New Insights into Decomposition of Metathesis-Active Methylidenes

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Abstract

Olefin metathesis is one of the most powerful tools in current use for the assembly of carbon-carbon bonds. The advent of easily-handled ruthenium catalysts, along with new awareness of ring-closing metathesis (RCM), led to widespread adoption of metathesis methodologies in synthetic organic chemistry. Relative robustness to air and water, and tolerance for an impressive range of functional groups, is attested to by the recent appearance of RCM in pharmaceutical manufacturing processes. However, challenges remain, particularly with respect to the ease with which these catalysts undergo loss of the critical Ru=CHR functionality that enables metathesis. This limits not only metathesis productivity, but also selectivity, because the Ru products can promote unwanted C=C migration reactions. Many decomposition pathways have been found to culminate in activation of the N-heterocyclic carbene (NHC; most typically an H2IMes) ligand. In consequence, NHC truncation is a widely accepted design solution. This thesis work was aimed at assessing the validity of this proposition from several perspectives.

Hundreds of metathesis catalysts are now known, but the second-generation Grubbs catalyst (GII) is still most widely used. This work began with examining the role of Lewis bases in promoting decomposition of the second-generation Grubbs catalyst, RuCl₂(H₂IMes)(PCy₃)(=CHPh) GII, under conditions of metathesis. Small Lewis donors, ranging from pyridine and DMSO to THF and water, were shown to greatly accelerate loss of the methylidene ([Ru]=CH₂) ligand. Associative donor binding was shown to promote dissociation of PCy₃, a powerful nucleophile which then attacks at the methylidene carbon. Attempts to probe the reversibility of this step revealed no reformation of the [Ru]=CH₂ unit, suggesting that nucleophilic attack to form a [Ru]–CH₂PCy₃⁺ moiety is the key decomposition event. Ensuing C-H activation of a ligand (e.g. the o-methyl of H₂Mes or IMes), with abstraction of a chloride ligand, results in elimination of [MePCy₃]Cl. Two potential preventative measures were examined. These involved, first, the use of phosphine scavengers to intercept the liberated PCy₃ ligand during metathesis, and second, truncation of an N-mesityl group to N-methyl to inhibit C-H activation. While phosphine scavenging proved somewhat successful in increasing metathesis yields, lower activity was observed for the catalyst with the modified NHC ligand.

The negative impact of a smaller NHC on catalyst activity is of particular interest, given that curtailed NHC bulk has been proposed as the key to improved catalyst robustness, as noted above.
To clarify this issue, truncation of the nitrogen substituents was taken to the extreme by replacing both \(N\)-mesityl groups with \(N\)-methyl. Accordingly, the reaction chemistry of the first-generation Grubbs catalyst, \(\text{RuCl}_2(\text{PCy}_3)_2(=\text{CHPh})\) \(\text{GI}\) with 1,3,4,5-tetramethylimidazol-2-ylidene (IME\(_4\)) was explored. The small size of this NHC ligand precludes access to a stable mono-IME\(_4\) catalyst corresponding to \(\text{GII}\): rather, an initial \(\text{cis-RuCl}_2(\text{IME}_4)_2(=\text{CHPh})\) species is thought to rapidly convert to a highly stable face-bridged dimer, the observed product. The latter complex exhibits minimal catalytic activity, even in the trivial RCM of diethyl diallylmalonate (DDM). Synthesis of the corresponding edge-bridged dimer was accomplished, but activity remained poor. To simulate an active catalyst, IME\(_4\) was added to \(\text{GIm}\). Complete loss of the methyldiene ligand was observed within minutes at RT. Importantly, however, decomposition was traced to rapid bimolecular coupling, with loss of the methyldiene ligand as ethylene, rather than nucleophilic abstraction. Coupling is inhibited for the benzylidene system by the increased steric bulk of [Ru]=CHPh relative to [Ru]=CH\(_2\), a feature well established in more conventional catalyst systems. We conclude that moving from H\(_2\)IMes to a smaller NHC to inhibit C-H activation is not a practical solution for improving catalyst robustness. Rather, catalyst redesign should focus on protecting the [Ru]=CH\(_2\) moiety to prevent loss of the methyldiene ligand via either nucleophilic abstraction or bimolecular coupling.
List of Contributions

Publications (F = Full Paper, C = Communication)


Manuscript in preparation.


Presentations (O = Oral; presenting author in bold)

O5. **S.A. Rufh** and D.E. Fogg “Examining Ligand Truncation as a Design Strategy in Metathesis Catalysts.” 100th Canadian Society for Chemistry Conference, Toronto, ON, May 28 – June 1, 2017


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Nathan Fielder, thank you for the tips on how to stay motivated to complete a task, and for reminding me to think outside the box.
List of Compounds
Organic and main group compounds

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Transition metal complexes

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| H_2Mes-Ru-Pcy_3-Cl |
| GIII     | Cl_{\sigma} & \parallel \]
| Ph-H_2Mes-Ru-py-Cl | GII-I  | Cl_{\sigma} & \parallel \]
| Ph-H_2Mes-Ru-py-PCy_3 |
| HI       | Cl_{\sigma} & \parallel \]
| Cy_3P-Ru-OPr-Cl | HII    | Cl_{\sigma} & \parallel \]
| H_2Mes-Ru-OPr-Cl |
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| Cl_{\sigma} & \parallel \]
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| Cl_{\sigma} & \parallel \]
| DMSO-Ru-DMSO-Cl | Ru-3a  | Cl_{\sigma} & \parallel \]
| Cl_{\sigma} & \parallel \]
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| Ru-3b    | Cl_{\sigma} & \parallel \]
| Cl_{\sigma} & \parallel \]
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| Cl_{\sigma} & \parallel \]
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| Cl_{\sigma} & \parallel \]
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| Cl_{\sigma} & \parallel \]
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1.1 Catalysis

Catalysts play an invaluable role in sustainable chemical manufacturing. As compounds that increase the rate of chemical reactions without being consumed, catalysts are a staple of “green chemistry”.\(^1\) Catalysis routinely enables the construction of new bonds via routes that are energetically demanding to access by stoichiometric means, while eliminating the waste associated with stoichiometric reactions. It is therefore ideally aligned with current global priorities for sustainable processes: reducing the energy required for chemical transformations, and reducing the proportion of waste. High demand for pharmaceuticals and plastics, buttressed by the expanding understanding of organometallic chemistry, has greatly advanced the implementation of transition-metal catalysis in chemical manufacturing over the past several decades. The broad importance of catalytic methodologies to human wellbeing is highlighted by the fifteen Nobel Prizes in Chemistry awarded in the field since 1901.\(^2\) Increasingly, these showcase advances with important potential to reduce the environmental footprint\(^3\) of pharmaceutical and specialty chemicals (e.g. agrochemicals) manufacturing: asymmetric catalysis (2001),\(^5\)\(^-\)\(^7\) palladium-catalyzed cross-coupling (2010),\(^8\)\(^,\)\(^9\) and olefin metathesis (2005).\(^10\)\(^-\)\(^12\) Of note in this context is the 2005 founding of the American Chemical Society’s Green Chemistry Institute (ACS-GCI), ACS GCI Pharmaceutical Roundtable (ACS GCIPR), which brings together leading pharmaceutical corporations (including AstraZeneca, Eli Lilly, GlaxoSmithKline, Merck, Pfizer, and Schering-Plough).

One measure of catalyst productivity is the number of times it can complete a catalytic cycle before decomposing (Figure 1.1).\(^13\) Understanding catalyst decomposition chemistry is imperative in
redesigning processes, or the catalysts themselves, for longer lifetimes. This thesis work focuses on improving our understanding of decomposition pathways in olefin metathesis, and identifying structural parameters that could contribute to the design of longer-lived catalysts.

Figure 1.1 A model catalytic cycle.

1.2 Olefin Metathesis

1.2.1 History, Development, and Significance of Olefin Metathesis

Olefin metathesis is a metal-catalyzed process in which two olefins react to form a new carbon-carbon double bond. Its applications encompass multiple reaction types (Figure 1.2), of which key examples are cross-metathesis (CM), ring-closing metathesis (RCM), ring-opening metathesis polymerization (ROMP), and acyclic diene metathesis (ADMET). Olefin metathesis has transformed synthetic organic chemistry. For their work in the development of metathesis catalysts and elucidation of the mechanism involved, Robert Grubbs, Richard Schrock, and Yves Chauvin were awarded the 2005 Nobel Prize in Chemistry.
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Figure 1.2 Major metathesis reactions. (a) Cross-metathesis, (b) ring-closing metathesis, (c) ring-opening metathesis polymerization, (d) acyclic diene metathesis.

One of the earliest documented findings of olefin metathesis is a 1955 patent by Anderson and Merckling of DuPont, which described the use of TiCl$_4$ as a catalyst in the ring-opening polymerization of norbornene.$^{14}$ Mo and W catalysts soon followed, for reactions such as the conversion of propylene to ethylene and butenes,$^{15}$ and the ring-opening polymerization of cyclopentene.$^{16}$ The term “olefin metathesis” was coined in 1967 by Calderon, who showed that bond cleavage and redistribution in fact occur at the C=C functionality.$^{17,18}$ While this established the basis for the olefin redistribution process, the mechanism was the subject of much debate. Several incorrect mechanisms were proposed, with various metal intermediates (Figure 1.3).$^{18-20}$ However, none of these correctly predicted the product distribution for all substrates examined.
A breakthrough in mechanistic understanding resulted from the work of Chauvin and Hérisson highlighting the role of the metal carbene (later termed a metal alkylidene) intermediate. The transformation was proposed to involve the [2+2] cycloaddition of an olefin with a metal alkylidene to form a metallacyclobutane (MCB) intermediate, and subsequent cycloreversion to release new metal alkylidene and olefin products (Scheme 1.1). This proposal was based in part on the observation of a 1:2:1 distribution of C9:C10:C11 products in the cross-metathesis of cyclopentene with 2-pentene, which is not possible for the “conventional mechanism” of Figure 1.3a. The Chauvin mechanism was subsequently supported by isotopic labelling studies.

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Industrial applications of metathesis began in the late 1960s. Petrochemicals benefitted from the implementation of metathesis for the conversion of low-cost propylene to butene and ethylene. In the Phillips Triolefin Process, a WO$_3$ catalyst supported on silica was used to catalyze this transformation, with subsequent isomerization to convert 2-butene into high-purity 1-butene. The reverse reaction, known as Olefin Conversion Technology (OCT), gained popularity in the late 1970s as the price of propylene increased. OCT represents an increasingly important application of metathesis in the petrochemicals sector today, as one means of addressing the “propylene deficit” arising from the expanding use of shale gas as a source of petrochemicals. Another major application of industrial metathesis is seen in the Shell Higher Olefin Process (SHOP), in which ethylene is converted into C10-20 $\alpha$-olefins by successive steps of oligomerization, isomerization, and finally metathesis. Olefin products generated by this process have important applications in detergents and lubricants. Finally, ROMP of cyclooctene, dicyclopentadiene, and norbornene is used in the production of polymers for applications ranging from Kevlar to optically clear plastics.

Expanding interest in olefin metathesis spurred the development of “well-defined” molecular catalysts bearing a metal-alkylidene bond (Figure 1.4a). In a breakthrough advance, Schrock reported in 1974 the first synthesis of a metal-alkylidene complex, Ta-1. (Of note, the metathesis of cis-2-pentene by a related Ta complex was subsequently described, although the claim of...
metathesis activity by any Ta catalyst has since been called into question). Significantly higher metathesis activity came with Schrock’s development of group 6 metal complexes: that is, Mo and W alkylidene complexes such as Mo-1 and W-1. These catalysts offered high, tunable activity, owing to the ease with which ligand bulk and electronic properties could be modified, and they are now commercially available.

A major limitation of these catalysts, however, is their instability. Their susceptibility to thermal decomposition, and their high sensitivity to oxygen and water, severely limited their uptake in organic synthesis. More robust catalysts were introduced in the 1990s, when Grubbs reported the first ruthenium metathesis catalysts (see, e.g., GI, Figure 1.4b). Despite their lower activity relative to the Schrock catalysts, the ease of handling of the ruthenium catalysts was the breakthrough that put metathesis methodologies into the hands of practicing organic chemists. The subsequent development of more reactive “second-generation” catalysts, bearing a stabilizing N-heterocyclic carbene (NHC) ligand in place of a phosphine, further expanded their scope. Of the second-generation catalysts reported in 1999 (GII\textsuperscript{37} and GII\textsuperscript{1};\textsuperscript{38} Figure 1.4b), GII remains the most popular metathesis catalyst used today, despite the commercially availability of more than 60 alternatives.\textsuperscript{39} Currently most important among these, in addition to GII, are phosphine-free catalysts such as HII (Figure 1.4b).
1.2.2 Recent Implementations of Metathesis in Industry

Despite the fact that olefin metathesis processes have been used for the production of petrochemicals and polymers since the 1960s, uptake in pharmaceutical and specialty chemicals manufacturing is very recent. The delay in implementation was partially due to sensitivity of the catalysts to oxygen, water, and protic or oxygen-donor functional groups, which greatly hindered their utility (particularly in synthesis of biologically-relevant molecules, which are often rich in N, O, and S moieties). While some of these problems are alleviated by use of ruthenium metathesis catalysts, other challenges hamper use in large-scale metathesis processes. These include removal of the ethylene byproduct, which promotes catalyst decomposition, and the high dilutions required for RCM macrocyclization. Nevertheless, applications of olefin metathesis in pharma have advanced.

One of the key areas of advance in pharma has been in the application of RCM to macrocyclization. In 2005, Boehringer-Ingelheim (BI) reported the first large-scale use of RCM, in a pilot production
of the Hepatitis C virus (HCV) inhibitor Ciluprevir for clinical trials (Scheme 1.2).⁴¹,⁴² This was a remarkable advance, as the first example of RCM on industrial scale. While Ciluprevir ultimately failed in clinical trials and was never commercialized, this pioneering work was influential in expanding consideration of RCM in pharmaceutical process chemistry. The first commercial process involving RCM was Johnson & Johnson’s route to HCV inhibitor Simeprevir,⁴³ rapidly followed by processes for two other HCV drugs, Paritaprevir⁴⁴,⁴⁵ and Vaniprevir⁴⁶ (AbbVie and Merck, respectively; Figure 1.5).

Scheme 1.2 Synthesis of Ciluprevir via RCM macrocyclization.

