

Olefin Metathesis: Life, Death, and Sustainability

Justin Alexander MacDonald Lummiss

Thesis submitted to the
Faculty of Graduate and Postdoctoral Studies
University of Ottawa
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Ottawa-Carleton Chemistry Institute
Faculty of Science
University of Ottawa

© Justin Alexander MacDonald Lummiss, Ottawa, Canada, 2015

Table of Contents

Abstract	v
Acknowledgements	vii
Abbreviations	viii
List of Compounds	x
Chapter 1. Introduction	1
1.1. Asymmetric Catalysis: Development and Industrial Uptake	2
1.2. Cross-Coupling: Development and Industrial Uptake	7
1.3. Olefin Metathesis: Development and Industrial Uptake	8
1.4. Ruthenium-Catalyzed Olefin Metathesis	11
1.5. Types of Metathesis Reactions	12
1.6. Commercially Available Pre-Catalysts	14
1.7. Molecular Metathesis Comes of Age	16
1.8. Scope of This Thesis	18
1.9. References	19
Chapter 2. Designing Routes to Catalysts and Intermediates Required for Subsequent Mechanistic Studies	24
2.1. Context, Objectives, and Overview of Content	24
2.1.1. Tables of Contents Entries (published work only)	25
2.2. High-Yield Routes to the Grubbs Methylidene Complexes	26
2.2.1. Introduction	26
2.2.2. Results and Discussion	29
2.2.3. Conclusions	30
2.2.4. Experimental Details for Section 2.2	31
2.3. Incorporating a ^{13}C Isotopic Label into the Active Site for the Grubbs Benzylidene and Methylidene Complexes	33
2.3.1. Introduction	33
2.3.2. Results and Discussion	35
2.3.3. Conclusions	44
2.3.4. Experimental Details for Section 2.3	44
2.4. Ethylene-Free Synthesis of *GIIIm	49
2.4.1. Introduction	49
2.4.2. Results and Discussion	49
2.4.3. Conclusions	52
2.4.4. Experimental Details for Section 2.4	52
2.5. Subsequent Advances	53
2.6. References	55
Chapter 3. Effect of NHC Saturation on Lifetime and Activity in Olefin Metathesis	59
3.1. Context, Objectives, and Overview of Content	59
3.1.1. Table of Contents Entries (published work only)	60
3.2. N-Heterocyclic Carbenes in Olefin Metathesis: Assessing and Understanding lifetime and stability of the resting-state methylidenes	61

3.2.1. Introduction	61
3.2.2. Results and Discussion	62
3.2.3. Conclusions	73
3.2.4. Experimental Details for Section 3.2	73
3.3. Subsequent Advances	74
3.4. References	75
Chapter 4. Donor-Induced Deactivation of the Grubbs Catalysts	77
4.1. Context, Objectives, and Overview of Content	77
4.1.1. Table of Contents Entries (published work only)	79
4.2. The Role of Amine Contaminants in Impeding Metathesis by the Second- Generation Grubbs Catalyst	81
4.2.1. Introduction	81
4.2.2. Results and Discussion	82
4.2.3. Conclusions	87
4.2.4. Experimental Details for Section 4.2	88
4.3. Intercepting a Key Intermediate in Donor-Induced Decomposition	91
4.3.1. Introduction	91
4.3.2. Results and Discussion	92
4.3.3. Conclusions	96
4.3.4. Experimental Details for Section 4.3	96
4.4. Scope of the Donor-Induced Decomposition Pathway	99
4.4.1. Introduction	99
4.4.2. Results and Discussion	99
4.4.3. Conclusions	102
4.4.4. Experimental Details for Section 4.4	103
4.5. Subsequent Advances	104
4.6. References	104
Chapter 5. Sustainable Metathesis: Augmenting the Complexity of Bio-Renewable Feedstocks via Olefin Metathesis	108
5.1. Context, Objectives, and Overview of Content	108
5.1.1. Table of Contents Entries (published work only)	110
5.2. Synthesis of High-Value Molecules from Essential Oils	110
5.2.1. Introduction	110
5.2.2. Results and Discussion	113
5.2.3. Conclusions	116
5.2.4. Experimental Details for Section 5.1	116
5.3. Subsequent Advances	120
5.4. References	121
Chapter 6. Conclusions and Future Directions	125
6.1. References	129
Appendices	130
A.NMR Spectra	130

B. Mass Spectra	151
C. Crystallographic Data	152
D. Handling of isotopically-labelled ethylene	155
E. References	155
F. List of Contributions	156

Abstract

Over the past 15 years, ruthenium-catalyzed olefin metathesis has emerged as a cornerstone synthetic methodology in academia. Applications in fine-chemicals and pharmaceutical manufacturing, however, are just beginning to come on stream. Industrial uptake has been impeded by economic constraints associated with catalyst costs. These are due both to direct costs (exacerbated by intellectual property issues), and to further pressure exerted by the low turnover numbers attainable, and the need for extensive purification to remove ruthenium residues.

From another perspective, however, these difficulties can be seen as arising from our rudimentary understanding of the fundamental organometallic chemistry of the Ru=CHR bond. In particular, we know little about the nature and reaction pathways of the Ru-methylidene unit present in the active species that propagates metathesis, and in the catalyst resting state. We know slightly more about the ruthenacyclobutane species, but still too little to guide us as to their non-metathetical reaction pathways, their contribution to deactivation relative to the methylidene species, and potential work-arounds.

This thesis work was aimed at improving our understanding of the reactivity, speciation, and decomposition of key ruthenium intermediates in olefin metathesis. A major focus was the behaviour and deactivation of species formed from the second-generation Grubbs catalyst $\text{RuCl}_2(\text{H}_2\text{IMes})(\text{PCy}_3)(=\text{CHPh})$ (**S-GII**), which dominates ring-closing metathesis. Also studied were derivatives of the corresponding IMes catalyst **A-GII**, containing an unsaturated *N*-heterocyclic carbene (NHC) ligand.

