat certain interactions: B3LYP treats medium range interactions (e.g. van der Waals, CH-π interactions) as unfavorable, whereas they are attractive and can lead to significant complex stabilization.

Significant advances in the ability of theoretical chemists to model these steps were obtained thanks to the development of suitable methodology for the description of metal-ligand bonding.[180] The role of non-covalent interactions is key in the binding and release of ligands, and therefore approaches that deal with these interactions are necessary to model these steps appropriately. Three major approaches are used to overcome this issue: (a) the use of a functional such as the Minnesota M06 functionals from the Truhlar group,[181,182] which accounts for these interactions correctly, which has been used by Truhlar, Hillier, *inter alia*; (b) the use of a dispersive correction to a functional such as B3LYP (termed B3LYP-D), introduced by Grimme[183] and also deployed by Solans-Monfort and

Jensen in the study of metathesis;[53,184] (c) the use of a functional such as BP86 to generate geometries, followed by the calculation of energies using M06 suite functionals, which is favored by Cavallo and co-workers.[43] The validity of many of these approaches has been explored using benchmarking studies based on metathesis (pre-)catalyst structures,[154,181,185] often *versus* data generated using high level coupled cluster methods. However, approach (c) may not be the most accurate, as the use of functionals such as B3LYP and BP86 may not reproduce the geometries of complexes in which dispersive interactions influence the structure of the molecule correctly, lowering the value of the energy calculations.

A key illustration of the effect of dispersive interactions is the study conducted by Truhlar on the initiation of **G1** and **G2**, where the bond dissociation energy (BDE) of the Ru-P bond was calculated using various levels of theory (**Table 14**).[179] Only M06-L predicts the order of BDE correctly. When the $RuCl_2$ fragment was removed from the calculations, M06-L predicted the difference in energy to be positive, while B3LYP predicted it to be negative; i.e. B3LYP sees the approach of the phosphine to the ligand sphere as energetically unfavorable, whereas M06-L sees this as favorable, in line with experiment. The energies obtained by Truhlar for the dissociation of phosphine from **G2** are consistent with those obtained experimentally from mass spectrometric studies carried out by Truhlar and co-workers.

Table 14. The energetics of **G1** and **G2**, calculated by Truhlar and co-workers.[179]

Method	**BDE (G1) (kcal mol^{-1})**	**BDE (G2) (kcal mol^{-1})**	**ΔBDE (kcal mol^{-1})**
Experiment			-3.4(2.0)
M06-L/TZQ	36.1	40.2	-4.1
M06-L/DZQ	41.7	45.2	-3.5
B3LYP/DZQ	19.0	17.4	1.6
BP86/DZQ	20.0	18.8	1.2
PW91/DZQ	26.1	25.7	0.4

Jensen has carried out detailed studies on the dissociation of phosphine from metathesis pre-catalysts, using BLYP-D-CP (with Grimme's dispersion corrections and counterpoise correction, to reduce basis set superposition error).[184] This functional was selected after a brief benchmarking study. Relaxed potential-energy surface scans were carried out, where the ruthenium-phosphorus distances in complexes **3** and **8** were stepped in increments (**Figure 33**). Maxima were observed at *ca.* 4 Å, which were used to obtain optimized structures for transition states with Ru-P distances of 3.95 Å (for **3**) and 3.97 Å (for **8**), and concomitant benzylidene rotation. Weakly-bound complexes resulted from dissociation, with Ru-P distances of 5 – 7 Å. Notably, there existed a significant difference in energy between the dissociation transition state and the infinitely-separated products (*ca.* 15 – 16 kcal mol^{-1}), and therefore the association of phosphine is *not* barrierless.

[Please insert Figure33]

Figure 33. Complexes studied by Jensen.

4.2.2 Binding of Alkenes

The binding and release of alkene substrates is a critical step in the metathesis mechanism. A key question was whether η^2-complexes and related MCBs are 'side bound' (*via cis*-dichloro intermediates) or 'bottom bound' (*via trans*-dichloro intermediates) (e.g. **Figure 34**). Cavallo used DFT calculations (B3LYP and BP86) to explore this topic, suggesting that the geometry depended strongly on a number of steric and electronic factors, with bulkier ligands favoring the bottom-bound geometry.[186] A later study by Goddard and co-workers considered potential energy profiles for the metathesis of *E*- and *Z*-2-butene using both B3LYP and M06 functionals.[128] Goddard concluded that *cis*-dichloro (bottom-bound) intermediates were favored throughout. In addition, it was noted that B3LYP treated the binding of alkenes incorrectly, finding this process to be endothermic (by 2.9 and 4.6 kcal mol^{-1} for *Z*- and *E*-2-butene, respectively), while experiment has shown that this process is in

fact *exothermic*.[27] M06 fared better, showing the binding of *Z*- and *E*-2-butene to be exothermic by 13.6 and 13.8 kcal mol^{-1}, respectively, due to its better treatment of medium-range interactions.