![Scheme 1.2 Synthesis of Ciluprevir via RCM macrocyclization.](image)

Figure 1.5 Structures of HCV drugs Simeprevir, Paritaprevir, and Vaniprevir

Parallel advances in cross-metathesis for specialty chemicals manufacturing have been claimed, although details are limited. These focus chiefly on high-performance rubbers⁴⁷ and metathesis of
renewable feedstocks. Metathesis of unsaturated plant oils derived from triglycerides, with successive transesterification, gives rise to many potential synthetic building blocks (Scheme 1.3).\textsuperscript{48,49} Elevance Renewable Sciences reported the opening of a manufacturing facility for the metathesis of palm oil in 2013. Given the volumes of unsaturated palm, soy, and canola oil produced annually,\textsuperscript{50} this gained much attention for the potential production of added-value specialty products from relatively low-cost renewable feedstocks. Key products include lubricants, fuels, waxes, synthetic oils, and precursors to other specialty chemicals.\textsuperscript{40,48,51}

\textbf{Scheme 1.3 Ethenolysis of plant oil triglycerides, and subsequent transesterification to yield high-value products.}

1.2.3 Significance of Catalyst Decomposition

The ruthenium metathesis catalysts are widely claimed to improve functional group tolerance relative to their group 6 predecessors. (This is often overstated: while true for aldehydes and alcohols, polar groups, for example, are often tolerated much better by the Mo and W catalysts).\textsuperscript{52} More generally, reports from industry have shown decreased yields or unwanted side reactions in Ru-catalyzed metathesis when trace impurities are present. This is problematic for both product purity and batch reproducibility.\textsuperscript{40} In BI’s industrial-scale synthesis of Ciluprevir, ppm levels of morpholine (present in the technical-grade toluene solvent) were identified as a key factor limiting metathesis productivity.\textsuperscript{41} Likewise, contaminating \textit{N}-methyl morpholine and triphenylphosphine were found to be detrimental in the synthesis of Simeprevir.\textsuperscript{53} In addition, residues from upstream
processes have been flagged as problematic, particularly N-donors such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or secondary amines.\textsuperscript{54} Catalyst decomposition has an adverse impact on process costs in large-scale syntheses,\textsuperscript{53} owing both to decreased productivity (TONs) and the capacity of decomposed Ru products to promote unwanted side reactions.\textsuperscript{55} Olefin isomerization is one of the most significant side reactions triggered by catalyst decomposition,\textsuperscript{52,56} generally resulting in the conversion of terminal olefins into internal olefins. Isomerization is widely believed to be promoted by hydridic ruthenium species (Ru-H) generated by catalyst decomposition. These Ru-H complexes may function via a hydride mechanism (Figure 1.6a), or a π-allyl mechanism (Figure 1.6b).\textsuperscript{56} However, Carolyn Higman of the Fogg group has shown that RuHCl(CO)(H\textsubscript{2}IMes)(PCy\textsubscript{3}), one of the candidates most commonly regarded as responsible for isomerization, is not kinetically competent to account for all isomerization observed during metathesis.\textsuperscript{57} In subsequent work, isomerization-active Ru nanoparticles (NPs) were shown to form under conditions of metathesis, although details of the pathways by which they are generated are not yet clear.\textsuperscript{58}

![Figure 1.6 Possible mechanisms for olefin isomerization promoted by Ru-H species.](image)

The decomposition products generated during metathesis can give important clues as to how catalyst decomposition occurs, and are therefore valuable in identifying weaknesses in catalyst or process design. To date, the majority of studies examining catalyst stability focus on the readily-
accessible precatalysts. However, these often fail to report on decomposition pathways during metathesis, as new vulnerabilities emerge in the active catalytic cycle (Scheme 1.4). Notably susceptible to decomposition are the metallocyclobutane (MCB) and the four-coordinate methylidene (which can react with free phosphine to generate the off-cycle resting state species GIIIm). The MCB intermediate is relatively short-lived, and therefore challenging to study. However, resting state methylidene complexes are isolable, permitting examination of their decomposition in the absence of substrate. Synthesis of GIIIm was first reported by Grubbs in 2001, albeit in low yields and purity. This important species represents the resting state of the catalyst during metathesis by GII. A breakthrough in studying its behaviour was the 2012 report by Justin Lummiss of the Fogg group of a clean, high-yield route to GIIIm and related species, and his subsequent development of a route to isotopically-labelled *GIIIm, bearing a $^{13}$C-labelled methylidene ligand.

In an important early study using then-available material, Hong and Grubbs reported the thermolysis of GIIIm in the absence of olefin. The complex was heated for 3 days at 55 ºC, after which dinuclear Ru complex was isolated in 46% yield, and methyl phosphonium salt [MePCy$_3$]Cl

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was observed (1; yield not reported) By analogy to chemistry established for other phosphine-bearing Ru alkylidenes, decomposition was proposed to occur by nucleophilic attack of PCy$_3$ at the methylidene carbon, following which a complex multi-step pathway was suggested (Scheme 1.5). This decomposition process is slow, however, occurring over a span of days, and is therefore unlikely to be a significant contributor to decomposition on the timescale of catalysis (hours). It should be noted that, as with the Ru-H species mentioned above, the dinuclear decomposition product is not kinetically competent to account for the competing isomerization observed during metathesis.

**Scheme 1.5 Grubbs’ proposed decomposition pathway for the thermolysis of GIIm.**

Although the Ru thermolysis product is probably ultimately irrelevant, a key suggestion in this paper was the nucleophilic attack by PCy$_3$ at the [Ru]=CH$_2$ carbon, with elimination of the methylidene functionality as methylphosphonium salt 1. This is in fact a primary vector for the decomposition of the four-coordinate methylidene species derived from GIIm. Justin Lummiss and William McClennan of the Fogg group demonstrated that attack at the methylidene
Chapter 1. Introduction

generates a transient \(\sigma\)-alkyl species,\(^{66}\) which decomposes by facile C-H activation of the cis-NHC ligand.\(^{61,67}\) This pathway is accelerated in the presence of pyridine, which promotes loss of PCy\(_3\), from GIIIm.\(^{66}\)

While this thesis work focuses primarily on the role of phosphine in decomposition of the active methylidene species, MCB decomposition is also important. This too can involve the PCy\(_3\) ligand present in GII, as demonstrated by Gwen Bailey of the Fogg group. Specifically, nucleophilic attack of PCy\(_3\) on methyl acrylate was shown to generate a highly basic enolate, which abstracts a proton from the active catalyst\(^{68}\) (likely from the MCB intermediate; Scheme 1.6). This has now been shown to be one specific example of a more general pathway, in which Brønsted bases with a wide range of base strengths (DBU, NEt\(_3\), and pyrrolidine) deprotonate the MCB, and thus limit catalyst lifetimes.\(^{69,70}\)

Scheme 1.6 Reaction of PCy\(_3\) with electron deficient olefins, and proposed deprotonation of MCB by phosphonium product.

1.3 Scope of this Thesis

As discussed above, phosphine-stabilized metathesis catalysts decompose rapidly in the presence of sterically accessible nitrogen donors, which promote nucleophilic attack of PR\(_3\) at the [Ru]=CH\(_2\) moiety. This thesis work examines the generality of this decomposition pathway, and assesses widely-accepted ideas regarding design criteria for longer-lived catalysts. One simple solution is to replace the phosphine ligand with a low-nucleophilicity alternative. Many phosphine-free catalysts are now available, including HIII. However, these are generally prepared from the

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phosphine catalysts, and are therefore more costly. Chapter 2 presents experimental details. Chapter 3 examines “donor-accelerated deactivation” of GII\textsubscript{m}, with particular respect to the capacity of weaker donors to promote decomposition, and probes the reversibility of PCy\textsubscript{3} attack at the methyldiene carbon. Two potential means of increasing catalyst robustness are also considered: first, the feasibility of using phosphine scavengers to prevent methyldiene abstraction, and second, the capacity to inhibit C-H activation of the NHC ligand by replacing one N-mesityl substituent with N-Me. In Chapter 4, the impact of truncating both nitrogen substituents to N-Me is examined. The reactions of the IMe\textsubscript{4} ligand with the first-generation Grubbs catalyst GI are explored, as well as the behaviour of a methyldiene intermediate generated by reaction of GII\textsubscript{m} with this ligand. Ligand truncation is shown to accelerate decomposition of the [Ru]=CH\textsubscript{2} moiety by an unexpected pathway. In Chapter 5, the key findings of this thesis work are reviewed, and future work is suggested.

1.4 References

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Chapter 2. Experimental Methods

2.1 General Procedures

2.1.1 Reaction Conditions

Reactions were carried out under N₂ using standard glovebox and Schlenk techniques,¹ unless otherwise noted. Clean glassware was oven-dried at 110 °C for at least 1 h, then allowed to cool under vacuum prior to use. Room temperature is ca. 25 °C for glovebox work, or 23 °C for Schlenk work. Reactions above RT were carried out using a thermostatted oil bath.

2.1.2 Reagents

Reagents PCy₃ (97%, Strem), CuCl (97%, Sigma-Aldrich), CuI (98%, Sigma-Aldrich), 2,6-dichlorobenzenethiol (97%, Alfa Aesar), HBF₄ (48 wt% in H₂O, Sigma-Aldrich), NaBF₄ (>98%, Sigma-Aldrich), NaBAr₄⁺ (98%, Strem), NaH (95%, Sigma-Aldrich), KH (99%, Fisher Scientific), potassium (98% in mineral oil, Sigma-Aldrich), ethylene (BOC Ultra-High Purity Grade 3.0, 99.9%, Linde), Amberlyst-15 ion exchange resin (Sigma-Aldrich), and standards 1,3,5-trimethoxybenzene (TMB, Sigma-Aldrich), dimethyl terephthalate (DMT, >99%) dodecane (>99%, Sigma-Aldrich), potassium hydrotris(1-pyrazolyl)borate (KTp, >99%, Sigma-Aldrich), pyrene (98%, Sigma-Aldrich), and anthracene (97%, Sigma-Aldrich) were used as received. Pyridine (>99%, Fisher), NEt₃ (99%, Alfa Aesar), DMSO (>99%, BDH), and MeCN (>99%, Fisher) were distilled from CaH₂ under N₂. Hexamethylphosphoramide, tetramethyl urea (both 99%, Sigma-Aldrich), diethyl diallylmalonate (DDM; 98%, Sigma-Aldrich), and deionized water were degassed by five consecutive freeze-pump-thaw cycles and stored under N₂ in the glovebox.

The following materials were prepared according to literature procedures: the first-generation Grubbs catalyst RuCl₂(PCy₃)₂(=CHPh) GI,² its methyldiene resting state RuCl₂(PCy₃)₂(=CH₂)
Chapter 2. Experimental Methods

GIm, the second-generation catalysts RuCl₂(NHC)(PCy₃)(=CHPh) (GII, NHC = H₂IMes; GII', NHC = IMes) and their corresponding methylidene species RuCl₂(NHC)(PCy₃)(=CH₂) (GIIm, NHC = H₂IMes; GIIm', NHC = IMes), alkylphosphonium species RuCl₂(CH₂PCy₃)(py)₃ Ru-2a and RuCl₂(CH₂PCy₃)(DMSO)₃ Ru-2b, H₂IMes, IMes, Merrifield-I, 1-methyl-3-(2,4,6-trimethylphenyl)imidazolium iodide 2a, and 1,3,4,5-tetramethylimidazole-2(3H)-thione 3.

2.1.3 Solvents

Dry, oxygen-free hexanes, THF, C₆H₆, CH₂Cl₂, C₇H₈, and Et₂O were obtained using a Glass Contour or Anhydrous Engineering solvent purification system (SPS), and stored in the glovebox. Karl-Fisher titrations prior to sieve treatment were performed on hexanes, THF, C₆H₆, and CH₂Cl₂ by Alexandre Goudreault of this research group: hexanes (4.1 ppm), THF (3.6 ppm), C₆H₆ (4.1 ppm), CH₂Cl₂ (5 ppm). Standard distillation methods were used to purify and degas other solvents: MeOH from I₂-activated Mg turnings, acetone from CaSO₄, and pentane (Fisher ACS grade, pre-dried for 24 h over MgSO₄) from P₂O₅. All organic solvents were stored in the glovebox over activated 4 Å sieves for at least 16 h prior to use, with the exception of MeOH (stored over 3 Å sieves) and acetone, which was not stored over sieves, as they cause self-condensation.

2.1.4 Deuterated Solvents

Deuterated solvents (Cambridge Isotopes or Sigma Aldrich) were used as received for the NMR analysis of air-stable species. For analysis of oxygen- and moisture-sensitive species, deuterated solvents were degassed by five consecutive freeze-pump-thaw cycles and stored in the glovebox over activated 4 Å sieves for at least 16 h prior to use, with the exception of DCE-d₄ which was obtained in ampoules packed under N₂ and used as received.
2.1.5 Instrumentation

2.1.5.1 NMR Spectroscopy

$^1$H, $^{13}$C{$^1$H}, $^{31}$P{$^1$H}, $^{19}$F, and $^1$H-$^1$H NOESY/EXSY NMR spectra were recorded on a Bruker Avance 300, Avance II 300, or Avance 400 spectrometer at RT unless otherwise noted. $^1$H and $^{13}$C{$^1$H} spectra were referenced to the residual proton or carbon signal of the deuterated solvent used; $^{31}$P{$^1$H} spectra were referenced externally to 85% H$_3$PO$_4$ at 0 ppm. For oxygen- and moisture-sensitive samples, spectra were acquired in screw-top (J. Young or Rotoflo) NMR tubes.

2.1.5.2 Gas Chromatography

GC quantification was performed on an Agilent 7890A or 7683B Series autosampling GC, each equipped with a flame ionization detector (FID) and an Agilent HP-5 polysiloxane column (30 m length, 320 μm diameter). An inlet split ratio of 10:1 was used, with an inlet temperature of 250 °C. Helium (UHP grade) was used as the carrier gas to maintain a column pressure of 11.5 psi, and the FID response was maintained between 5 – 2000 ρA. Samples were diluted with CH$_2$Cl$_2$ (ACS reagent grade) prior to injection, giving analyte concentrations of ca. 5 mM. Retention times for substrates, products, and internal standards were confirmed by GC-MS and NMR analysis. For GC quantification, calibration curves (peak area vs. concentration) were constructed for substrates and products relative to internal standard (decane or dodecane) in the relevant concentration regime, to account for the dependence of signal intensity on detector response. Conversions and yields for catalytic runs were measured by integration of peak areas for the analyte relative to internal standard, and compared to the initial ratios.

2.1.5.3 MALDI-TOF Mass Spectrometry

Mass spectra were recorded on a Bruker Daltonics UltraFleXtreme MALDI time-of-flight (MALDI-TOF) spectrometer interfaced to an N$_2$-filled glovebox. Matrix (pyrene or anthracene;
100 mM) and analyte (5 mM) stock solutions were prepared in the glovebox in either C₆H₆ or CH₂Cl₂, and mixed in a 25:1 ratio, giving a final matrix to analyte ratio of 500:1. MALDI target plates were spotted by the dried-droplet method in ca. 2 μL aliquots, then inserted into the spectrometer loading chamber via a custom-designed anaerobic interface. Samples were analyzed immediately to minimize premature matrix evaporation.

2.2 Experimental Data for Chapter 3

2.2.1 Impact of Lewis Donors on RCM with RuCl₂(H₂IMes)(PCy₃)(≡CHPh) GII

In a representative procedure using H₂O as the donor, a Schlenk tube was loaded with diethyl diallylmalonate (48 mg, 0.2 mmol), dodecane (34 mg, 0.2 mmol; internal standard), H₂O (90 μL, 0.01 mmol) and toluene (1.8 mL). An aliquot was removed for GC-FID analysis to establish the starting ratio of DDM to dodecane. To the flask was added catalyst GII from a stock solution in toluene (33 μL of a 3.0 mM solution containing 12.8 mg GII in 5.0 mL toluene; 0.001 mmol, 0.05 mol%). The reaction was heated for 2 h at 50 ± 1 °C in an oil bath in the glovebox. A sample was then removed, quenched with KTp (10 mg/mL in THF; 10 equiv vs GII), and analyzed by GC-FID; see Appendix A1.3, Figure A7, and Table 3.1 in Chapter 3.
2.2.2 Reaction of RuCl$_2$(IMes)(PCy$_3$)(=CH$_2$) GIIm’ with Lewis Donors

In these experiments, the total methylidene integration ($^1$H NMR analysis) was measured vs. the internal standard TMB after 2 h and 4 h at 50 °C, and percent decomposition was calculated. $^{31}$P{$^1$H} NMR analysis was used to identify deactivation products. A representative procedure using 10 equivalents of DMSO as the Lewis donor is shown below.