The methylidene complexes $\text{RuCl}_2(\text{NHC})(\text{PCy}_3)(=\text{CH}_2)$ (**GII**) represent the resting state of the catalyst during ring-closing and cross-metathesis reactions: that is, the majority Ru species present during catalysis. Mechanistic studies of these key intermediates have been restricted, however, by the low yields and purity with which they could be accessed. Initial work therefore focused on designing a clean, high-yield route to the second-generation Grubbs methylidene complexes **S-GII** and **A-GII**. These routes were subsequently expanded to develop access to isotopically-labelled derivatives. Locating a ^{13}C -label at the key alkylidene site, in particular, offers a powerful means of tracking the fate of the methylidene moiety during catalyst deactivation.

Access to **GIIm** enabled detailed studies of the behaviour and decomposition of the Grubbs catalysts. First, the long-standing question of the impact of saturation of the NHC backbone (i.e. IMes vs. H₂IMes) was examined. Dramatic differences in the behaviour of the two complexes were traced to profound differences in PCy₃ lability arising from the diminished π -acidity of the IMes ligand. Secondly, the vulnerability of **GIIm** to nucleophiles was examined. This is an important issue from the perspective of decomposition by adventitious nucleophiles in the reaction medium during catalysis, but also reflects on substrate scope. For amine additives, the dominant deactivation pathway was shown to typically involve attack on the resting-state methyldiene complex, not the metallacyclobutane, which has often been regarded as the most vulnerable intermediate. In addition, the sigma-alkyl intermediate formed by nucleophilic attack of displaced phosphine at the methyldiene carbon was trapped by moving to the first-generation complex, and using a nitrogen donor (pyridine) that cannot promote decomposition via N–H activation pathways. Interception of this long-suspected species led to the proposal of “donor-induced” deactivation as a general decomposition pathway for Grubbs-class catalysts.

Finally, the capacity of phosphine-free catalysts to overcome the shortcomings of the second-generation Grubbs catalysts was demonstrated, in a case study involving application of cross-metathesis (CM) to the synthesis of a high-value antioxidant. An efficient CM methodology was developed for the reaction of renewable essential-oil phenylpropenoids with vinyl acrylates. This work illustrates a new paradigm in sustainable metathesis. Rather than degrading unsaturated feedstocks via metathesis (a process that can be termed “metathe[LY]sis”), it demonstrates how metathesis with directly-functionalized olefins can be used to augment structure and function.

From the perspective of organometallic chemistry and catalyst design, key comparisons built into this thesis are the effect of the NHC ligand (IMes vs. H₂IMes) and its trans ancillary ligand on the efficient entry into catalysis; the susceptibility to nucleophilic attack of the alkylidene ligand (benzylidene vs. methyldiene) vs. the metallacyclobutane; and the effect of replacing a phosphine ancillary ligand with a non-nucleophilic donor.

From a practical standpoint, Chapter 2 brings new *life* to metathesis with the high-yield synthesis of the resting state species, Chapters 3 and 4 examine the deactivation, or *death*, of the methyldiene complexes, and Chapter 5 establishes a new paradigm for olefin metathesis within the context of *sustainable* synthesis.

Acknowledgements

First and foremost, I wish to thank Prof. Deryn E. Fogg for showing me the ropes and teaching me the craft. I am tremendously grateful for the comprehensive and rigorous training you have provided. I truly appreciate and will miss our countless discussions grappling with and arguing over scientific ideas. You lead by example, and I hope in my future endeavours that I am able to achieve the level of rigor, passion and dedication you display on a daily basis. It has been an absolute pleasure, and I can't thank you enough.

Secondly, I need to thank all members of the Fogg lab. Each and every one of you has enriched my graduate experience. Thank you for your useful discussions, constructive feedback, encouragement, and willingness to lend a hand. While you have all played an important role in my development, I'd like to specifically thank the senior members of the Fogg lab when I started (Seb, Johanna, and Nick) for taking the time to mentor me.

I also wish to recognize the hard work of the many technical experts that I have had the pleasure of working with: Dr. Glenn Facey (uOttawa NMR Facility Manager), Dr. Robert McDonald (University of Alberta, X-Ray Crystallography Laboratory), Dr. Serge Gorelsky (uOttawa Computational Chemistry Facility Manager), and Roxanne Clement (uOttawa High Throughput Facility Manager). I also thank both the Provincial Government of Ontario and the University of Ottawa for the financial support they have provided during the course of my graduate studies.

To my friends that have become accustomed to my "radio-silence" for days on end while I tirelessly focus the entirety of my efforts on a particular task, thank you for your never ending encouragement, support, and patience.

To my family, I thank you for your unconditional love, support, encouragement, and understanding.

"When we become more fully aware that our success is due in large measure to the loyalty, helpfulness, and encouragement we have received from others, our desire grows to pass on similar gifts. Gratitude spurs us on to prove ourselves worthy of what others have done for us. The spirit of gratitude is a powerful energizer." — Wilferd A. Peterson