[Please insert Figure34]

Figure 34. Comparison of *cis*- and *trans*-dichloro intermediates.

As revealed by Sanford, second-generation complexes have a far greater affinity for alkene over phosphine compared to first-generation analogues;[29] despite their lower initiation rate, the former complexes are much more likely to engage in productive metathesis. Straub has investigated the difference in reactivity of $14e^-$ methylidene complexes derived from **G1** and **G2** with alkenes using DFT methods (at the B3LYP/LACV3P**+ level of theory) by modelling the potential conformers for the methylidene-ethene η^2-complexes (**Figure 35**).[187] Of the four possible conformers, only one is reactive and can lead on to a MCB. In this reactive conformer, the methylidene protons are in the Cl-Ru-Cl plane, and the ethene is aligned parallel to the methylidene for reaction to occur. Straub discovered *via* DFT calculations that the energetics of these η^2-complexes were quite different in first- (L = PCy_3) and second-generation (L = SIMes) systems; the latter system favored the reactive conformer more than the former. This is in agreement with the known greater reactivity of **G2** with alkenes compared to **G1**; if the binding of alkene to the metal center is more likely to result in metathesis, then this would manifest as a change in the apparent selectivity for alkene over phosphane.

[Please insert Figure35_color or Figure35_bw]

Figure 35. The four conformers of the complex between methylidene and ethene;[187] relative energies are in kcal mol^{-1} using the B3LYP density functional.

The release of alkene has also been postulated to be a key step in the metathesis mechanism. Solans-Monfort and co-workers studied the mechanism of the initiation of complexes such as **GH2**, and revealed that the barrier for release of the alkoxystyrene ligand was considerable (**Scheme 61**).[53]

Later studies by Hillier and co-workers suggested that this was related to the need for concomitant rotation of the alkylidene ligand.[31] It is therefore important to survey all steps of the catalytic cycle, as many steps present barriers that may affect the overall rate of reaction.

[Please insert Scheme61]

Scheme 61. Release of alkene ligands during initiation of Hoveyda-type complexes; energies are relative to pre-catalyst plus *N*,*N*-diallylmethanesulfonamide starting material.[53]

4.2.3 Calculation of Reaction Profiles

Several researchers have sought to produce reaction profiles in order to explore mechanistic aspects and structure/activity relationships in metathesis chemistry. These can be broadly divided into studies of catalyst structure and substrate structure. Selected examples are provided here, as a detailed discussion of all DFT studies is beyond the scope of this manuscript.

Cavallo and co-workers have assessed various catalyst motifs using DFT methods. The IPr*-bearing complex **143** reported by Nolan (**Figure 36**),[188] was studied *in silico* and compared to the IPr analogue **144**.[189] The bulky ligand was found to reduce the phosphine dissociation rate, but favor other steps in the initiation reaction with ethene to form the methylidene, such as the dissociation of bulkier alkenes. Other studies have considered species such as **145**, which have not been prepared experimentally.[190]

[Please insert Figure36]

Figure 36. Complexes studied by DFT calculations.[189,190]

In terms of assessing the effect of substrate structure on reactivity, Hillier and Percy have conducted one of the few detailed theoretical studies on how specific structural modifications influence the PES.[191] In this study, the RCM reactions of simple dienes with **G2** (or **GH2**; the initiation was not considered) to form cyclopentene, cyclohexene, cycloheptene, *cis*-cyclooctene, *cis*-

cyclononene and *cis*-cyclodecene were investigated using the M06-L density functional (**Figure 37**). Detailed conformational analyses were conducted, so that the most appropriate conformations were modelled throughout the PES. PESs were presented for each substrate, from the methylidene plus substrate to methylidene plus product. The profiles for the synthesis of *cis*-cyclononene and *cis*-cyclodecene were rather high in energy, in agreement with experimental observations that these products do not form, even at very low concentrations.[104] The profile for *cis*-cyclooctene synthesis involved relatively high energy intermediates, in agreement with this reaction not proceeding fast enough to be monitored by kinetic experiments.[115] However, there were places where experiment and theory did not appear to agree closely, for example, in details of the RCM to form 5-7 membered rings. [115] MCB breakdown appears to present the highest barrier on the PES, yet this barrier is smaller for cycloheptene than for cyclohexene, even though the former is slower to form. The PES suggests that cyclopentene formation ought to be very slow, due to the especially low energy of the cyclic η^2-complex and high barrier for MCB breakdown, yet it forms almost as fast as cyclohexene. The overall equilibrium constant for ring-formation may also play a role; as has been shown, the overall thermodynamic efficiency of ring closing varies significantly.[104] Clearly, further studies are necessary to harmonize theory and experiment, and before DFT can be used effectively to rationalize and especially predict the rates of RCM reactions.