In the glovebox, a J. Young NMR tube was charged with GIIm’ (231 μL of a 43.3 mM stock solution in C$_6$D$_6$; 0.01 mmol) and TMB (ca. 1 mg), followed by 369 μL of C$_6$D$_6$ to bring the sample to a total concentration of 17 mM GIIm’. The sample was removed from the glovebox and a $^1$H NMR spectrum was measured to establish the GIIm’: TMB ratio at t$_0$. The NMR tube was returned to the glovebox and DMSO (7 μL, 0.1 mmol, 10 equiv) was added. The sample was shaken to mix and heated in an oil bath at 50 °C. At 2 h and 4 h, $^1$H and $^{31}$P{$^1$H} NMR spectra were obtained. For DMSO (10 equiv) after 2 h: $^{31}$P{$^1$H} NMR (121 MHz, C$_6$D$_6$): δ 40.7 (s, 88%, GIIm’), 33.9 (s, 7%, [MePCy$_3$]Cl), 10.4 (s, 5%, PCy$_3$). $^1$H NMR (300 MHz, C$_6$D$_6$): δ 18.75 (s, 88%, [Ru]=CH$_2$ of GIIm’). For representative spectra for the DMSO experiment above, see Appendix A1.2, Figures A5 and A6.

2.2.3 Probing Reactivity of RuCl$_2$(CH$_2$PCy$_3$)$_3$ (L = py, DMSO) σ-alkyl Complexes Ru-2

In a representative procedure, a solution of Ru-2a (11 mg, 0.016 mmol) and DMT (ca. 3 mg, internal standard) in C$_6$D$_6$ (660 μL) was added to a J. Young NMR tube in the glovebox. A $^1$H NMR spectrum was measured to establish the starting ratio of Ru-2a to DMT. The sample was returned to the glovebox, and DDM (40 mL, 0.16 mmol, 10 equiv) was added. The tube was shaken vigorously to effect mixing. No colour change was observed. $^1$H NMR spectra measured at 15 min and 2 h showed no alkylidene signals, and no RCM product. The tube was then heated to 80 °C. No change was evident after 24 h.

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2.2.4 Representative Procedure for RCM in the Presence of Phosphine Scavengers

RCM of DDM was carried out in both THF (0.1 mol% GII) and toluene (0.005 mol% GII), with catalyst loading such that the control experiments did not afford complete conversion to the ring-closed product. Scavengers used: CuCl, CuI, Amberlyst-15 resin, benzyl iodide, and Merrifield-I resin. A representative procedure is given with CuI in THF.

A 4 mL vial in the glovebox was charged with DDM (48 mg, 0.2 mmol), dodecane (34 mg, 0.2 mmol; internal standard), and THF (1.9 mL). An aliquot was removed for GC-FID analysis to establish the starting ratio of DDM to dodecane. CuI (19 mg, 0.1 mmol, 50 mol%) and GII (16 μL of a 13 mM stock containing 10.9 mg GII in 1.0 mL THF; 0.0002 mmol, 0.1 mol%) were then added, and the suspension was stirred at room temperature for 24 h. A sample was then removed, quenched with KTp (10 mg/mL in THF), and analyzed by GC-FID (see Figure 3.4, Chapter 3).

2.2.5 Synthesis of 1-methyl-3-(2,4,6-trimethylphenyl)imidazolium tetrafluoroborate 2b

Synthesis of 1-methyl-3-(2,4,6-trimethylphenyl)imidazolium iodide 2a was prepared by the method reported by Strassner et al. Conversion to the tetrafluoroborate salt 2b was effected by dissolving 2a (1.00 g, 3.05 mmol) in H2O (60 mL) and adding HBF4 (0.5 mL, 4 mmol, 1.3 equiv) dropwise. The solution was left to stir for 16 h, after which a black precipitate (I2) had formed. The latter was removed by filtration, and the filtrate was concentrated by rotary evaporation to give quantitative yield of 2b.

1H NMR (CDCl3): δ 9.29 (s, 1H, N-CH-N), 7.76 (t, JH-H = 1.6 Hz, 1H, MeNCH=CH), 7.19 (t, JH-H = 1.7 Hz, 1H, Mes-N-CH=CH), 6.99 (s, 2H, Mes-H), 4.24 (s, 3H, N-CH3), 2.33 (s, 3H, Mes p-CH3), 2.06 (s, 3H, Mes o-CH3). See Appendix A1.1, Figure A1.
2.2.6 Synthesis of 1-methyl-3-(2,4,6-trimethylphenyl)imidazole-2-ylidene (IMeMes)

Free IMeMes was prepared by analogy to the method for H₂IMes. Accordingly, imidazolium tetrafluoroborate salt 2b (870 mg, 3.0 mmol) was deprotonated with NaH (188 mg, 7.8 mmol, 2.6 equiv) in THF (15 mL) to afford the product as a brown oil. Yield: 540 mg (2.7 mmol, 90%). \(^1\)H NMR (C₆D₆): \(\delta 6.77\) (s, 2H, Mes-H), \(6.40\) (d, \(3J_{H-H} = 3.6\) Hz, 1H, Me-N-CH), \(6.40\) (d, \(3J_{H-H} = 3.6\) Hz, 1H, Mes-N-CH), 3.47 (s, 3H, N-C₃H₃), 2.13 (s, 3H, Mes p-CH₃), 2.10 (d, 4JH-H, 6H, Mes o-CH₃). See Appendix A1.1, Figure A2.

2.2.7 Synthesis of RuCl₂(PCy₃)(IMeMes)(=CHPh) Ru-6

RuCl₂(PCy₃)(IMeMes)(=CHPh) Ru-6 was prepared by a glovebox method analogous to that for GII, using IMeMes in place of H₂IMes. Accordingly, IMeMes (185 mg, 0.925 mmol, 2.7 equiv) was slowly added to a stirred solution of GI (280 mg, 0.340 mmol) in THF (7.5 mL) at room temperature. Stirring was continued until no GI remained (\(^1\)H NMR analysis; 48 h). Amberlyst-15 resin (434 mg, 2.04 mmol, 6 equiv) was then added to sequester the free PCy₃, and the suspension was stirred for 2.5 h at room temperature. The resin was filtered off, and the filtrate was concentrated to a black solid. Yield Ru-6/7: 206 mg (82%). Key \(^1\)H NMR data (300 MHz, C₆D₆): \(\delta 19.88\) ppm (s, 20%, Ru-6 rotamer), 19.74 ppm (s, 32%, Ru-7), 19.37 ppm (s, 48%, Ru-6 rotamer). \(^{31}\)P\(^{\{1\}H}\) NMR (121 MHz, C₆D₆): 35.4 (s, 34%, Ru-6), 10.4 (s, 66%, PCy₃). See Appendix 1.1, Figure A3. For VT \(^{31}\)P\(^{\{1\}H}\) NMR spectrum, see Appendix A1.1, Figure A4.
2.2.8 Activity of Ru-6 in the RCM of DDM

A 4 mL vial in the glovebox was loaded with diethyl diallylmalonate (48.1 mg, 0.2 mmol), dodecane (34.1 mg, 0.2 mmol; internal standard), and toluene (2 mL). An aliquot was removed for GC-FID analysis to establish the starting ratio of DDM to dodecane. To the vial, catalyst Ru-6 was added (250 μL of a 11.9 mg/2 mL stock solution in toluene, 0.002 mmol, 1 mol%; note that catalyst is a mixture of ca. 68% Ru-6 and 32% Ru-7). The reaction was heated at 40 ± 1 °C in an oil bath in the glovebox. Aliquots were removed at 15 min, 2 h, 5 h, and 25 h, quenched with KTp (10 mg/mL in THF; 10 equiv vs GII), and analyzed by GC-FID.

2.3 Experimental Data for Chapter 4

2.3.1 Synthesis of 1,3,4,5-tetramethylimidazol-2-ylidene (IMe₄)

In a modified version of a reported procedure,¹² thione 3 (1.51 g, 9.66 mmol) was dissolved in THF (60 mL) in a Schlenk flask in the glovebox, and the solution was chilled to -35 °C. Metallic potassium was removed from the mineral oil in which it was stored, cut into small pieces and rinsed with hexanes. Potassium chunks (4.5 g, 115 mmol, 12 equiv) were added to the chilled Schlenk flask, a condenser was attached, and the system was sealed and removed to the Schlenk line. The reaction was refluxed under N₂ for 4 h, over which time the potassium began to break into small fragments. A colour change from yellow to pale purple occurred within 1 h, and to pale green after an additional 2 h. The flask was returned to the glovebox, and the suspension filtered through Celite. The product was washed through with THF (3 x 5 mL), and the clear yellow filtrate was stripped to a tan solid, which was dissolved in C₆H₆ (10 mL) and filtered again. The filtrate was concentrated and the solid was washed with pentane (3 x 5 mL) to give clean IMe₄ as a pale yellow solid. Yield: 539 mg (45%). H NMR (300 MHz, C₆D₆): δ 3.37 (s, 6H, N-C₃H₃), 1.58 (s, 6H, C-CH₃). See Appendix A2.1, Figure A8.

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2.3.2 Synthesis of [Ru$_2$(μ-Cl)$_3$(IMe)$_4$($≈$CHPh)$_2$]Cl Ru-11a

In the glovebox, a white powder of free IMe$_4$ (38 mg, 0.3 mmol, 2.1 equiv) was added to a purple solution of GI (120 mg, 0.15 mmol) in 15 mL C$_6$H$_6$. The solution immediately changed colour to brown. The solution was stirred for 18 h at 23 °C, over which time a green solid deposited. The solid was collected on a fine frit, and washed with benzene (3 x 2 mL) and pentane (3 x 2 mL) to obtain Ru-11a as an emerald-green powder. Yield: 50 mg (67%).

$^1$H NMR analysis of the combined brown filtrate and washings revealed multiple alkylidene-containing products. $^1$H NMR of Ru-11a (DCE-d$_4$, 500 MHz, 298 K; for numbering system, see the Appendix A2.1, Figure A9: δ 20.93 (br s, $\Delta\omega_{1/2}$ = 6.6 Hz, [Ru]=CHPh, H$_{15}$), 20.71 (br s, $\Delta\omega_{1/2}$ = 12.3 Hz, [Ru]=CHPh, H$_{15}$), 20.43 (br s, $\Delta\omega_{1/2}$ = 9.2 Hz, [Ru]=CHPh, H$_{15}$), 7.48 (t, $^3$J$_{H-H}$ = 7.0 Hz, 1H, H$_{19}$), 7.41 (d, $^3$J$_{H-H}$ = 7.4 Hz, 2H, H$_{17}$), 7.29–7.04 (overlapping multiplet, 2H, H$_{18}$), 4.39 (s, 3H, H$_1$), 3.93 (s, 3H, H$_4$), 2.83 (s, 3H, H$_8$), 2.14 (s, 3H, H$_2$), 2.05 (s, 3H, H$_3$), 1.96 (s, 3H, H$_7$), 1.68 (s, 3H, H$_6$), 1.51 (s, 3H, H$_5$). $^{13}$C-$^1$H NMR (DCE-d$_4$, 125.7 MHz, 298 K) δ 322.7 (C$_{16}$, located via the $^1$H-$^{13}$C HMQC correlation with H$_{15}$), 172.6 (C$_9$ or C$_{10}$), 171.6 (C$_{10}$ or C$_9$), 154.8 (C$_{16}$), 130.3–128.3 (overlap; C$_{17}$, C$_{18}$, C$_{19}$), 126.7 (C$_{11}$), 126.3 (two overlapping s, C$_{12}$, C$_{14}$), 125.1 (C$_{13}$), 36.4 (C$_4$), 35.4 (C$_1$), 34.6 (C$_8$), 32.5 (C$_5$), 9.9–8.9 (4 overlapping s, C$_2$, C$_3$, C$_6$, C$_7$).

Satisfactory microanalysis could not be obtained, despite multiple attempts. For $^1$H-$^1$H EXSY/NOESY spectrum, see Appendix 2.1A, Figure A10.

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2.3.3 Assessment of [Ru$_2$(μ-Cl)$_3$(IMe)$_4$(=CHPh)$_2$]Cl Ru-11a Activity in RCM of DDM

A 4 mL vial was loaded with diethyl diallylmalonate (481 mg, 2 mmol), decane (285 mg, 2 mmol) and DCE (0.62 mL). A ca. 10 μL aliquot was removed for GC-FID analysis to establish the starting ratio of substrate to decane. Ru-11a (10.2 mg, 0.01 mmol, 1 mol% Ru) was then added, and the reaction was stirred open to a well-purged glovebox atmosphere for 24 h. Aliquots were taken from the stirred reaction at specific time intervals, quenched with KTp, diluted with CH$_2$Cl$_2$ on the bench, and analyzed by GC-FID. See Figure 4.4 in Chapter 4.

2.3.4 Synthesis of [Ru$_2$(μ-Cl)$_3$(IMe)$_4$(=CHPh)$_2$]BF$_4$ Ru-11b

In the glovebox, a 20 mL vial was loaded with Ru-11a (49.7 mg, 0.0487 mmol), NaBF$_4$ (10.7 mg, 0.0974 mmol, 2 equiv), and CH$_2$Cl$_2$ (5 mL). The reaction was stirred for one hour at room temperature, and reaction completion was determined by $^{19}$F NMR (no change by $^1$H NMR when counterion changed from Cl$^-$ to BF$_4^-$). $^{19}$F NMR (CH$_2$Cl$_2$, 282 MHz) δ -149.9 (s), -150.0 (s). See Appendix A2.1, Figure A11.

2.3.5 Synthesis of [RuCl(IMe)$_4$(=CHPh)$_2$][BAr$_4$F]$_2$ Ru-12

In the glovebox, a 2-necked round bottom flask was charged with Ru-11a (48.6 mg, 0.0476 mmol), NaBAr$_4$F (84.7 mg, 0.0956 mmol, 2.0 equiv), and 10 mL CH$_2$Cl$_2$. The green solution was taken to the Schlenk line and refluxed for 1 h. The reaction was returned to the glovebox and filtered through Celite to remove NaCl. The product was washed through with CH$_2$Cl$_2$ (3 x 2 mL), and the filtrate was concentrated to a dark green solid. Yield Ru-12: 57 mg (45%). $^1$H NMR (300 MHz, CDCl$_3$): δ 19.66 (s, 1H, [Ru]=CPh), 7.71
(s, 8H, BArF o-H), 7.53 (s, 4H, BArF p-H), 7.94–6.79 (overlapping m, 9H, [Ru]=CHPh), 4.57 (s, 3H, IMe4 N-Me), 4.39 (s, 3H, IMe4 N-Me), 2.13 (s, 3H, IMe4-Me), 2.09 (s, 3H, IMe4-Me), 1.60 (s, 3H, IMe4-Me), 1.30 (s, 3H, IMe4-Me), 1.07 (s, 3H, IMe4-Me). See Appendix A2.1, Figure A12.