Abbreviations

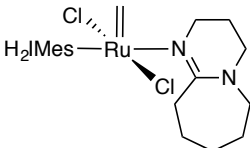
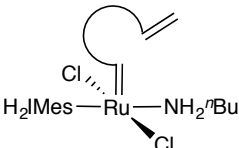
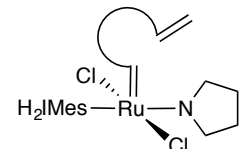
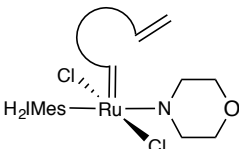
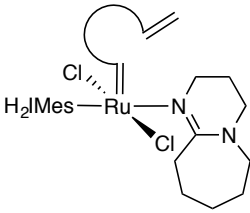
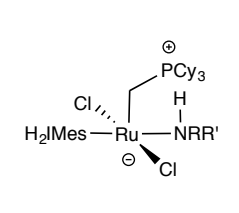
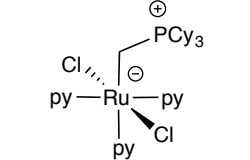
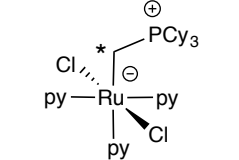
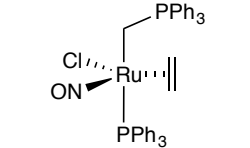
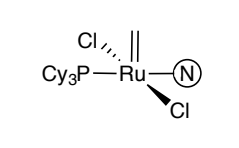
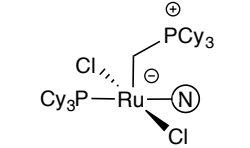
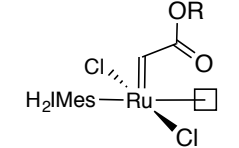
ADMET	Acyclic diene metathesis
API	Active pharmaceutical ingredient
CM	Cross metathesis
COSY	Correlation spectroscopy
DBU	1,8-Diazabicycloundec-7-ene
DCE	1,2-dichloroethane
DFT	Density functional theory
DMSO	Dimethylsulfoxide
equiv	equivalents
ESI	Electrospray ionization
EXAFS	Extended X-ray absorption fine structure
EXSY	Exchange spectroscopy
EYCM	Enyne cross metathesis
GC-FID	Gas chromatography-Flame ionization detection
HCV	Hepatitis C virus
H ₂ IMes	1,3-bis-(2,4,6-trimethylphenyl)imidazolin-2-ylidene
HMBC	Heteronuclear multiple bond correlation experiment
HMQC	Heteronuclear multiple quantum coherence
HSQC	Heteronuclear single quantum coherence
Hz	Hertz
IMes	1,3-bis-(2,4,6-trimethylphenyl)imidazol-2-ylidene
IR	Infrared
MCB	Metallacyclobutane
MDMA	3,4-methylenedioxy-methamphetamine
Mes	Mesityl
MS	Mass spectrometry
Ⓝ	Amine ligand
NHC	<i>N</i> -heterocyclic carbene
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect spectroscopy

ORTEP	Oak ridge thermal ellipsoid plot program
ppm	Parts per million ($\mu\text{g/g}$)
py	Pyridine
RCM	Ring closing metathesis
RCEYM	Ring closing enyne metathesis
ROM/CM	Ring opening metathesis/cross metathesis
ROMP	Ring opening metathesis polymerization
RT	Room temperature
SHOP	Shell higher olefin process
THF	Tetrahydrofuran
THN	1,2,3,4-tetrahydronaphthalene
TMB	1,3,5-trimethoxybenzene
TMS	Tetramethylsilane
TLC	Thin layer chromatography
TOF	Turnover frequency
TON	Turnover number
Tp	Hydrotris(pyrazolyl)borate
XAFS	X-ray absorption fine structure
XRD	X-ray diffraction

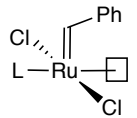
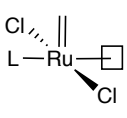
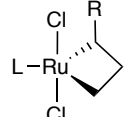
List of Compounds

Ruthenium complexes

#	Compound	#	Compound
GI		GIm	
*GI		*GIm	
^DGI		^DGIm	
S-GII		S-GIIIm	
*S-GII		*S-GIIIm	
^DS-GII		^DS-GIIIm	
A-GII		A-GIIIm	
S-III		Ru-1(N1)	
Ru-2(N2)		Ru-2(N3)	
Ru-2(N4)		Ru-3(N1)	
Ru-3(N2)		Ru-3(N3)	

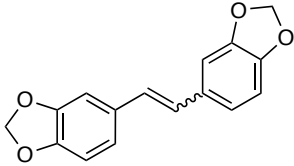
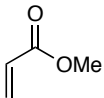
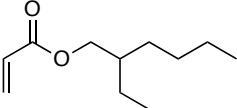
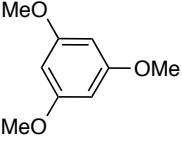
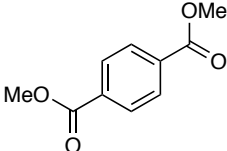
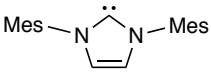
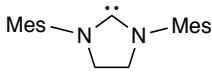
Ru-3(N4)		Ru-4(N1)	
Ru-4(N2)		Ru-4(N3)	
Ru-4(N4)		Ru-5	
Ru-6		*Ru-6	
Ru-7		Ru-8	
Ru-9		Ru-10	

Intermediates in Metathesis

#	Compound	#	Compound
A		B	
MCB			

Organic Compounds

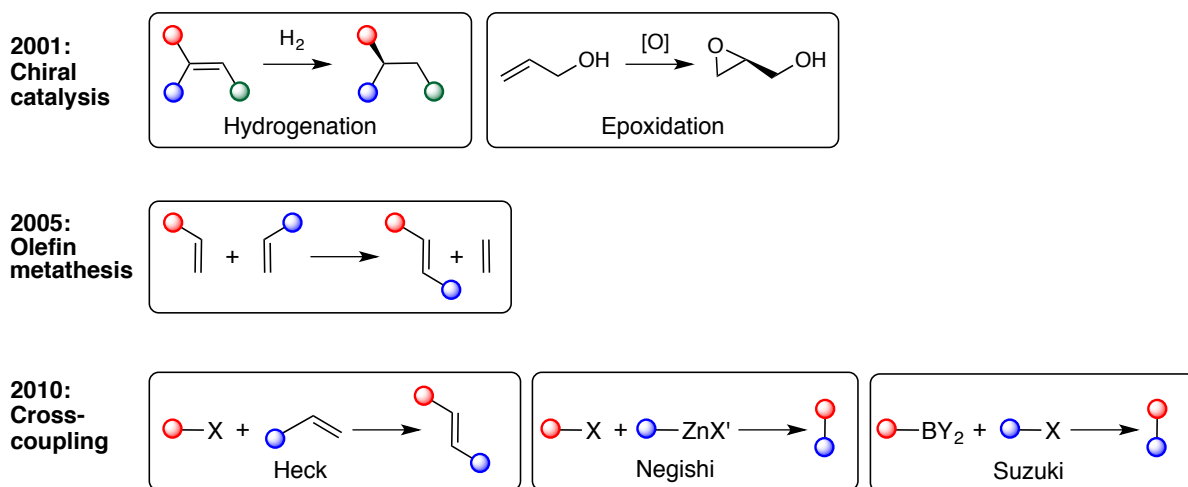
#	Compound	#	Compound
N1	NH ₂ ⁿ Bu	N2	
N3		N4	
P1	[MePCy ₃]Cl	*P1	[¹³ CH ₃ PCy ₃]Cl
P2	Unknown singlet 28.5 ppm (³¹ P NMR; C ₆ D ₆)	P3	Unknown singlet 46.1 ppm (³¹ P NMR; C ₆ D ₆)
P4	Unknown singlet 36.4 ppm (³¹ P NMR; C ₆ D ₆)	P5	Unknown singlet 59.2 ppm (³¹ P NMR; C ₆ D ₆)
1		2	
3		4a	
4b		4c	
5a		5a'	
5a''		5b	
5b'		5b''	
5c		5c'	
5c''		6a	
6b		6c	
7a		7b	