[Please insert Figure37]

Figure 37. PESs for RCM of simple α,ω-dienes; numbers in the legend refer to the final ring size (cyclopentene to *cis*-cyclodecene).[191]

4.2.4 Future Directions

While studies of mechanism in alkene metathesis have been conducted by a number of researchers, the quantitative exploration of structure/activity relationships is relatively rare.

With the increasing availability and decreasing cost of computer power, the evaluation of a range of structural motifs is achievable. Jensen has carried out QSAR studies, using the B3LYP

functional to model metathesis reactions mediated by a range of complexes.[192] However, this information appears to have yet to be acted upon, suggesting important future roles for the synergistic application of experimental and theoretical methods. Much work at present is conducted by experimental and theoretical chemists working almost in isolation, yet more integrated ways of working can potentially bring benefits to the field.

The study of the initiation of Hoveyda-type complexes has been hampered by the issues involved in treating the entropy of intermolecular reactions. Opinions differ on the best way to treat this issue, with some researchers preferring to consider a 'pre-activated' complex in which the two reactants are present in the same initial DFT calculation,[31,55] while others prefer to treat the two reagents at infinite separation.[53] Calculations of the thermodynamics of ring-closing have met similar issues, with a correction being required to calibrate DFT data (using experimental EM data) to obtain sensible EM values.[104] When no such correction is applied, DFT calculations significantly overestimate the energetic benefits of ring closure, and thus overestimate EM.

The utility of computational studies may be somewhat limited by the study of simple static intermediates and transition states on the PES. The increasing power of computers makes the study of dynamic processes more achievable, although this still requires expending considerable computational time. Cavallo and co-workers recently studied the flexibility of NHC ligands in intermediates on the catalytic cycle for alkene metathesis, and how this is affected by the structure of the *N*-substituents and backbone substituents of the NHC.[193] Different NHCs led to different distributions of $\%V_{bur}$ in the various intermediates. The challenge still remains to correlate this to experimentally-observed catalytic activity.

5. Summary and Outlook

In summary, we have presented and discussed selected examples of (predominantly experimental) studies of how structure can affect reactivity, broadly divided into how pre-catalyst structure affects the rate of delivery of the active catalyst into solution, and how the structure of the substrate affects its reactivity in alkene metathesis reactions.

Our understanding of the initiation mechanisms for the two most common categories of ruthenium-based metathesis pre-catalyst, namely heteroleptic NHC/phosphine ruthenium benzylidenes or indenylidenes, and Hoveyda-type complexes bearing a chelating ether ligand, is now relatively advanced. In particular, the last few years have seen this area receive the focus it is due. Phosphine-bearing complexes must typically dissociate a phosphine first, before the alkene can co-ordinate, although an exception to this general rule is known. In contrast, Hoveyda-type complexes typically involve ligand exchange with some concerted character, although for some pre-catalysts some dissociative character can also exist.

The vast body of synthetic literature has allowed us to develop broad and general guidelines for the reactivity of alkene metathesis substrates. Based on the substitution pattern of substrates, it is now possible to identify potential challenges, and understand the movement of the metal center during the reaction.

An exciting range of tools has been brought to bear in the study of alkene metathesis, both theoretical and experimental. Metathesis as an area has benefitted immensely from the development of new and more useful density functionals, the use of high field/low temperature NMR spectroscopy, and the development of mass spectrometric techniques.

While synthetic chemists have applied metathesis in an extraordinary range of fascinating and useful transformations to prepare a spectacular diversity of molecules and materials, our quantitative knowledge of structure/activity relationships is still relatively limited. There are also many dimensions to many of these relationships; reactivity in alkene metathesis does not depend simply and independently on catalyst or substrate structure, but often requires correctly matching of attributes and properties. There is no single ‘best’ metathesis catalyst; rapid initiators work best at lower

temperatures yet slow initiating complexes are favored for high temperature reactions. While pre-catalysts with bulky NHC ligands appear to be most active for less hindered substrates, those with less bulky NHCs have been shown to be best for the synthesis of tri- and tetrasubstituted alkenes. The pioneering work of many researchers who make catalysts (Grubbs, Hoveyda, Nolan, Cazin, Blechert, Grela, Slugovc, Verpoort, Mauduit and Fogg, to name a selection) has provided us with a wonderful palette of metathesis catalysts, but it is only through detailed and persistent analysis and quantification that the interplay of structure and reactivity in alkene metathesis can be revealed, allowing the intelligent design of reaction systems and the selection of reaction conditions. There is much to be done, and physical organic chemists have a key role to play.

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