Complete removal of grease from the Ru dimer was not possible, as the complex oils out of aromatic and aliphatic solvents.

2.3.6 Synthesis of potassium 2,6-dichlorobenzenethiolate (4)

The synthesis was adapted from the method reported by Jensen. Modifications included the use of pyridine in workup, and of KH suspended in mineral oil, rather than solid KH. In the glovebox, a Schlenk flask was charged with potassium hydride (30 wt% in mineral oil, 1.09 g, 8.16 mmol, 1.5 equiv) and THF (10 mL). Dropwise addition of a solution of 2,6-dichlorobenzenethiol (1.005 g, 5.615 mmol) in THF (30 mL) to the stirred mixture caused a milky white suspension to form, accompanied by H2 gas. After 30 min, the flask was removed to the Schlenk line and heated to 50 °C for 25 min under N2. THF was removed by vacuum, leaving a white residue which was returned to the glovebox. The solid was dissolved in a minimum volume of pyridine, and the solution was filtered through a plug of Celite, which was washed with pyridine until washings were colourless. The combined filtrate was concentrated until a white precipitate began to deposit. Hexanes (10 mL) were then added to precipitate a white solid, which was collected on a fine frit and washed with hexanes (4 x 5 mL). The solid was dried under vacuum. Yield: 0.513 g (42%). The product was insoluble in benzene, but 1H NMR analysis in C6D6 was nevertheless useful in confirming complete consumption of the thiol precursor (SH singlet 4.35 ppm).
2.3.7 Synthesis of Ru(S(2,6-dichlorobenzene))₂(PCy₃)₂(=CHPh) Ru-13

The synthesis was adapted from the method reported by Jensen, but modified to use C₆H₆ in the workup rather than THF. In the glovebox, purple GI (0.100 g, 0.122 mmol) was suspended in C₇H₇ (4 mL) and THF (1 mL), and potassium 2,6-dichlorobenzenethiolate 4 (57.0 mg, 0.26 mmol, 2.2 equiv) was added to the stirred reaction. A dark brown solution was present after 2 h at RT. The solvent was stripped off, and the brown residue was redissolved in C₆H₆ (8 mL). The solution was filtered through Celite and concentrated to the point of saturation. Slow, dropwise addition of pentane afforded a purple-brown precipitate. The suspension was cooled to -35 °C, and the precipitate was filtered off while cold, washed with -35 °C pentane (4 x 2 mL), and dried under vacuum. Ru-13 was isolated as a purple-brown solid (83.0 mg, 61% yield).

¹H NMR (300 MHz, C₆D₆) δ 15.85 (d, ⁴J_H-H = 11.5 Hz, 1H, [Ru]=C₇H₇), 7.62 (d, ³J_H-H = 6.9 Hz, 2H, o-Ph), 7.03 (m, 3H, m-Ph, p-Ph), 6.85 (d, ³J_H-H = 7.9 Hz, 4H, m-SAr), 6.25 (t, ³J_H-H = 8.0 Hz, 2H, p-SAr), 2.76 – 0.32 (m, 66H, PCy₃). ³¹P{¹H} NMR (121 MHz, C₆D₆) δ 54.9 (s). See Appendix A2.1, Figure A13.

2.3.8 Addition of IMe₄ to Ru(S(2,6-dichlorobenzene))₂(PCy₃)₂(=CHPh) Ru-13

Using 1 equiv IMe₄: In the glovebox, a solution of Ru-13 (335 μL of a 10.0 mg/670 μL stock solution in C₆D₆; 0.0045 mmol) in C₆D₆ (500 μL) was prepared in a 4 mL vial. To the stirred brown solution, IMe₄ (26 μL of a 10.0 mg/460 μL stock solution in C₆D₆; 0.0045 mmol, 1.0 equiv) was added dropwise. The solution was stirred for 4 d at RT, until no further changes were observed for the ¹H NMR alkylidene integrations. Over this time, no colour change was observed. Key NMR signals: ¹H NMR (300 MHz, C₆D₆): δ 20.00 (s, 5%, [Ru]=CHPh of bis-IMe₄ complex Ru-15),
16.73 (s, 18%, [Ru]=CHPh of mono-IMe₄ complex Ru-14), 15.85 (d, 3J₃H-P = 11.3 Hz, 77%, [Ru]=CHPh of Ru-13). See Appendix A2.2, Figure A14a.

Using 2 equiv IMe₄: In the glovebox, a solution of Ru-13 (335 μL of a 10.0 mg/670 μL stock solution in C₆D₆; 0.0045 mmol) in C₆D₆ (300 μL) was prepared in J. Young NMR tube. To this brown solution, IMe₄ (11 μL of a 10.0 mg/100 μL stock solution in C₆D₆; 0.0090 mmol, 2.0 equiv) was added. After 24 h at RT, no colour change was observed. Key NMR signals: ¹H NMR (300 MHz, C₆D₆): δ 20.00 (s, 34%, [Ru]=CHPh of bis-IMe₄ complex Ru-15), 16.73 (s, 9%, [Ru]=CHPh of mono-IMe₄ complex Ru-14), 15.85 (d, 3J₃H-P = 11.1 Hz, 57%, [Ru]=CHPh of Ru-13). ¹H NMR (300 MHz) of alkylidene region after addition of CDCl₃ (0.3 mL): δ 21.11, 20.83, 20.34 (three singlets, 35%, Ru-11a); 19.95 (d, 3J₃H-P = 15.3 Hz, 8%, Ru-14); 15.71 (d, 3J₃H-P = 11.8 Hz, 57%, Ru-13). See Appendix A2.2, Figure A14b.

2.3.9 Reaction of GIm with IMe₄

In the glovebox, pink GIm (6.6 mg, 0.0088 mmol) and DMT (ca. 1 mg; internal standard) were dissolved in C₆D₆ (1 mL) in a J. Young NMR tube, and the initial ratio of methylidene signal to DMT were established by ¹H NMR. IMe₄ (4.5 mg, 0.036 mmol, 4.1 equiv) was added to this solution, affording an immediate colour change from pink to pale orange, with deposition of a grey precipitate. ¹H NMR (300 MHz, C₆D₆) of supernatant: δ 3.71 (s, 12H, Ru-16 N-CH₃), 1.96‒1.07 (overlapping m, 66H, PCy₃), 1.79 (s, 12H, Ru-16 C-CH₃). See Appendix A2.2, Figure A15. ³¹P{¹H} NMR (121 MHz, C₆D₆): δ 10.4 (100%, PCy₃). See Appendix A2.2, Figure A16. ¹H NMR (300 MHz, CDCl₃) of precipitate (key identified signals): δ 3.82 (s, 6H, 5 N-CH₃), 3.34 (q, 2H, 3J₃H-H = 7.5 Hz, 5 C-CH₂-CH₃), 2.25 (s, 6H, 5 C-CH₃), 1.28 (t, 3H, 2J₁H-H = 7.4 Hz, 5 CH₂-CH₃). See Appendix A2.2, Figure A17. Key MALDI-TOF MS signals from supernatant are summarized in Appendix A2.3, Table A1. For mass spectrum, see Appendix A2.3, Figure A18. Key MALDI-
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TOF MS signal from precipitate: (anthracene matrix; m/z) 153.089 (C\textsubscript{7}H\textsubscript{17}N\textsubscript{2}, imidazolium salt 5; calcd 153.139). See Appendix A2.3, Figure A19.

2.4 References

Chapter 3.  Phosphine-Mediated Catalyst Decomposition: Assessment of Problems and Potential Solutions

Parts of this Chapter have been published. Sections 3.2.1 and 3.2.2 are reprinted with permission from: Donor-Induced Decomposition of the Grubbs Catalysts: Lewis Donors Accelerate Methylidene Abstraction. William L. McClennan, Stephanie A. Rufh, Justin A. M. Lummiss, and Deryn E. Fogg.* J. Am. Chem. Soc. 2016, 138, 14668-14677. (http://pubs.acs.org/doi/abs/10.1021%2Fjacs.6b08372) Copyright 2016 American Chemical Society. Further permissions related to the material excerpted should be directed to the ACS.

Author contributions: McClennan, Rufh, Lummiss, and Fogg wrote the manuscript. Decomposition studies of GIIm were carried out by McClennan, decomposition studies of GIIm’ by Rufh. Catalysis with GII in the presence of donors carried out by Rufh.

3.1 Introduction

Primary and secondary amines,1-4 as well as pyridine5,6 and other nitrogen donors,2,4,6-8 are known to be detrimental to metathesis productivity. This is particularly problematic in pharmaceutical manufacturing, where even trace amounts of such impurities have been shown to negatively impact RCM yields and batch reproducibility.9-14 A common decomposition product for the second-generation Grubbs catalyst (GII) is the methylphosphonium salt [MePCy3]Cl 1.15 Hong and Grubbs observed this byproduct, albeit in unknown amounts, following thermolysis of the resting-state methylidene species RuCl2(H2IMes)(PCy3)(=CH2) GIIm (Scheme 3.1).15 At the time, it was unclear whether formation of 1 occurred by intramolecular migration of PCy3 (as reported by the Diver group for decomposition of GI by isocyanides),16 or by PCy3 loss and intermolecular attack.

Scheme 3.1 Thermolytic decomposition of GIIm in the absence of olefin

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The second possibility would account for the slow rate of this process (which requires days at 55 °C in benzene), given the very low lability of the PCy₃ ligand in GIIIm.¹⁷,¹⁸ Importantly, however, Justin Lummiss of the Fogg group demonstrated that this decomposition pathway is dramatically faster (<5 min) in the presence of pyridine.⁵ This was proposed to be due to accelerated loss of PCy₃ from GIIIm following pyridine binding, which enables formation of σ-alkyl species Ru-1a (Scheme 3.2a) by nucleophilic attack of free PCy₃ on the [Ru]=CH₂ moiety. Elimination of the alkylphosphonium ligand as phosphonium salt 1 was attributed to C-H activation of a mesityl o-CH₃ group on the H₂IMes ligand and chloride abstraction. While Ru-1a is a transient intermediate, it was successfully trapped for the first-generation Grubbs methylidene (GIm), for which σ-alkyl species Ru-2a was isolated in 95% yield (Scheme 3.2b).

**Scheme 3.2 Accelerated decomposition of methylidene complexes on exposure to pyridine.**

(a) Pathway proposed for GIIIm. (b) Pathway observed for GIm.

(a) 

\[
\text{H}_2\text{IMes} \xrightarrow{10 \text{ py}} \left[ \text{H}_2\text{IMes} \xrightarrow{\text{Cl}_2} \text{Ru} \xrightarrow{\text{PCy}_3} \right] \text{Ru-1a (not observed)} \]

(b) 

\[
\text{Cy}_3\text{P} \xrightarrow{10 \text{ py}} \left[ \text{Cy}_3\text{P} \xrightarrow{\text{Cl}_2} \text{Ru} \xrightarrow{\text{PCy}_3} \right] \text{Ru-2a (95%)} \]

\[
\left. \begin{array}{c}
\text{Cl}_2 \\
\text{Cl}
\end{array} \right\} \text{Cl}_2, \text{RT} \xrightarrow{60 \ ^\circ \text{C}} 1 \ (59\%) + \text{PCy}_3 \ (19\%) + \text{unidentified products} \ (22\%) \]

Percentage shown is the proportion of total $^{31}$P-¹H NMR integration.

On longer thermolysis (18 h at 60 °C), tris-pyridine intermediate Ru-2a decomposed to yield several products, among which [MePCy₃]Cl 1 predominated (59% of total $^{31}$P-¹H NMR integration). The longer lifetime of the σ-alkyl intermediate Ru-2a relative to Ru-1a was attributed.
to the presence of the H$_2$IMes ligand in the latter. Through C-H activation, the mesityl groups offer a proton source in proximity to the [Ru]-CH$_2$PCy$_3$ functionality. Elimination of 1 and cyclometallation (Scheme 3.3) is rapid.

**Scheme 3.3 C-H activation of H$_2$IMes, and its subsequent cyclometallation.**

This Chapter examines the scope of this decomposition pathway with respect to donor. Of particular interest is the effect of oxygen donors such as water and THF, given that metathesis in aqueous and ethereal media has been promoted as a potentially “greener” approach to process chemistry.$^{19-23}$ As well, several potential means of limiting such PR$_3$-promoted decomposition pathways are examined. While avoiding phosphine ligands in the catalyst is the most obvious solution (and many phosphine-free catalysts are now commercially available; Figure 3.1), their higher cost is unfavourable. An alternative solution involves use of a phosphine scavenger to remove free PCy$_3$ from the system following initiation, but before methylidene abstraction can occur (Scheme 3.4). This could offer improved catalyst productivity for existing catalysts; that is, without the need for new catalysts designed for tolerance toward nucleophiles.

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Figure 3.1 A selection of phosphine-free metathesis catalysts

Scheme 3.4 Transforming PCy₃-stabilized GII into a phosphine-free catalyst with a phosphine scavenger.

Phosphine scavenging during metathesis has used chiefly copper(I) halides. The Grubbs group showed that the ill-defined salt CuCl improves turnover numbers (TONs) in simple RCM reactions promoted by GI, although catalyst lifetimes suffered, with catalyst death sometimes observed before 95% conversion.²⁴ Results of phosphine-scavenging in metathesis with CuCl were not as impressive in second-generation systems, however. In a later study, Grubbs examined the impact of CuCl in cross-metathesis reactions of methyl vinyl ketone, with 5 mol% GII + 1.0 PCy₃ as the catalyst.²⁵ In this report, yields dropped by 50% relative to the control reaction with no added CuCl. Conversely, Lipshutz and co-workers reported that CuI in fact increased yields in GII-
promoted cross-metathesis of acrylates. This proved most effective when metathesis was performed in ethereal solvents rather than the usual chlorinated or aromatic solvents.

Phosphine sequestration has also been pursued in synthesis of metathesis catalysts. Of particular interest are resin additives (Figure 3.2), which are attractive for the simplicity of workup. Thus, in synthesis of complexes such as GII, the byproduct PCy₃ can be removed by simple filtration, rather than extraction with pentane, which results in product losses. Building on a patent by Verpoort and co-workers, Bianca van Lierop of the Fogg group described the efficacy of sulfonic acid resin Amberlyst-15 in the synthesis of a range of second-generation metathesis catalysts from their first-generation analogues. This resin is highly effective in the removal of free PCy₃ (as well as excess NHC). However, extended exposure of the Ru products in solution causes competing decomposition. The Lipshutz and Morris groups independently reported that neutral Merrifield resins (specifically, the iodide resin Merrifield-I) could be successfully used as a phosphine scavenger. In the Morris work, Merrifield-I was used to remove PPh₃ and O=PPh₃ byproducts formed in the synthesis of Ru hydride complexes, albeit with the caveat of halide exchange. In the present chapter, CuCl, CuI, Amberlyst-15, and Merrifield-I were explored as candidates for phosphine sequestration during metathesis. Benzyl iodide was also examined, as a molecular analogue to the Merrifield-I resin.