7c		MA	
EA		OA	
TMB		DMT	
IMes		H₂IMes	

Chapter 1. Introduction

A core objective in chemical synthesis is the development of energy-efficient methods for the assembly or elaboration of carbon skeletons. Increasing pressure on both energy and resource reserves has been a trend worldwide over the past 40 years, with particularly dramatic changes in the last decade. The opportunity to address issues of sustainability has inspired many researchers to explore new horizons in homogeneous catalysis. Simultaneously, related demands and new opportunities in the fine-chemicals and pharmaceutical sectors have driven adoption of the resulting methodologies in chemical manufacturing.¹

Advances in homogeneous catalysis have been recognized with the Nobel Prize in Chemistry no less than three times in the past 15 years (**Scheme 1.1**). The 2001 Nobel Prize was awarded for the development of asymmetric catalysis: to William Knowles² and Ryoji Noyori,³ for asymmetric hydrogenation, and Barry Sharpless,⁴ for asymmetric oxidation. Yves Chauvin,⁵ Robert Grubbs,⁶ and Richard Schrock⁷ were honoured in 2005 for their development of olefin metathesis for organic chemistry. In 2010, Richard Heck, Ei-ichi Negishi,⁸ and Akira Suzuki⁹ were recognized for the development of Pd-catalyzed cross-couplings for organic synthesis. These awards testify to the importance of homogeneous catalysis among the forefront scientific developments of the past two decades. They also underscore the capacity of homogeneous catalysis to transform practice in synthetic organic chemistry and, ultimately, chemical manufacturing.



Scheme 1.1. Summary of the advances in homogeneous catalysis that have been recognized by Nobel Prizes.

Outlined below are the major developments in catalyst design for which these Nobelists were recognized, and examples of leading “active pharmaceutical ingredients” (APIs) that are accessible as a result of their advances. Where possible, studies are cited that describe the challenges associated with translation of the catalytic methodologies from the lab bench to industrial manufacturing processes. Underlying many of these challenges – turnover numbers, reaction rates / throughput time, and purification – is the economic necessity of bringing catalyst costs into line with the price that the market will bear for the final product.¹⁰ (The flip side of this issue is the growing controversy over pharmaceutical pricing, and the tension between drug companies and health insurers over escalating prices for breakthrough therapies. If the potential of new catalytic methodologies is to be realized, however, it is essential to amortize costs for products that occupy accessible pricing regimes).

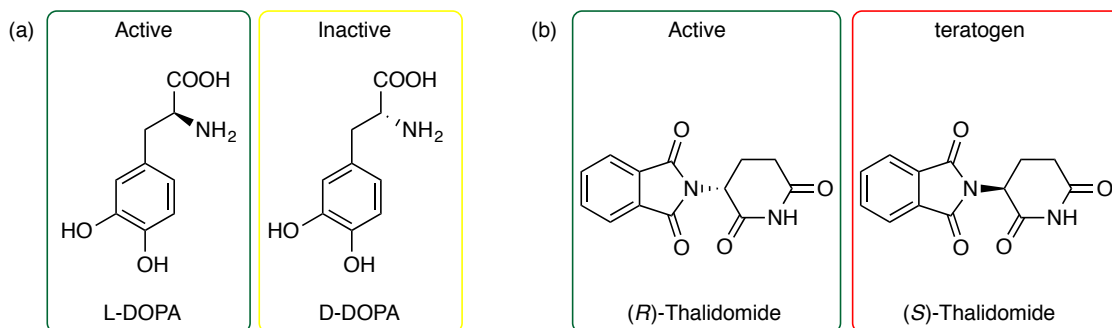
Hydrogenation, cross-coupling, and metathesis will be treated below in order of their adoption in fine chemicals and pharma, rather than according to the Nobel chronology. A common feature shared by hydrogenation and cross-coupling catalysis, which expedited their implementation in process chemistry, is the regeneration of the active site (a metal-bound hydride or alkyl) in every catalytic cycle. This is not the case for olefin metathesis, in which the active site must be conserved between cycles; that is, loss of alkylidene corresponds to loss of metathesis activity. This enhanced vulnerability reinforces the need to understand and address the organometallic pathways that lead to catalyst inhibition and deactivation.

1.1. Asymmetric Catalysis: Development and Industrial Uptake

In the 1950s, Arvid Carlsson at the University of Lund demonstrated that dopamine functions as a neurotransmitter in the brain, and that administering its metabolic precursor L-DOPA (**Scheme 1.2a**) could relieve Parkinson’s-like symptoms in animals.¹¹ L-DOPA rapidly emerged as a drug target for the clinical treatment of Parkinson’s disease, and indeed continues to be the gold standard for therapy.¹² More broadly, this advance crystallized awareness of the high sensitivity of biology to chirality. This awareness was soon reinforced by revelations of the devastating side effects of the sedative thalidomide (**Scheme 1.2b**), in which one enantiomer was widely believed[†] to carry the desired therapeutic effect, with the

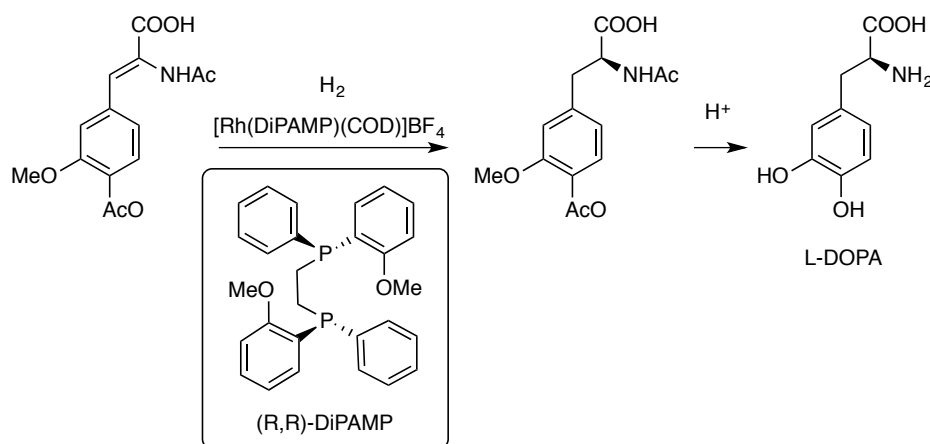
[†] In fact, the two enantiomers exhibit equivalent teratogenic potential in some animal models, and chiral inversion is rapid in humans.

other being a potent teratogen.¹³ The therapeutic implications were not lost on pharma, but the challenge for decades remained the development of efficient chemical methods for the synthesis of single-enantiomer drugs.



Scheme 1.2. Examples of the importance of chirality in biology: (a) L-DOPA, (b) Thalidomide.

Work by Knowles, Horner, Kagan and others in the 1970s demonstrated that metal catalysts bearing a chiral phosphine ligand could transfer chirality to a non-chiral substrate,^{14,15} and laid the foundation of the field of asymmetric catalysis. At Monsanto, Knowles applied these insights to the synthesis of L-DOPA itself, and developed an efficient rhodium-catalyzed route to the drug via asymmetric hydrogenation of dehydroamino acids.² This led to the first industrial process for asymmetric hydrogenation (**Scheme 1.3**): it also stimulated worldwide interest in the phenomenon and potential of asymmetric catalysis as a route to chiral compounds. An enabling advance on which the Knowles methodology relied was the development of the first highly enantioselective chiral phosphine ligand, DiPAMP. The scope of the Rh-DiPAMP catalyst was limited, however, and only enamides (that is, dehydroamino acids) were reduced with high enantioselectivity.



Scheme 1.3. Asymmetric hydrogenation in the synthesis of L-DOPA.

In subsequent work in the 1980s, Noyori developed the atropisomeric BINAP ligand, which expanded the scope of asymmetric hydrogenation to permit efficient H_2 -hydrogenation of other privileged $\text{C}=\text{C}$ bonds, as well as transfer hydrogenation of both functionalized and unfunctionalized ketones.¹⁶ A further asset of the Noyori catalysts, from a manufacturing perspective, was the move to ruthenium in place of rhodium. Ruthenium is the cheapest of the platinum group metals, and is historically less subject to market volatility (**Figure 1.1**). Rhodium is the most costly of the precious metals, routinely trading at 20 to 30 times the price of ruthenium (and reaching a high of over \$10,000 USD per ounce at the height of the 2008 financial crisis). Indeed, for the Noyori-class catalysts, ligand costs contribute more to catalyst prices than the metal. The functionalized BINAP ligand accounts for 7% of the Aldrich price of $\text{RuCl}_2[(R)\text{-}2,2'\text{-bis[di(3,5-xylyl)phosphino]}\text{-}1,1'\text{-binaphthyl}][(\text{1R,2R})\text{-}1,2\text{-diphenylethylenediamine}]$, for example, vs. 1% for the ruthenium content.

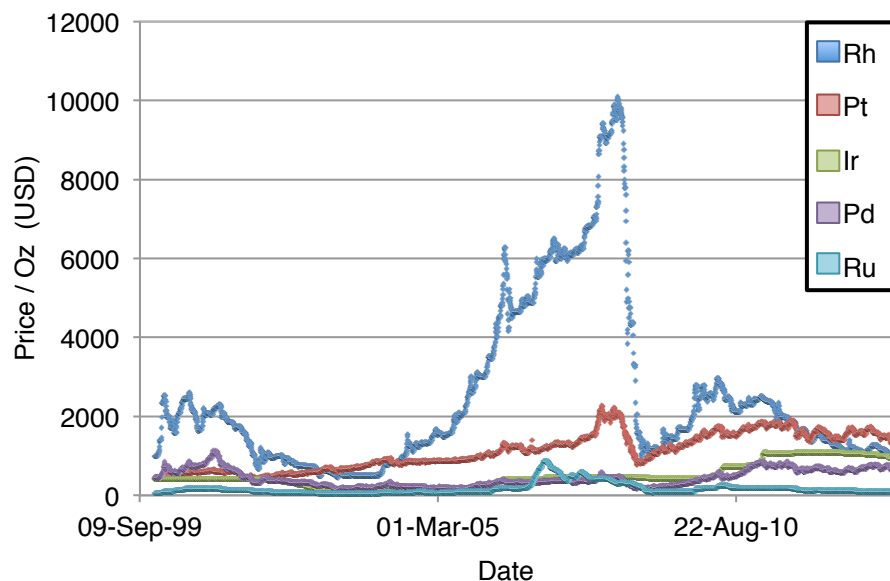
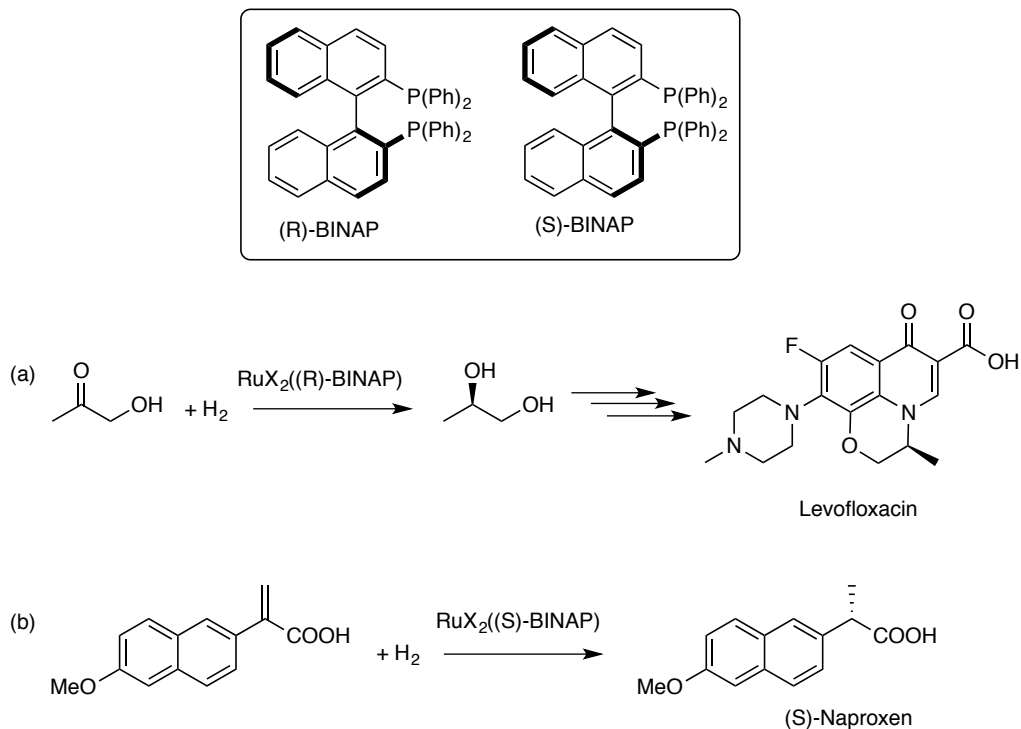