![Figure 3.2 Amberlyst and Merrifield resins explored](image-url)
A more fundamental approach to improving catalyst lifetime is ligand redesign, as noted above. In a recent review, Crabtree commented that “slimming” of the NHC ligand is expected to be the key to preventing C-H activation.\textsuperscript{31} The Blechert group reported that truncating an H\textsubscript{2}IMes mesityl group to methyl (Figure 3.3) resulted in metathesis activity comparable to \textbf{GII}.\textsuperscript{32} However, decomposition was not examined. A final aspect of this Chapter therefore sought to examine whether C-H activation is indeed inhibited for the smaller NHC. To that end, the previously unreported unsaturated analogue, IMeMes (the structure of which provides a bridge to the fully truncated IMe\textsubscript{4} ligand discussed in the next Chapter) was synthesized and incorporated into a Grubbs-type catalyst.

![Figure 3.3 Structures of NHC ligands: H\textsubscript{2}IMes and variants with truncated N-groups.](image)

3.2 Results and Discussion

3.2.1 Impact of Lewis Donors on Metathesis with \textbf{GII}

The deleterious impact of amines in metathesis reactions catalyzed by \textbf{GII}\textsuperscript{2} was noted above. The rapidity of decomposition, and the co-formation of [MePCy\textsubscript{3}]Cl \textbf{1}, testify to the capacity of such N-donors to decompose the catalyst by methylidene abstraction. To assess the impact of weaker donors, we examined the metathesis productivities attainable for diethyl diallylmalonate (DDM) in the presence of added water or methanol, or in neat THF, MeCN, or DMSO. DDM was chosen as a test substrate in this chemistry because it is very readily cyclized, and any inhibiting effect is therefore an indication of serious problems.
The results are collected in Table 3.1. In the control experiment in anhydrous toluene, RCM was quantitative after 2 h at 50 °C at a catalyst loading of 0.05 mol%. This corresponds to a turnover number of 2,000. In neat THF, RCM activity dropped by more than 30%, to a TON of 1,440. The presence of 5% degassed H₂O in toluene caused a 65% drop in TON. With 5% MeOH, MeCN, and DMSO, the impact was even more detrimental: for the DMSO reaction, metathesis was essentially quenched. As noted above, the ease with which DDM normally undergoes RCM underlines the severity of this degradation in performance. It is worth pointing out that use of lower temperatures (i.e. reaction at 30 °C) does not inhibit methylidene abstraction. Indeed, the impact of donors on total metathesis productivity was in general even more deleterious at 30 °C, in keeping with prior findings that rates of metathesis increase faster at higher temperature than rates of decomposition.⁷,³³

Table 3.1 Donor-Accelerated Decomposition: Impact of Weak Donors on Metathesis Productivity

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent medium</th>
<th>%conv. (TON)⁶</th>
<th>%conv. (TON)⁷</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>50 °C</td>
<td>30 °C</td>
</tr>
<tr>
<td>1</td>
<td>toluene</td>
<td>100 (2000)⁶</td>
<td>100 (2000)⁷</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>72 (1440)</td>
<td>13 (260)</td>
</tr>
<tr>
<td>3</td>
<td>20:1 toluene–H₂O</td>
<td>35 (700)</td>
<td>24 (480)</td>
</tr>
<tr>
<td>4</td>
<td>20:1 toluene–MeOH</td>
<td>18 (360)</td>
<td>5 (100)</td>
</tr>
<tr>
<td>5</td>
<td>20:1 toluene–MeCN</td>
<td>13 (260)</td>
<td>17 (340)</td>
</tr>
<tr>
<td>6</td>
<td>20:1 toluene–DMSO</td>
<td>1 (20)</td>
<td>1 (20)</td>
</tr>
</tbody>
</table>

⁶Calibrated GC-FID analysis; ± 2% in replicate runs. ⁷Quantitative within 10 min. ⁸Quantitative within 60 min.
3.2.2 Accelerated Decomposition of GIIm’ in the Presence of Lewis Donors

To confirm that the damaging impact of these additives is indeed due to accelerated methyldiene abstraction, their reactions with the resting-state methyldiene complexes (both GIIm and its less labile IMes analogue GIIm’) were explored. Experiments with GIIm were carried out by Billy McClennan of the Fogg group. Shown in Table 3.2 is the proportion of [MePCy3]Cl formed, and the proportion of GIIm or GIIm’ lost, after 2 h. In all cases, these amounts tally closely, indicating that methyldiene abstraction is indeed the major pathway. The extent of decomposition should be compared to a baseline value of 10% or 3% for GIIm or GIIm’, respectively, in base-free control experiments (entry 1). Values for pyridine are shown as the final table entry, for comparison. In all cases, the trend seen with the IMes complex GIIm’ parallels that with GIIm. While stronger Ru–PCy3 binding for GIIm’ relative to GIIm (in which the NHC backbone is saturated) lessens the impact on decomposition rates, it is important to note that this also limits entry into the active cycle for metathesis.

The NEt3, phosphoramide, and urea additives shown in entries 2–4 were chosen for the detrimental impact of these and related nitrogen bases reported in other contexts, including in metathesis promoted by phosphine-free catalysts. None show any significant impact, indicating that the Lewis basicity of the donor is irrelevant, if steric congestion hampers access to the methyldiene ligand. This is consistent with a prior finding by Justin Lummiss of this research group, which indicated that added DBU did not trigger methyldiene abstraction during metathesis by GIIm.2 Recent work by Gwen Bailey of this research group confirms that the negative impact of such bulky Lewis bases is due to deprotonation of the metallacyclobutane intermediate.37 Of note, however, even relatively weak donors such as MeCN, THF, and H2O accelerate decomposition (entries 5–7). Addition of MeCN had minimal impact in small amounts (10 equiv),
but decomposition was quantitative at 2 h in neat MeCN (entries 5a, 5b). Similarly, while 10 equiv THF and H₂O proved relatively innocuous, a 10-fold increase led to ca. 30% or 50% decomposition, respectively, notwithstanding the weak oxophilicity of these ruthenium complexes. The heightened effect of water and methanol, relative to THF (entries 7a and 9, vs 6a), may be due to attractive hydrogen-bonding interactions between these H-bond donors and the chloride ligands. Additional decomposition pathways could be envisaged for these protic entities. While many reports take for granted the idea that water is well tolerated by Ru catalysts,¹⁹,²⁰,³⁸ the Cazin group recently showed otherwise.³⁹ Likewise, methanol could be profoundly destructive, particularly if methoxides can be generated.⁴⁰ However, the phosphonium salt 1 was the sole or dominant phosphorus product in all cases, indicating that methylidene abstraction is the principal vector for decomposition.

Table 3.2 Loss of GIIm and GIIm’, and Yield of [MePCy₃]Cl (1) on Treatment with L-Donors (n Equiv.) for 2 h at 50 °C

<table>
<thead>
<tr>
<th>Entry</th>
<th>L-donor</th>
<th>n</th>
<th>% GIIm lost (% 1 formed)</th>
<th>% GIIm’ lost (% 1 formed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>0</td>
<td>10 (10)</td>
<td>3 (N.D.)</td>
</tr>
<tr>
<td>2</td>
<td>NEt₃</td>
<td>10</td>
<td>11 (11)</td>
<td>3 (N.D.)</td>
</tr>
<tr>
<td>3</td>
<td>O=P(NMe₂)₃</td>
<td>10</td>
<td>13 (13)</td>
<td>3 (N.D.)</td>
</tr>
<tr>
<td>4</td>
<td>O=C(NMe₂)₂</td>
<td>10</td>
<td>16 (16)</td>
<td>100 (83)</td>
</tr>
<tr>
<td>5a</td>
<td>MeCN</td>
<td>10</td>
<td>11 (11)</td>
<td>3 (N.D.)</td>
</tr>
<tr>
<td>5b</td>
<td>neat</td>
<td></td>
<td>100 (100)</td>
<td></td>
</tr>
<tr>
<td>6a</td>
<td>THF</td>
<td>10</td>
<td>20 (20)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>6b</td>
<td></td>
<td>100</td>
<td>30 (30)</td>
<td></td>
</tr>
<tr>
<td>7a</td>
<td>H₂O</td>
<td>10</td>
<td>25 (25)</td>
<td>10 (10)</td>
</tr>
<tr>
<td>7b</td>
<td></td>
<td>100</td>
<td>49 (49)</td>
<td></td>
</tr>
<tr>
<td>8a</td>
<td>DMSO</td>
<td>10</td>
<td>35 (35)</td>
<td>18 (16)</td>
</tr>
<tr>
<td>8b</td>
<td></td>
<td>100</td>
<td>93 (93)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>MeOH</td>
<td>10</td>
<td>49 (49)</td>
<td>29 (29)</td>
</tr>
<tr>
<td>10</td>
<td>pyridine</td>
<td>10</td>
<td>100 (100)</td>
<td>100 (90)</td>
</tr>
</tbody>
</table>

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Chapter 3. Phosphine-Mediated Catalyst Decomposition

\[ ^6\text{C}_6\text{D}_6 \text{ solvent, } [\text{Ru}] = 20 \text{ mM.} \text{ % Loss of } \text{GIIm}^* \text{ determined by } ^1\text{H NMR analysis, by integration of the methylidene signal vs internal standard (TMB); % 1 by } ^{31}\text{P}\{^1\text{H}\} \text{ NMR analysis, as a percentage of total integration. N.D. = not determined; peak intensity insufficient for reliable } ^{31}\text{P}\text{ NMR integration. GIIm}^* \text{ completes the mass balance, except where noted.}^b \text{ Complete in <10 min at RT.} \text{ For } L = \text{ py, free PCy}_3 \text{ accounts for the discrepancy between % GIIm}^* \text{ lost and % 1 formed.}^c

The capacity of MeCN, THF, DMSO, H\(_2\)O, and MeOH to accelerate methylidene abstraction is important in understanding the poor metathesis performance of phosphine-functionalized catalysts in these solvents.\(^{19,20,41,42}\) More generally, it provides the first clear explanation for low metathesis productivities in polar media, despite the correlation between solvent polarity and faster initiation (phosphine loss)\(^{18}\) established for GII. This behavior is of particular note given interest in metathesis in water and “green” solvents, often bearing ether donors.\(^{19-23}\) The impact of water holds arguably even greater significance, given its ubiquity as a contaminant in synthetic and process chemistry.

3.2.3 Probing the Reversibility of Nucleophilic P\(_3\)Cy Attack

An important question in this chemistry is whether P\(_3\)Cy attack at the [Ru]=CH\(_2\) carbon to form the [Ru]–CH\(_2\)P\(_3\)Cy species is truly irreversible. If it is reversible, re-entry into the catalytic cycle and further metathesis should be possible (Scheme 3.5a). A simple test would involve reaction of an isolated \(\sigma\)-alkyl complex with a substrate such as DDM, to see if metathesis is observed. Ideally, such a complex would bear a strong donor (e.g. an NHC or P\(_3\)Cy ligand), which confers metathesis activity. However, C-H activation of such complexes is too high to permit isolation. In the H\(_2\)IMes system, the \(\sigma\)-alkyl complex cannot be observed, let alone isolated, while the IMes derivative is only transiently observed.\(^{43}\) The only isolable \(\sigma\)-alkyl complexes known to date are the tris-L complexes Ru-2,\(^5,43\) in which L represents pyridine and DMSO. While these compounds may be

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insufficiently electron-rich at Ru to support metathesis, treatment with simple substrate DDM was pursued, in hopes that even minimal metathesis activity might be observed.

In these experiments (Scheme 3.5), the σ-alkyl complexes Ru-2 were treated with DDM, the high metathesis activity of which was noted above (Scheme 3.5b). No metathesis was observed for pyridine-stabilized Ru-2a on addition of 10 equiv DDM, even after 24 h at 80 °C. DMSO-stabilized Ru-2b was treated with a larger excess of DDM (100 equiv) under the same conditions, but again, no metathesis activity was observed. As noted above, the absence of metathesis activity in this experiment is not explicit evidence that PCy₃ attack at [Ru]=CH₂ is irreversible. This could potentially be probed further by (a) testing with norbornene, which readily undergoes metathesis with less electron-rich Ru centers; (b) undertaking ligand exchange of Ru-2b with a truncated NHC, to ensure metathesis activity without undergoing C-H activation. The latter option was explored by indirect means in a later section of this Chapter.

Scheme 3.5 Probing the reversibility of PCy₃ attack at [Ru]=CH₂: Reaction of σ-alkyl complexes Ru-2 with DDM

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3.2.4 Impact of Phosphine Scavengers in Metathesis with GII

As exemplified above, the productivity of GII drops significantly when metathesis is performed in neat THF, owing to the susceptibility to donor-accelerated decomposition. The next phase of study therefore focused on examining whether phosphine scavengers could improve the metathesis activity of GII in this solvent. Reports have shown that copper(I) halides can increase metathesis yields with GII in ether and in the presence of methanol. However, a report by Grubbs showed that, in THF, several phosphine-scavenging additives (HCl/Et₂O, CuCl₂, CuCl, B(C₆F₅)₃, Ni(COD)₂, and AlCl₃) all lowered cross-metathesis yields with GII relative to the scavenger-free control. The following candidates were screened in the RCM of the benchmark substrate DDM: copper (I) chloride and iodide (CuCl, CuI); Amberlyst-15 resin; benzyl iodide (BnI), and Merrifield-I resin (Figure 3.4). Conditions were chosen such that the control reactions did not reach completion, leaving room for improvement in the presence of phosphine scavengers. Thus, in the absence of additives, RCM was carried out using GII for 24 h at RT in toluene or THF. Catalyst loadings were increased by 20 times in THF to compensate for the lower activity in this solvent: that is, to 0.005 mol% GII in toluene, and 0.1 mol% in THF. RCM yields in these control experiments reached 61% and 81%, respectively.

CuCl proved to be highly detrimental to metathesis activity in both solvents (as indeed it did when used in the CM of the electron-deficient substrate methyl vinyl ketone). In sharp contrast, CuI increased yields by 26% (to 87%) in C₇H₈, and by 19% (to 100%) in THF. Of note is its efficacy in toluene, despite Lipshutz’ finding that ethereal solvents were more effective than aromatic and chlorinated solvents. Amberlyst-15 resin severely reduced activity in toluene (to ca. 10% RCM yield), but had essentially no impact in THF. Yields in THF do not reach those observed for CuI and Merrifield-I, likely due to competing catalyst decomposition in the presence of Amberlyst-15:

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Daniel Luis do Nascimento of the Fogg group has shown that GII exposed to 4 equiv Amberlyst-15 (THF, RT) undergoes a strikingly high 54% decomposition after just 2 h. To account for the detrimental impact of the resin in toluene compared to THF, it is suggested that in THF the catalyst is relatively stabilized by solvent binding, forming a six-coordinate complex. In toluene, however, no such stabilization is possible, and the five- and four-coordinate catalyst species are more vulnerable to decomposition by resin reactivity.