Figure 1.1 Johnson-Matthey base prices for the platinum group metals over the period 1999-2014. Averages (US dollars): \$2,319 (Rh); \$1,136 (Pt); \$491 (Ir); \$469 (Pd); \$153 (Ru).¹⁷

The Noyori hydrogenation catalysts and their descendants have seen extensive use in pharmaceutical and fine-chemicals manufacturing, including in the production of enantiopure agrochemicals (**Table 1.1**).^{18,19} Two notable examples from pharma are illustrated in **Scheme 1.4**: the synthesis of a chiral precursor to the antibiotic Levofloxacin,³ and the final step in the synthesis of Naproxen, one of the leading non-steroidal anti-inflammatory drugs (NSAID) in current use.²⁰

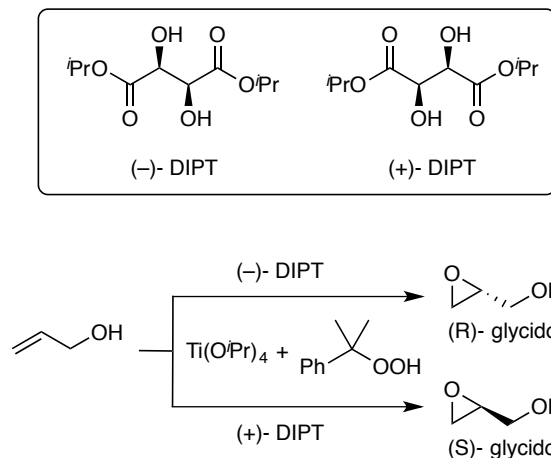
Table 1.1. Selected examples of catalytic hydrogenation in pharma and fine chemicals processes.¹⁸

Process Scale	Target	Company
Production	Penem antibiotics	Takasago
Production	Ofloxacin intermediates	Takasago
Production	Aliskiren building block	Solvias, DSM, BASF
Production	Adrenaline, Phenylephrine	Boehringer-Ingelheim
Production	Citronellol	Takasago, Roche
Production	(+)-cis-Methyl Dihydrojasmonate	Firmenich
Production	S-Metolachlor	Ciba-Geigy/Novartis/Solvias
Pilot	R-3,5-Bis-trifluoromethylphenyl Ethanol	Solvias/Rohner, Merck
Pilot	Taranabant intermediates	Merck



Scheme 1.4. Asymmetric hydrogenation of carbonyl and olefinic bonds enabled by a Noyori catalyst in pharma: (a) Levofloxacin, (b) Naproxen. Inset shows the atropisomeric BINAP ligands.

In parallel work, Sharpless developed titanium catalysts for converting allylic alcohols to chiral epoxides. Here an optically pure dialkyl tartrate auxiliary was used to transfer asymmetry in the enantioselectivity-determining step. The first industrial synthesis using this technology, implemented by Arco Chemical for the conversion of allyl alcohol to (R)- and (S)-glycidol (**Scheme 1.5**), was disclosed in 1990.²¹ Sharpless also developed osmium-mediated asymmetric aminohydroxylation and dihydroxylation reactions, which convert alkenes into chiral amino-alcohols or diols, respectively. In both of these reactions, the origin of asymmetry is a chiral amine pro-ligand, which also accelerates the reaction of osmium tetroxide with alkenes. The cinchona alkaloid–OsO₄ system, in particular, was a breakthrough that revolutionized asymmetric dihydroxylation.²²

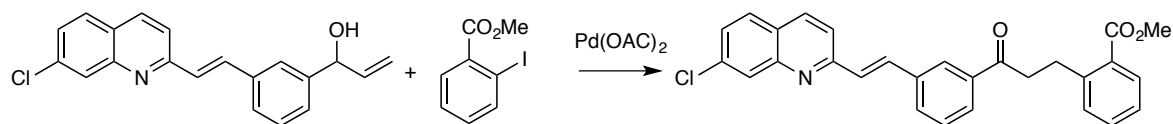


Scheme 1.5. Arco route to (R)- and (S)-glycidol using the Sharpless epoxidation.

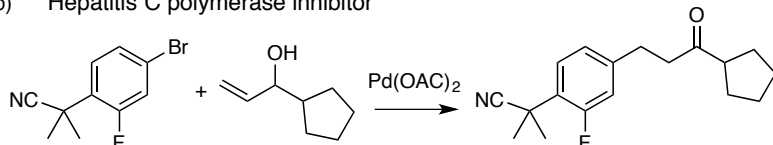
1.2. Cross-Coupling: Development and Industrial Uptake

Recent reviews by Sigman,²³ de Vries,¹⁰ and Snieckus²⁴ describe applications of Pd-catalysed coupling in the pharmaceutical, agrochemical and fine chemicals industries. The first palladium-catalyzed cross-coupling reactions were reported in 1968 by Heck at Hercules Corp.²⁴ The stoichiometric organomercury compounds originally required to generate the Pd-alkyl intermediates were rapidly supplanted by aryl halides, with the discovery that these oxidatively add to palladium.²⁵ This culminated in the development of the Heck (or Mizoroki-Heck) reaction for coupling organohalides and alkenes. A showcase application in pharmaceutical synthesis is Merck's synthesis of Singulair (**Scheme 1.6a**).²⁶ Insights into challenges in the implementation of this chemistry appear in a report from Pfizer describing the synthesis of a hepatitis C protease inhibitor on 40-kg scale (**Scheme 1.6b**).²⁷

(a) Singulair

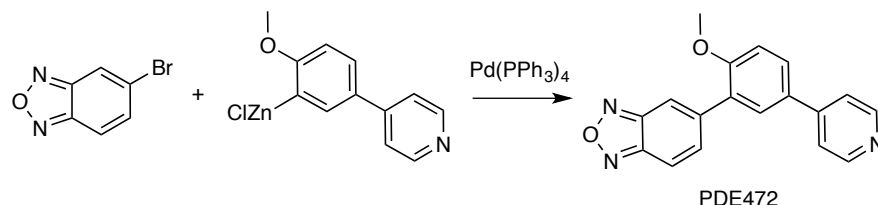


(b) Hepatitis C polymerase inhibitor



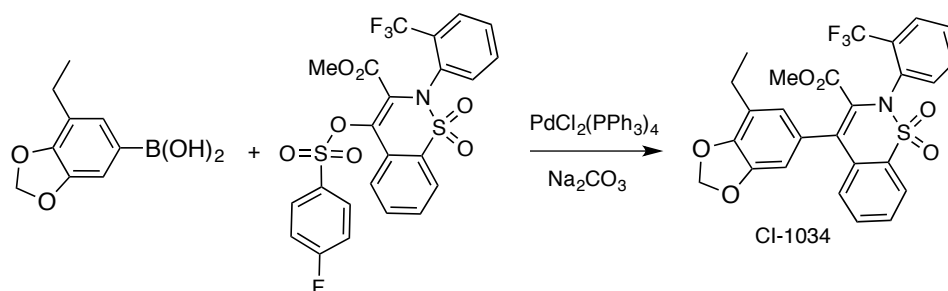
Scheme 1.6. Use of the Heck reaction in synthesis of APIs: (a) en route to Singulair, (b) en route to a Hepatitis C polymerase inhibitor.

In 1977, Negishi and Jutand reported the first cross-coupling using zinc reagents. The Negishi reaction is unique in its scope, enabling coupling of sp -, sp^2 -, and sp^3 -hybridized carbon centers. A report from Novartis describes implementation of the Negishi reaction on pilot-plant scale to support Phase 1 clinical trials of the asthma drug candidate PDE472 (**Scheme 1.7**).²⁸



Scheme 1.7. Negishi reaction used in the Novartis synthesis of PDE472 on pilot-plant scale.

In 1979, Suzuki reported the cross-coupling of organoboranes and organohalides. Advantages of the Suzuki reaction in the industrial context are the stability and low toxicity of organoboranes and their inorganic by-products. The Suzuki coupling reaction was implemented by Merck in the early 1990s for manufacturing of the antihypertensive drug Losartan.¹⁰ It is now widely used in the commercial production of APIs and agrochemicals: indeed, the fungicide Boscalid, brought to market by BASF in 2002, is manufactured in what is regarded as the world's largest Suzuki process (1,000 tons/year). Technical challenges associated with the 80 kg-scale production of CI-1034, a clinical candidate for treating pulmonary hypertension, appear in a Pfizer report (**Scheme 1.8**).²⁹



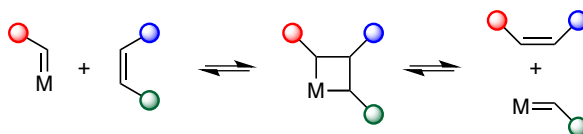
Scheme 1.8. Suzuki reaction used in production-scale synthesis of antihypertensive drug candidate CI-1034.

1.3. Olefin Metathesis: Development and Industrial Uptake

Olefin metathesis is the child of industry, and one of its earliest examples emerged in a 1955 DuPont patent filing.³⁰ This described a process for ring-opening metathesis polymerization (ROMP; see later) of the strained bicyclic olefin norbornene. The active

catalyst was generated in situ by reaction of TiCl_4 with a reducing agent (EtMgBr or $\text{LiAl}(\text{C}_4\text{H}_9)_4$). Metathesis processes based on related, structurally ill-defined but highly active catalyst systems rapidly found further industrial application.³¹ In a major advance, Royal Dutch Shell exploited this new “olefin-shuffling” methodology to manipulate the olefin stream obtained from ethylene oligomerization. A broad range of linear internal olefins is generated in the Shell Higher Olefin Process (SHOP) process, from which the desired chain lengths are collected and the undesired fractions recycled for isomerization and re-subjection to metathesis.³² Despite the significance of these developments, the catalysts used are limited in their tolerance for oxygen-containing or protic functionalities. The field of metathesis was transformed by the development of molecular metathesis catalysts, particularly those based on the less oxophilic late transition metal ruthenium.³³

An enabling advance in the synthesis of well-defined metathesis catalysts was Chauvin’s mechanistic work, which revealed the key structural features required. In his seminal 1971 paper, Chauvin proposed that metathesis proceeds via metal alkylidene and metallacyclobutane species, which enable a series of [2+2] cycloaddition and cycloreversion steps (**Scheme 1.9**).³⁴



Scheme 1.9. The Chauvin mechanism of cycloaddition and cycloreversion for olefin metathesis.