Use of the Merrifield resin in toluene enabled metathesis yields comparable to CuI. Improvements were also seen in THF, though to a lesser extent (maximum 93% RCM). The improved performance relative to the control reaction is particularly striking given that formation of GII-I via halide exchange is a potential side reaction promoted by Merrifield-I (Scheme 3.6). Indeed, Morris exploited this capacity of the resin to synthesize RuH((R)-binap)(PPh₃) from its chloride analogue, and Daniel do Nascimento of the Fogg group noted partial halide exchange when using Merrifield-I as a scavenger in the metathetical synthesis of (e.g.) HI from GI. Halide exchange is difficult to reconcile, however, with the reduced metathesis activity reported by Dias and Grubbs for GII-I relative to GII. While a 250-fold increase in initiation rate was reported for GII-I relative to the parent chloride catalyst (probably due to the increased steric bulk of the iodide ligand (which aids in displacing PCy₃), net metathesis activity was reportedly comparable to or lower than that of GII. Attempts to use BnI as a soluble resin mimic were unsuccessful, as its use had no impact on TONs. The higher efficacy of the resin may be due to the multivalent effect, where clustering of active sites increases binding affinity for the phosphine. It is worth noting that phosphine-free catalyst HII reaches 100% conversion in both solvents under analogous conditions.
The foregoing demonstrates that the performance of phosphine-stabilized GII can be improved without resorting to a more costly phosphine-free catalyst, although the performance of the leading phosphine-free catalyst HII is not surpassed. While Amberlyst-15 resin and BnI were ineffective, CuI and Merrifield-I showed increased TONs relative to the control experiment. While CuI has previously been used as a phosphine scavenger in metathesis, use of Merrifield-I was not previously reported. Preliminary results show that Merrifield-I came a close second to CuI, with
the significant advantage of being readily removed by filtration after reaction, and not introducing an additional load of heavy metals (with potentially broader, unwanted activity, including redox activity). This study was limited, however, to RCM of DDM with GII. An expanded survey of substrate and catalyst scope is needed to assess its use more rigorously. Overall, these results also have major implications regarding the ability to achieve higher metathesis yields in greener solvents (many of which contain ether donors, which are detrimental to catalyst lifetime).

3.2.5 Synthesis and Use of a Metathesis Catalyst Bearing an IMeMes Ligand

To examine whether curtailed NHC bulk prevents C-H activation, the unsaturated carbene ligand IMeMes was explored, in which one N-mesityl group of IMes is truncated to N-Me (Figure 3.3, page 36). IMeMes was selected in preference to its saturated analogue H$_2$IMeMes, because faster rotation of the unsaturated carbenes about the Ru–NHC bond is expected to further retard C-H activation. For saturated NHCs, in contrast, the higher multiple-bond character in the Ru-C$_{NHC}$ bond means that this ligand is held rigidly in position, favouring C-H activation.

Free IMeMes was generated from imidazolium salt 2a (itself synthesized by a literature method) according to the methodology established for IMes. The iodide salt was converted to its tetrafluoroborate salt 2b by treatment with HBF$_4$, and free carbene IMeMes was generated by deprotonation of 2b with NaH (Scheme 3.7).
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Scheme 3.7 Synthesis of free IMeMes.

Catalyst Ru-6 was then prepared by treatment of GI with IMeMes. Bis-NHC complex Ru-7 was also formed as a minor product (ca. 32%, Scheme 3.8), even when the NHC was added slowly. Disubstitution with the IMeMes ligand is due to its reduced size relative to H₂IMes, as the latter is too bulky to form a bis-NHC complex. The impact of small NHC size on catalyst synthesis will be further discussed in Chapter 4.

Scheme 3.8 Synthesis of Ru-6, with formation of minor product Ru-7.

Also of note, two Ru-6 alkylidene singlets are detected by ¹H NMR analysis (19.88 ppm, 20%; 19.37 ppm, 48%). These are assigned to NHC rotamers (Figure 3.5). Consistent with this, variable temperature ³¹P{¹H} NMR (121 MHz, protio-THF; see Appendix A1.1, Figure A4) showed separation of the phosphine singlet (δᵮ 35.4 ppm at RT) into two singlets (δᵮ 35.5, 35.4 ppm) of Ru-6 at –60 °C.

Figure 3.5 Rotamers of Ru-6

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Despite the presence of ca. 32% Ru-7 contaminant, Ru-6 was tested in the RCM of DDM. Complete cyclization required over 5 h at 40 °C (Figure 3.6), even at a catalyst loading of 1 mol%. In comparison, GII achieves complete cyclization within 2 h at a loading of 0.05 mol% at 30 °C. While Ru-6 can indeed catalyze metathesis, its reduced activity relative to GII points toward limitations that will be explored in Chapter 4.

**Figure 3.6 Rate curve for the RCM of DDM with Ru-6 (1 mol%).**

### 3.3 Conclusions and Future Work

Despite the widespread use of GII in metathesis, its shortcomings are apparent: phosphine-mediated side-reactions are tied directly to catalyst decomposition. The data in this Chapter show that its decomposition is accelerated in the presence of sterically accessible Lewis donors, even weak oxygen donors. The negative impact of such donors on metathesis activity demonstrated in

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benchmark RCM reactions highlights limitations on the potential utility of phosphine-stabilized catalysts in “green” ethereal or aqueous solvent media.

We then sought to probe the reversibility of nucleophilic attack by PCy$_3$ at the [Ru]=CH$_2$ moiety, to examine whether nucleophilic attack, or ensuing C-H activation of the NHC ligand, is the key deactivating event. This was complicated by the inability to isolate a σ-alkyl complex with a strong donor ligand, such as PCy$_3$ or H$_2$IMes. Despite this, it was shown that tris-L σ-alkyl complexes Ru-2 did not form metathesis-active species even under forcing conditions. To probe this further, a reaction with a stronger driving force, such as ROMP of a norbornene derivative, could be tested instead.

If PCy$_3$ attack at [Ru]=CH$_2$ is accepted as irreversible, inhibiting attack may plausibly be considered key to improving catalyst lifetime. This is particularly important in donor solvents, which can accelerate decomposition. We therefore explored the use of phosphine scavengers in metathesis. It was shown that phosphine sequestration by Merrifield-I was effective in increasing TONs in the RCM of DDM, although it does not surpass CuI in this capability. However, the rich chemistry associated with Cu(I) may introduce problematic behaviour depending on substrate choice, which may be circumvented by the use of Merrifield-I. To assess this, a broader substrate scope should be examined, with particular consideration to the compatibility of scavengers with functionalized olefins.

Finally, we considered the possibility that C-H activation of the NHC ligand is the key deactivating event, meaning catalyst redesign should focus on curtailing the size of the NHC $N$-substituents. To examine this, a new catalyst bearing an NHC ligand with one $N$-mesityl truncated to an $N$-methyl was synthesized. Metathesis was relatively slow even with the benchmark substrate DDM,
however full cyclization was achieved nonetheless. Given its activity, this catalyst is not an improvement on the standard H$_2$IMes, although it may still be a more stable analogue. To probe this, future experiments should focus on testing its robustness toward nucleophilic phosphine attack by synthesizing the analogous methylidene complex of Ru-6. If a stable σ-alkyl intermediate is intercepted, this would show that C-H activation is in fact stalled by the reduced NHC size. However, the rate of the initial phosphine attack may be accelerated by the lack of steric protection at the methylidene, and should also be considered.

3.4 References

(36) While binding of tertiary amines such as NEt3 to Ru centers has been established, the complexes involved are typically less sterically congested arylphosphine derivatives. For a discussion of such complexes and their degradation products, see: (a) Fogg, D. E.; James, B. R. *Inorg. Chem.* 1995, 34, 2557–61. For examples of Ru complexes containing macrocyclic, tetradentate tertiary amines, see: (b) Wong, C.-Y.; Lee, F.-W.; Che, C.-M.; Cheng, Y. F.; Phillips, D. L.; Zhu, N. *Inorg. Chem.* 2008, 47, 10308–10316, and references therein.

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Chapter 3. Phosphine-Mediated Catalyst Decomposition


Chapter 4. The Deleterious Effect of NHC Truncation on Catalyst Design

Sections 4.1, 4.2.1, 4.2.2, and 4.2.3 of this Chapter have been published in: Synthesis and Dynamic Behaviour of a Dimeric Ruthenium Benzylidene Complex Bearing a Truncated N-Heterocyclic Carbene Ligand. Carolyn S. Higman, Stephanie A. Rufh, Robert McDonald, and Deryn E. Fogg. *J. Organomet. Chem.* 2017, 847, 162-166 (special issue in honour of John Gladysz). (https://doi.org/10.1016/j.jorganchem.2017.03.033) Copyright 2017 Elsevier; reprinted with permission.

**Author contributions:** Higman, Rufh, and Fogg wrote the manuscript. The synthesis of Ru-11a was developed by Higman, and repeated multiple times by Rufh. NMR characterization of Ru-11a was carried out by Higman and Rufh; catalysis with Ru-11a by Rufh.

4.1 Introduction

As noted in Chapter 3, NHC activation is a common structural feature in decomposition products formed by second-generation metathesis catalysts (Figure 4.1).

More generally, intramolecular C-H activation is known to plague $N$-mesityl and other $N$-aryl NHCs, as well as their $N$-ethyl or $N$-isopropyl counterparts, and could potentially account for the poor metathesis activity of $N$-Pr NHC complexes. Modification of the NHC ligand to curb such pathways (commonly via approaches involving, in Crabtree's phrase, "slimming" the NHC substituents) has been highlighted as a key strategy for catalyst redesign in olefin metathesis.

![Figure 4.1 Ruthenium metathesis catalysts of the Grubbs and Herrmann classes (structures of GI and GII are reproduced here for convenience).](image)

In studies designed to examine the validity of this proposition, we sought to access an analogue of GII bearing a truncated NHC ligand. In the IMe$_4$ ligand (IMe$_4$ = 1,3,4,5-tetramethylimidazol-2-ylidene; Figure 4.2), geometric constraints prohibit C-H activation. Relatively few ruthenium...
complexes of IMe₄ have been reported, in comparison to the ubiquitous H₂IMes and IMes derivatives. The Whittlesey group has developed routes to hydride complexes bearing one, two, or four such ligands. The sole example explored within the context of olefin metathesis is indenylidene complex Ru-8a (Figure 4.2), although related IMe₂ catalysts are known, including Ru-8b and benzylidene complex Ru-9, a mixed-NHC analogue of the Herrmann catalyst HC (see Figure 4.1). These complexes exhibited low metathesis activity (requiring temperatures of ≥100 °C), but this is expected from the need to lose a strongly donating NHC ligand to open up a vacant site for olefin binding. Synthesis of a Grubbs-class IMeₙ catalyst was therefore of interest.

![Figure 4.2 Ruthenium metathesis catalysts bearing the IMeₙ ligand.](image)

Attempts to prepare a mono-IMe₄ complex analogous to GII, however, yielded multiple products. While RuCl₂(IMe₄)(PCy₃)(=CHPh) was ultimately isolated by Carolyn Higman of this research group, the synthetic chemistry was complicated by competing formation of poly-NHC byproducts. One aim of the present work was to clarify the nature of these species. The first part of this Chapter describes deliberate efforts to synthesize the bis-NHC complex RuCl₂(IMe₄)₂(=CHPh) Ru-10. The facile dimerization of this species to afford [Ru₂(μ-Cl)₃(IMe₄)₄(=CHPh)₂]Cl Ru-11a accounts for the inability to access a mono-Ru product. Dimeric Ru-11a exhibits a rich dynamic behaviour at room temperature, which results in observation of three [Ru]=CHPh rotamers despite the putative equivalence of the two benzylidene sites. As such face-bridged dimers are notoriously unreactive.
in metathesis,\textsuperscript{28-31} a more reactive, edge-bridged dimer\textsuperscript{32} was prepared by abstracting a bridging chloride ligand. Like its parent dimer, this complex showed minimal metathesis reactivity, despite the fact that re-opening of the dimer should give access to a basal site cis to the alkylidene ligand. This could indicate that NHC truncation has a \textit{negative} impact on metathesis activity.

Many of the recent advances in understanding the decomposition of Grubbs-class catalysts\textsuperscript{5,33,34} (Chapter 3) were enabled by Justin Lummiss’ successful development of a high-yield synthetic route to the resting-state methylidene complexes GIIm and GIIm’. The corresponding IMe\textsubscript{n} complexes, however, are unknown. Incorporation of IMe\textsubscript{4} into a methylidene complex was thus regarded as a priority in seeking to establish whether NHC truncation has a positive or negative impact. The last part of this Chapter describes efforts to access such a complex, and unexpected revelations about the deleterious impact of attenuating NHC bulk.

\textbf{4.2 Results and Discussion}

\textbf{4.2.1 Synthesis of Face-Bridged Ru Benzylidene Dimer [Ru(μ-Cl)\textsubscript{3}(IMe\textsubscript{4})(=CHPh)\textsubscript{2}]Cl (Ru-11a)}

Treating a solution of GI in benzene with a slight excess of IMe\textsubscript{4} (2.1 equiv) at ambient temperatures caused an immediate colour change from purple to brown, with slow deposition of a green solid. After 18 h, no further starting material was evident by \textsuperscript{1}H NMR analysis, and the precipitate was filtered off and washed with benzene and hexanes. The product proved completely insoluble in hydrocarbon solvents (benzene, toluene, hexanes, pentane) or diethyl ether, and sparingly soluble in THF, but was soluble in chlorinated solvents. \textsuperscript{31}P{\textsuperscript{1}H} NMR analysis in deuterated dichloroethane (DCE-d\textsubscript{4}) indicated a phosphine-free complex, as anticipated, but three benzylidene singlets were evident in the \textsuperscript{1}H NMR spectrum. NOESY-NMR studies revealed that these are due to a single, conformationally mobile ruthenium complex. Unexpectedly, however,
X-ray analysis of crystals grown by Carolyn Higman from CH₂Cl₂-pentane revealed that this species was not a mono-ruthenium product of type Ru-10, but rather dimeric Ru-11a (Scheme 4.1). Formation of Ru-11a suggests either preferential formation of cis-Ru-10, or isomerization of initially-formed trans-Ru-10 (plausibly driven by the unfavourable trans effect of two strongly σ-donating NHC ligands, in conjunction with the low steric demand of the IMe₄ ligand). Dimerization of cis-RuCl₂L₂(=CHR) precatalysts has been reported,[28,29,31,36] where not prohibited by ligand bulk or rigidity.[32,37-40] Indeed, in early studies by the Fogg group on Ru-phosphine derivatives, facile formation of such triply-bridged dimers was identified as a key decomposition pathway for cis-dichloro metathesis catalysts.[28,29]

Scheme 4.1 Synthesis of IMe₄ complex Ru-11a.⁴

⁴ A single rotamer is shown, for convenience.

4.2.2 Molecular Dynamics Study: [Ru]=CHPh and Ru-NHC Rotation

¹H NMR analysis of Ru-11a in DCE-d₄ at 500 MHz revealed three broad singlets in the alkylidene region, in a ratio of 10:4:1 (Figure 4.3a). These were assigned to the rotational isomers depicted, on the basis of the number and strength of [Ru]=CHPh–NMe correlations observed in ¹H-¹H NOE experiments. These data support the staggered [Ru]=CHPh conformation depicted, notwithstanding the mobility indicated by the breadth of the [Ru]=CHPh signals. Conformer C
indeed corresponds to the structure observed crystallographically. X-ray analysis of GII, in comparison, shows the benzylidene ligand eclipsed with the Cl–Ru–Cl axis. The singlet multiplicity of the [Ru]=CHPh signal for GII likewise indicates a 90° dihedral angle between [Ru]=CH and Ru–P in solution.

Figure 4.3 (a) Rotational isomers of Ru-11a, viewed down the Cl–Ru=CHPh bond, and 1H-1H EXSY NMR spectrum showing exchange coupling of all three benzylidene protons. (b) Rotational exchange of NMe and CMe groups, and 1H-1H EXSY NMR spectrum showing corresponding exchange coupling (500 MHz, 298 K, DCE-d4).

The inequivalence of the adjacent IMe₄ ligands on a given Ru centre in Ru-11a implies that the NHC environments are distinguished by the orientation of these ligands relative to the [Ru]=CHPh vector. Efforts to probe this point by generating the corresponding methyldiene analogue were
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thwarted by the low metathesis activity described in Section 4.2.3, and rapid decomposition upon treatment of first-generation methylidene (GIm) with IMe₄ (details deferred to Section 4.2.5).

Key exchange correlations between the three rotamers of Ru-11a are summarized in Figure 4.3b. Solid arrows indicate exchange between methyl groups within the same NHC ligand, arising from rotation about the Ru-NHC bond. (Additional, through-space interactions of the benzylidene proton with four \( N\text{-Me} \) groups are evident in the \(^1\text{H}-^1\text{H NOESY} \) spectrum: see Appendix A2.2, Figure A10). Facile rotation of unsaturated NHC ligands about the M–C₉NHC bond is regarded\(^{42,43} \) as a reflection of their poor \( \pi \)-acceptor capability, relative to the corresponding saturated NHCs,\(^{43-45} \) in which stronger Ru→NHC backdonation results in a greater degree of double-bond character.

Accordingly, the ease of rotation of the IMe₄ ligand is consistent with a high proportion of single-bond character in the Ru–C₉NHC bond, amplified by the relative freedom from steric restrictions of this small NHC.

Also of note in Figure 4.3b is exchange of the methyl protons on adjacent NHC ligands (dashed arrows), signifying benzylidene rotation. Rotation about the [Ru]=CHPh bond offers experimental insight into the extent of double-bond character present in this moiety, when steric restrictions are eliminated. This has important potential implications for the stability of the [Ru]=CHR carbon. A more covalent, “Schrock-like” bond, for example,\(^{46,47} \) should affect the vulnerability of the alkylidene carbon to nucleophilic attack. Further, benzylidene rotation has been related to initiation, in a DFT study of GII using the M06L functional.\(^{48} \) PCy₃ loss was reported to occur only from the rotamer in which the benzylidene ligand is eclipsed with the NHC–Ru–PCy₃ axis, and inhibited benzylidene rotation in GII was proposed as a key contributor to the inverse trans effect established experimentally.

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Efforts by Carolyn Higman to extract activation parameters for Ru–NHC and [Ru]=CHPh rotation were frustrated by the complexity of the system revealed by variable-temperature NMR experiments.\textsuperscript{35} At 70 °C, the benzylidene signals for B and C coalesce, while the most downfield peak (A) remains a broad hump at its original location. At low temperature (-80 °C), yet more rotamers emerge. The participation of multiple species with different populations (i.e. different exchange parameters) precluded Eyring analysis.

Even on a qualitative basis, however, the rotational behaviour of the benzylidene ligand in sterically unencumbered Ru-11a is potentially informative. In GII, benzylidene rotation is restricted by steric conflict with the PCy\textsubscript{3} ligand\textsuperscript{49} and π-π interactions between the phenyl and mesityl rings,\textsuperscript{50} and hence does not report on the extent of double-bond character in the [Ru]=CHPh moiety. The facile rotation about the [Ru]=CHPh bond observed in Ru-11a is hence of interest, particularly for the potential inference of limited backdonation from the metal. In the extreme, this could point toward the validity of the Ru(II) descriptor.\textsuperscript{47} An unanswered question, however, remains the ease with which the Ru=C d\textsubscript{π}-p\textsubscript{π} orbital can rotate via linear combination with two different atomic Ru d orbitals, without a reduction in bond order.

4.2.3 Assessing RCM Activity of Ru-11a

While the principal focus of this study was the identification and solution behaviour of face-bridged dimer Ru-11a, a brief assay of its metathesis activity was also undertaken. These experiments were conducted in dichloroethane, given the limited solubility of Ru-11a in non-chlorinated solvents. As expected from the behaviour previously established for such face-bridged, coordinatively saturated dimers,\textsuperscript{28,29} RCM activity was very low. Thus, even the readily-cyclized diene diethyl diallylmalonate (DDM) underwent no reaction over 3 days at 40 °C in the presence of 1 mol% Ru-11a (Figure 4.4). Addition of HCl (1 equiv per Ru)\textsuperscript{51} resulted in marginal
improvement, with 14% RCM after 72 h. In the presence of Amberlyst-15, an acidic ion exchange resin (8 equiv, 4 equiv per Ru), the RCM yield reached >50% after 72 h, possibly owing to abstraction of an IMe$_4$ ligand. These results reinforce the point that formation and dimerization of cis-dichloro ruthenium structures can provide an efficient decomposition pathway for metathesis catalysts.

![Figure 4.4 Attempted RCM of DDM by Ru-11a alone (green triangles), or with added HCl (filled orange squares), or Amberlyst-15 resin (blue squares).](image)

The low metathesis activity of the dimers above is expected from the high stability of the Ru$_2$(μ-Cl)$_3$ configuration, which impedes binding of olefin at a site cis to the benzylidene ligand. In contrast, related edge-bridged dimers exist in equilibrium with their mononuclear counterparts, and can exhibit high metathesis activity. Chloride abstraction from Ru-11a was therefore undertaken, to see if an edge-bridged derivative would exhibit improved performance.

### 4.2.4 Synthesis and Catalytic Activity of Edge-Bridged Dimer Ru-12

While addition of NaBF$_4$ to Ru-11a at RT effected only counterion exchange, edge-bridged Ru-12 was obtained by reaction with NaBAR$_4$ under more forcing conditions (Scheme 4.2). We anticipated significantly improved metathesis activity for Ru-12, given the precedents noted
above. Reaction with the readily-cyclized substrate DDM, however, resulted in only 5% RCM after 5 h at RT in CH₂Cl₂, at a catalyst loading of 1 mol%. The low activity may be due to facile regeneration of face-bridged Ru-11 in solution, as NMR analysis post-metathesis revealed the three alkylidene singlets characteristic of this species, with no evidence of either Ru-12 (δH 19.66 ppm in CDCl₃) or a methylidene resting-state species. The insolubility of Ru-12 in aromatic and aliphatic solvents, and its minimal solubility in THF, limited examination of its behaviour in non-chlorinated solvent.

**Scheme 4.2 Synthesis of edge-bridged dimer Ru-12.**

![Scheme 4.2](image)

### 4.2.5 Reaction of IMe₄ with a bis-thioaryoxide analogue of GI

The chemistry above demonstrates that reaction of GI with IMe₄ does not afford access to a Grubbs-class, mono-IMe₄ catalyst. Instead, the small size of the NHC ligands results in installation of multiple IMe₄ ligands. Similar results were reported outside the context of metathesis by the Whittlesey²⁰⁻²² and Hepp⁵³ groups. To circumvent this problem, reaction of IMe₄ with the thioaryoxide GI analogue Ru-13 was examined. The precursor was synthesized by Jensen’s
procedure, it is self adapted from the original Fogg aryloxide methods (Scheme 4.3). A notable feature of the bis-SAr analogue of III, synthesized by Nikita Panov of the Fogg group, is the ease with which it reverts to its chloride parent in chlorinated solvents (unpublished work). While this is a limitation in the context of catalysis, it was viewed as a potential asset in the present work, as the thioaryloxide ligands can serve as bulky protecting groups to aid in installation of a single NHC ligand, subsequent replacement of which could generated the target complexes.

Accordingly, bis-thioaryloxide complex Ru-13 was treated with one equivalent of IMe4 at RT in C6D6. Even after 4 d, at which point conversion had reached only ca. 25%, the bis-IMe4 product was observable (18% Ru-14; 5% Ru-15; Scheme 4.3). The initially-formed mono-IMe4 complex Ru-14 evidently reacts with IMe4 at a rate comparable to that at which starting Ru-13 undergoes ligand exchange.

Scheme 4.3 Synthesis of thioaryloxide complex Ru-13, and reaction with IMe4.
The mono- and bis-IMe₄ complexes are easily separated, however. Thus, on dissolving the mixture in CH₂Cl₂, the bis-IMe₄ complex Ru-15 is converted to dimer Ru-11a, while the mono-IMe₄ complex Ru-14 chlorinates to form the desired product, GII’’ (Scheme 4.4). Somewhat unexpectedly, Ru-13 is not converted to chlorinated analogue GI, perhaps due to protection of the Ru centre by the two bulky PCy₃ ligands.

Separation of Ru-11a from the mixture was achieved by dissolving in C₆H₆ and filtering off the dimer. However, Ru-13 and the desired product GII’’ could not be separated, as their solubilities were too closely similar.

**Scheme 4.4 Deprotection of Ru-thioaryloxide complexes by treatment with CDCl₃**

4.2.6 Treatment of GIm with IMe₄

The difficulty in terminating reaction at a mono-IMe₄ analogue of GII points toward the ease with which this sterically unprotected Ru centre can undergo unwanted reactions. We speculated that the reaction of the active species with nucleophiles might be a further instance of such problematic behaviour. To explore this point, we sought to examine the behaviour of the methylidene complex formed by reacting the first-generation methylidene complex GIm with IMe₄. While we

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anticipated that the even greater steric accessibility of RuCl$_2$(IMe$_4$)(PCy$_3$)(=CH$_2$) GII$''$, relative to benzylidene GII$''$, could cause rapid decomposition, we hoped that the rapidity of decomposition and the nature of the decomposition products (e.g. [MePCy$_3$]Cl) might confirm much more facile methylidene abstraction in this system. Unexpectedly, while decomposition was indeed fast, PCy$_3$ attack at the methylidene moiety was not a factor.

Addition of IMe$_4$ in any proportion from 1–4 to GIm in C$_6$D$_6$ (Scheme 4.5) resulted in immediate colour change from pink to orange, and deposition of a pale grey precipitate. $^1$H NMR analysis indicated formation of identical products in all cases, differing only in yield relative to starting GIm. For the reaction with a fourfold excess of IMe$_4$, the supernatant showed complete loss of the methylidene singlet for GIm (19.41 ppm) within 10 min at RT, and no new methylidene signals were observed. Integration against an internal standard revealed 50% known RuCl$_2$(IMe$_4$)$_4$ (Ru-16; identified by NMR$^{53}$ and MALDI-TOF analysis), which accounts for half the consumed NHC.

$^{31}$P{$^1$H} NMR analysis showed solely free PCy$_3$. This is a key piece of evidence, indicating not merely loss of both phosphine ligands from GIm, but also that loss of the methylidene ligand is not due to abstraction by PCy$_3$, which would generate [MePCy$_3$]Cl 1 ($\delta_P$ 34.5 ppm). To account for the insolubility of alkylphosphonium salt 1 in C$_6$D$_6$, the precipitate was redissolved in CDCl$_3$ for analysis, revealing no other $^{31}$P-containing products. An important question, however, is the mass balance with respect to methylidene – that is, the fate of the methylidene ligand.

Scheme 4.5 NMR-tube reaction of GIm with excess IMe$_4$. 

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A potential vector for methylidene loss is bimolecular elimination of ethylene. Bimolecular coupling (BMC) of methylidene complexes is well precedented in the chemistry of early metal complexes, notably Mo and Re,\cite{57-60} and has recently been demonstrated within the second-generation Ru catalysts by Gwen Bailey of this research group.\cite{61} To examine whether C$_2$H$_4$ is liberated in the present reaction, the experiment was repeated in a completely filled J. Young NMR tube, to preclude partitioning of gaseous ethylene into the headspace. Again, no free ethylene was observed at the expected chemical shift ($\delta_H$ 5.25 ppm).

An alternative possibility is scavenging of liberated ethylene by binding to Ru, as observed by Gladysz and coworkers in Re systems.\cite{59,60} While the details are obscured by the instability of this species, as outlined below, a proposed pathway is depicted in Scheme 4.6. In the initial reaction of GIm with IMe$_4$, the PC$_3$ ligands are displaced and cis-Ru-17 is formed, as in the benzylidene system (Section 4.2.1 above). Rapid bimolecular coupling gives methylidene-bridged dimer Ru-18, which eliminates ethylene to afford ethylene-bound Ru-19, and a coordinatively unsaturated Ru center, which reacts with the remaining IMe$_4$ to form Ru-16. Ethylene complex Ru-19 appears to be unstable, and exhaustive efforts have not enabled its spectroscopic observation. The ultimate fate of ethylene, however, appears to be insertion into the Ru–IMe$_4$ ligand to liberate imidazolium salt 5. Thus, MALDI-TOF analysis of the grey precipitate that deposits shows 5 as a primary product (Appendix A2.3, Figure A19), and a well-defined ethyl pattern is observed by $^1$H NMR analysis (3.34 ppm, q, $^3$J$_{H-H}$ = 7.5 Hz, 2H, CH$_2$; 1.28 ppm, t, $^3$J$_{H-H}$ = 7.5 Hz, 3H, CH$_3$).

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A potential pathway by which imidazolium salt 5 could form is shown in Scheme 4.7. Strong backbonding from the electron-rich Ru center in Ru-19 may favour the metallacyclopentene structure shown. Abstraction of a proton from an N-CH$_3$ group could plausibly convert the bound olefin to an ethyl ligand, insertion of which into an IMe$_4$ ligand could liberate Et–IMe$_4$. Abstraction of a chloride ligand, as for [MePCy$_3$]Cl, is well precedented. Such migratory insertion of an alkyl group onto an adjacent NHC carbon has been reported for Pd$^{62-65}$ and Ni$^{66-68}$ systems. In these scenarios, reductive elimination of the alkyl imidazolium salt is facile provided effective overlap of the C$_{alkyl}$ and C$_{NHC}$ $p$ orbitals.$^{69}$ Of particular note, the Cavell group reported decomposition of bis-IMe$_4$ complexes of Pd and Ni by migratory methyl insertion/reductive elimination, with liberation of the respective methyl imidazolium salt (a methyl analogue to ethyl imidazolium salt 5).$^{67}$
Scheme 4.7 Proposed reaction of intermediate Ru-19 to liberate imidazolium salt 5.

While full characterization of the Ru decomposition products has not yet been achieved, these preliminary results demonstrate that NHC truncation greatly increases the susceptibility of the methylidene species to decomposition via BMC. Notably, this susceptibility completely inhibits methylidene abstraction by free PCy$_3$, a primary vector for decomposition in the parent H$_2$IMes and IMes systems. The absence of any such coupling in the benzylidene system is consistent with the increased steric bulk of the benzylidene ligands relative to methylidene, which commonly retards this decomposition pathway for [M]=CHR derivatives.$^{1,61}$

4.3 Conclusions and Future Work

The foregoing gives insight into the impact of NHC truncation on the behaviour of metathesis catalysts. While incorporation of a small NHC in such complexes has been suggested as a method to inhibit catalyst decomposition by C-H activation, this Chapter highlights several challenges arising from the steric accessibility of the Ru centres. First, the reaction of GI with IMe$_4$ was shown to effect displacement of both PCy$_3$ ligands. Facile dimerization precluded isolation of the putative intermediate cis-RuCl$_2$(IMe$_4$)$_2$(=CHPh) Ru-10, instead affording the face-bridged ruthenium dimer [Ru$_2$(μ-Cl)$_3$(IMe$_4$)$_4$(=CHPh)$_2$]Cl Ru-11a. The small size of the IMe$_4$ ligand results in a rich dynamic behaviour for Ru-11a in solution, with rapid rotation of both the NHC and the benzylidene ligands on the NMR timescale. This complex exhibited poor metathesis activity, even in the simple RCM of DDM. This low productivity was attributed to the high
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thermodynamic stability associated with face-bridged dimers, and was not resolved by abstraction of a bridging chloride to give edge-bridged \([\text{RuCl}(\text{IME}_4)_2(=\text{CHPh})][\text{BAR}_4^2]\) \textbf{Ru-12}. Despite precedents for improved catalytic activity with edge-bridged dimers, this was precluded by reformation of face-bridged \textbf{Ru-11a} during metathesis. Metathesis activity requires access to complexes bearing just one NHC per Ru.

Another potential route to a mono-IME\(_4\) complex was therefore explored, in which the steric bulk of the anionic ligands of \textbf{GI} was increased from Cl to thioaryloxide. However, difficulties were again encountered with NHC over-addition, and incomplete consumption of the first-generation starting complex. These difficulties in accessing complexes bearing one IMe\(_4\) ligand per Ru argue against the viability of such \textbf{GII} analogues in catalyst redesign. While useful, however, these findings with benzylidene IMe\(_4\) complexes did not report on the original question: does a small NHC inhibit decomposition of the active catalyst, or does it instead result in faster methylidene abstraction, owing to a lack of protection at the Ru centre?

Installation of IMe\(_4\) in the active methylidene complex showed that the truncated NHC is in fact deleterious, resulting in rapid loss of the methylidene ligand. Unexpectedly, however, decomposition did not involve methylidene abstraction by free PCy\(_3\), the pathway described in Chapter 3 as a major vector for decomposition of Grubbs-class catalysts. Instead, bimolecular coupling resulted in elimination of ethylene. The absence of any [MePCy\(_3\)]Cl coproduct indicates that such coupling out-competes nucleophilic attack on the methylidene ligand. NHC truncation is thus detrimental owing to the increased steric accessibility of the methylidene site. Catalyst redesign for longer lifetimes should therefore focus not on NHC truncation, but on steric protection of the methylidene ligand.
4.4 References

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Chapter 5. Conclusions and Future Work

Notwithstanding the important place of olefin metathesis in contemporary organic synthesis, catalyst decomposition remains an obstacle to full deployment of metathesis methodologies in sustainable chemical manufacturing. The need for improved understanding of the pathways responsible, and potential solutions, provide a context for the work outlined in this thesis. Initial studies examined a key weakness of phosphine-stabilized catalysts, the susceptibility of the off-cycle resting state RuCl₂(H₂IMes)(PCy₃)(=CH₂) GIIIm to “donor-accelerated decomposition.” This pathway involves displacement of the phosphine ligand by sterically accessible Lewis donors, which promotes rapid nucleophilic attack by PCy₃ at the [Ru]=CH₂ carbon. A key finding was the ease with which even weak Lewis bases such as THF, MeOH, and H₂O promote this decomposition pathway. The impact of such donors on RCM yields, even for a readily-cyclized substrate, has important implications for metathesis in “green” solvents such as ethers and water. These results are also important in giving the first direct insight into the negative impact of water on productivity in Ru-catalyzed olefin metathesis. While the immediate focus of this work was on phosphine-mediated decomposition, broader questions center on the potential for such weak donors to promote abstraction of the methylidene ligand by other, non-phosphine, nucleophiles.

Attention was then turned to potential solutions, beginning with methods for limiting methylidene abstraction. First, the use of phosphine scavengers in metathesis was examined, to determine whether the performance of phosphine-stabilized catalysts in donor solvents could be improved. An iodide version of the Merrifield resin, which was previously unreported as a scavenger during metathesis reactions, was shown to increase RCM yields in both toluene and THF. Although CuI remained a more efficient scavenger in both solvents, the use of Merrifield-I (particularly in
metathesis of functionalized olefins) offers an attractive alternative, in view of the rich oxidation chemistry established for Cu(I) salts. Additionally, Merrifield-I is advantageous for this purpose due to its complete insolubility in organic solvents, which facilitates purification post-metathesis. Further studies of substrate scope with the Merrifield-I resin are recommended, to determine its compatibility with various functional groups, and its effectiveness relative to CuI.

An alternative means of inhibiting catalyst decomposition is curtailing the size of the NHC ligand to prevent C-H activation. In this work, two truncated versions of the benchmark NHC ligand H$_2$IMes were examined, in which one or both mesityl ligands are truncated to methyl. The “one-armed” NHC IMeMes was incorporated into a new Ru catalyst, RuCl$_2$(IMEMes)(PCy$_3$)(=CHPh) Ru-6, which displayed modest activity in the RCM of readily-cyclized DDM. This suggests that ligand truncation is ineffective as a strategy for improving catalyst activity. To probe the impact of small NHC size on catalyst decomposition, the more dramatically truncated IMe$_4$ ligand was examined.

Use of IMe$_4$ gave unequivocal evidence that small NHC ligands are detrimental to catalyst lifetimes. First, it was shown that the reaction of IMe$_4$ with the first-generation Grubbs catalyst RuCl$_2$(PCy$_3$)$_2$(=CHPh) GI results in uncontrolled loss of both PCy$_3$ ligands. Poor steric protection at the Ru centre enables dimerization, generating a highly stable face-bridged complex [Ru$_2$Cl$_3$(IME$_4$)$_4$(=CHPh)$_2$]Cl Ru-11a. The metathesis activity of this dimer is poor, as expected from the behaviour of related triply-bridged complexes. Abstraction of a bridging chloride to synthesize edge-bridged analogue [RuCl(IMe$_4$)$_2$(=CHPh)]$_2$[BAr$_4$F]$_2$ Ru-12 did not significantly improve activity. Efforts to access an active catalyst bearing one IMe$_4$ ligand per Ru were undertaken by use of bulky arylthiolate ligands in place of chlorides, but were unsuccessful.
Deeper insight came from studies probing the impact of small NHC size on decomposition of methylidene species. The widespread belief that a truncated NHC could curb decomposition by inhibiting C-H activation was shown to be invalid. Rather, this work showed that [Ru]=CH\(_2\) decomposition is faster when IMe\(_4\) is present. This was exemplified by the reaction of the first-generation methylidene complex RuCl\(_2\)(PCy\(_3\))\(_2\)(=CH\(_2\)) (GIm) with excess IMe\(_4\). Both PCy\(_3\) ligands were displaced by IMe\(_4\), and immediate loss of all methylidene signals was observed by \(^1\)H NMR. Surprisingly, however, this rapid decomposition is not due to abstraction of the sterically unprotected methylidene by PCy\(_3\), as expected from the chemistry of Chapter 3. Instead, bimolecular coupling causes loss of the methylidene ligand, with the ethylene byproduct ultimately inserting into a Ru-IMe\(_4\) bond. This highlights the striking susceptibility of sterically unprotected Ru centres to bimolecular decomposition, and shows that small NHC ligands, such as IMe\(_4\), are profoundly detrimental. Future work should therefore focus on larger σ-donating ligands of the NHC or CAAC class (CAAC = cyclic alkyl amino carbene) to protect the [Ru]=CH\(_2\) moiety against both bimolecular coupling and nucleophilic abstraction.
Appendices

Appendix 1. Supplementary Data for Chapter 3

A1.1 NMR Spectra for Compounds Synthesized

Figure A1. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 1-methyl-3-(2,4,6-trimethylphenyl)imidazolium tetrafluoroborate (2b). Residual solvent impurities are denoted with *.
Figure A2. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 1-methyl-3-(2,4,6-trimethylphenyl)imidazole-2-ylidene (IMeMes). Residual solvent impurities are denoted with *.
Figure A3. NMR spectra ($C_6D_6$) showing key chemical shifts for complexes $\text{RuCl}_2(\text{IMeMes})(\text{PCy}_3)(=\text{CHPh})$ Ru-6 and $\text{RuCl}_2(\text{IMeMes})_2(=\text{CHPh})$ Ru-7, and their relative proportions formed. (a) $^1H$ NMR spectrum (300 MHz), alkylidene region only. Proportions given are percentages of total alkylidene integration. (b) $^{31}P\{^1H\}$ NMR spectrum (121 MHz) before resin treatment to remove free $\text{PCy}_3$. Proportions given are percentages of total $^{31}P$ integration.
Figure A4. Variable temperature $^{31}$P{$^1$H} NMR spectra (121 MHz, protio-THF) of RuCl$_2$(IMeMes)(PCy$_3$)(=CHPh) Ru-6, showing separation of (a) phosphine singlet at RT into (b) two phosphine singlets at $-60^\circ$C.
Appendices

A1.2 NMR Spectra for Monitored Reactions

Figure A5. Decomposition of GIIm’ in the presence of 10 DMSO (50 °C) measured by $^1$H NMR (300 MHz, C$_6$D$_6$), vs DMT (internal standard). (a) Before addition of DMSO (t = 0), 100% GIIm’. (b) After addition of DMSO (t = 2 h), 88% GIIm’.
Figure A6. Decomposition of GIIm’ in the presence of 10 DMSO (50 °C) measured by $^{31}$P-$^1$H NMR (121 MHz, C₆D₆). (a) Before addition of DMSO (t = 0), 100% GIIm’. (b) After addition of DMSO (t = 2 h), 88% GIIm’, 7% [MePCy₃]Cl (1), 5% PCy₃.
A1.3 Representative GC Data

Figure A7. GC-FID trace for RCM of DDM by RuCl$_2$(H$_2$IMes)(PCy$_3$)(=CHPh) GII in the presence of 90 μL water at 2 h.
Appendix 2. Supplementary Data for Chapter 4

A2.1 NMR Spectra for Compounds Synthesized

Figure A8. $^1$H NMR spectrum (300 MHz, C₆D₆) of 1,3,4,5-tetramethylimidazol-2-ylidene (IMe₄). Residual solvent impurities are denoted with *.
Figure A9. $^1$H NMR spectrum of $[\text{Ru}_2\text{Cl}_3(\text{IMe}_4)_4(\equiv\text{CHPh})_2]\text{Cl}$ Ru-11a (DCE-d$_4$, 500 MHz, 298 K). Residual solvent impurities are denoted with *.
Figure A10. $^1$H-$^1$H EXSY/NOESY spectrum (300 MHz, CD$_2$Cl$_2$) of [Ru$_2$Cl$_3$(IMe)$_4$(=CHPh)$_2$]Cl Ru-11a. EXSY correlations are shown in black; NOESY correlations are shown in red.
Figure A11. NMR spectra (CH$_2$Cl$_2$) of [Ru$_2$Cl$_3$(IMe$_4$)$_4$(CHPh)$_2$]BF$_4$ Ru-11b. (a) $^1$H NMR spectrum (300 MHz). CH$_2$Cl$_2$ solvent peak denoted with *. (b) $^{19}$F NMR spectrum (282 MHz).
Figure A12. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of [RuCl(IMe$_4$)$_2$(CHPh)$_2$][BAR$_4^F$]$_2$ Ru-12. Residual solvent impurities denoted with *.
Figure A13. $^1$H NMR spectrum (300 MHz, C$_6$D$_6$) of Ru(S(2,6-dichlorobenzene))$_2$(PCy$_3$)$_2$(=CHPh) Ru-13.
Appendices

A2.2 NMR Spectra for Monitored Reactions

Figure A14. $^1$H NMR spectra (300 MHz, C$_6$D$_6$) showing final alkylidene distribution from the reaction of Ru(S(2,6-dichlorobenzene))$_2$(PCy)$_3$(=CHPh) Ru-13 with (a) 1.0 equiv IMe$_4$, (b) 2.0 equiv IMe$_4$. Proportions given are percentage of total alkylidene integration.
Appendices

Figure A15. Decomposition of GIm in the presence of 4 IMe₄ (RT) measured by ¹H NMR (300 MHz, C₆D₆), vs DMT (internal standard). (a) Before addition of IMe₄ (t = 0), 100% GIm. (b) After addition of IMe₄ (t = 1 h), complete loss GIm, 50% Ru-16 formed.
Figure A16. Decomposition of Glm in the presence of 4 IMe₄ (RT) measured by $^{31}$P{¹H} NMR (121 MHz, C₆D₆). (a) Before addition of IMe₄ (t = 0), 100% Glm (by total $^{31}$P integration). (b) After addition of IMe₄ (t = 1 h), complete loss Glm, PCy₃ is only P-containing product formed.
Figure A17. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of isolated precipitate from the decomposition of RuCl$_2$(PCy$_3$)$_2$(=CH$_2$) Glm in the presence of 4 equiv IMe$_4$. Key identified peaks from imidazolium salt 5 are labelled.
A2.3 MALDI-TOF Mass Spectra

Figure A18. MALDI-TOF mass spectrum (matrix = pyrene) from the decomposition of RuCl₂(PCy₃)₂(=CH₂) in the presence of 4 equiv IMes (product from supernatant). For a summary of key peak assignments, see Table A1 below.
### Table A1. Summary of key MALDI-TOF data from Figure A16.

<table>
<thead>
<tr>
<th>Fragment</th>
<th>Assignment on spectrum</th>
<th>m/z observed</th>
<th>m/z calculated</th>
</tr>
</thead>
<tbody>
<tr>
<td>RuCl$_2$(IME$_4$)$_4$</td>
<td>not observed</td>
<td>-</td>
<td>668.24</td>
</tr>
<tr>
<td>M-[2 Cl]</td>
<td>F</td>
<td>598.388</td>
<td>598.30</td>
</tr>
<tr>
<td>M-[IME$_4$]</td>
<td>E</td>
<td>546.219</td>
<td>544.14</td>
</tr>
<tr>
<td>M-[Cl]‒[IME$_4$]</td>
<td>D</td>
<td>509.247</td>
<td>509.17</td>
</tr>
<tr>
<td>M-[2 Cl]‒[IME$_4$]</td>
<td>C</td>
<td>474.274</td>
<td>474.20</td>
</tr>
<tr>
<td>M-[2 IMe$_4$]</td>
<td>B</td>
<td>420.105</td>
<td>420.04</td>
</tr>
<tr>
<td>M-[Cl]‒[2 IMe$_4$]</td>
<td>A</td>
<td>385.133</td>
<td>385.07</td>
</tr>
</tbody>
</table>
Figure A19. MALDI-TOF mass spectrum (matrix = anthracene) from the decomposition of RuCl₂(PCy₃)₂(=CH₂) in the presence of 4 equiv IMe₄ (product from precipitate). Key identified isotope pattern for imidazolium salt 5 shown.