The first well-defined metathesis catalysts followed soon after, with Schrock’s pioneering synthesis of first tantalum,³⁵ and subsequently tungsten³⁶ and molybdenum³⁷ catalysts (**Figure 1.2a**). A key step toward industrial utilization of the molecular metathesis catalysts came with Grubbs’ development of more robust and, critically, easily-handled catalysts based on ruthenium (**Figure 1.2b**).³⁸⁻⁴¹

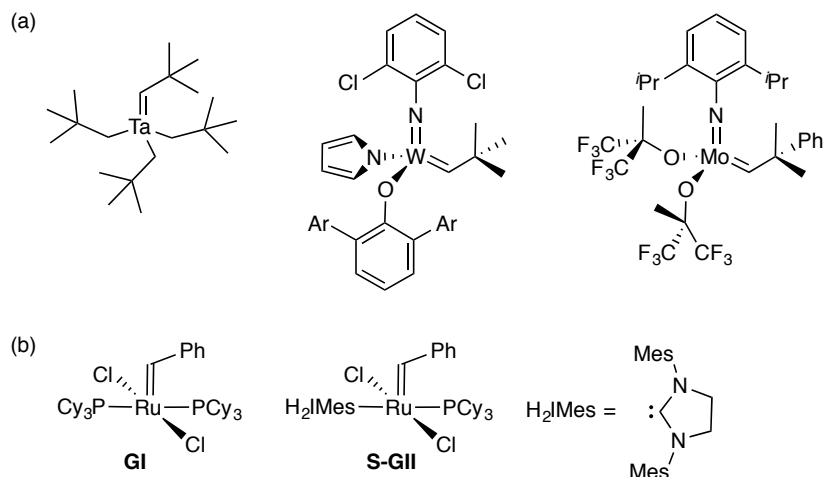
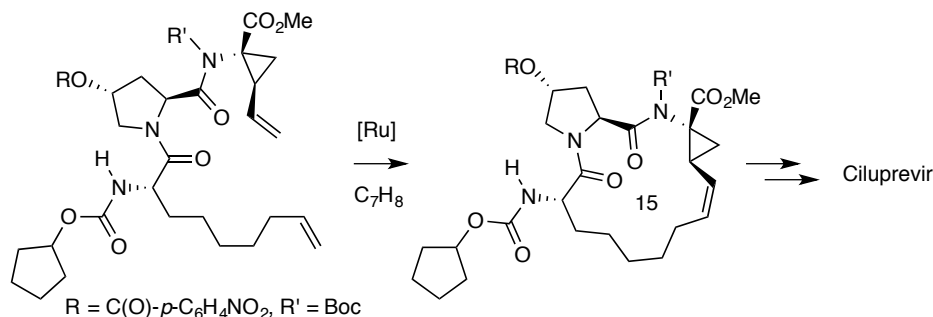


Figure 1.2. Key developments in the synthesis of metathesis catalysts containing (a) Group 5 and 6; (b) Group 8 transition metals.

At the time the Nobel Prize was awarded, Boehringer-Ingelheim had begun a pioneering program aimed at using RCM for the key macrocyclization step in the synthesis of a Hepatitis C virus (HCV) inhibitor, Ciluprevir (**Scheme 1.10**).⁴² Refinements continued over the next decade, and the key RCM macrocyclization was performed on pilot scale (up to 20 kg at a time) to support clinical trials. While Ciluprevir was ultimately withdrawn from Phase 1 clinical trials due to its cardiac toxicity, this work spurred intensive research into other macrocyclic peptidomimetics as HCV inhibitors (and indeed for the treatment of other viral infections, including the human immunodeficiency virus, HIV).^{43–45} Related applications of metathesis in fine chemicals and pharma have now begun to emerge. It will be noted that implementation of metathesis methodologies in these contexts has proceeded much more slowly than hydrogenation or cross-coupling. Reasons for this lag are discussed below, following a brief overview of Ru-catalyzed olefin metathesis, and of the active species generated in various metathesis manifolds.

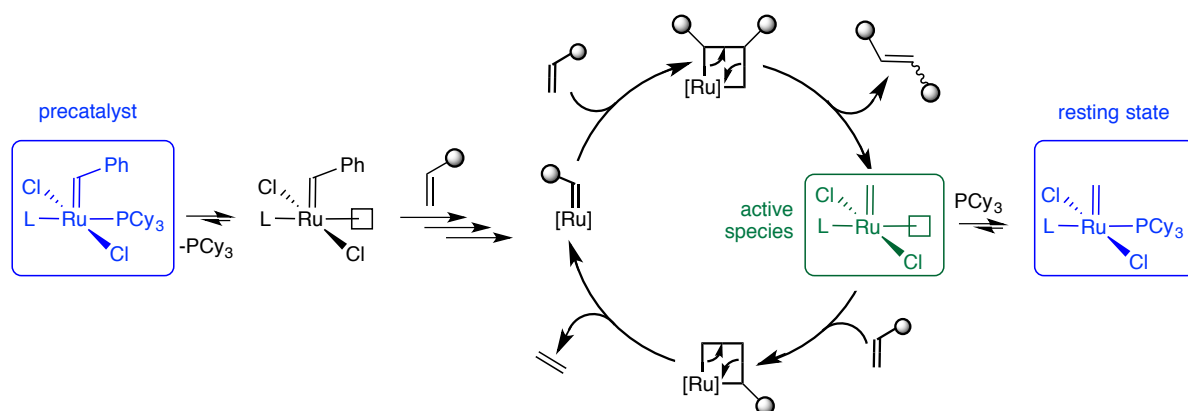


Scheme 1.10. The key RCM step in the Boehringer-Ingelheim synthesis of the peptidomimetic drug Ciluprevir (BILN 2061).

1.4. Ruthenium-Catalyzed Olefin Metathesis

The active species in olefin metathesis is a four-coordinate alkylidene complex (**Scheme 1.11**). Ruthenium precatalysts, however, are almost invariably five-coordinate, being stabilized by a donor ligand that serves as a placeholder for incoming olefin. Initiation by ligand loss⁴⁶ is thus commonly the first step in olefin metathesis. (In a variant on this dissociative pathway, some catalysts initiate via an associative pathway involving prior coordination of substrate, and subsequent loss of the placeholder ligand).⁴⁷

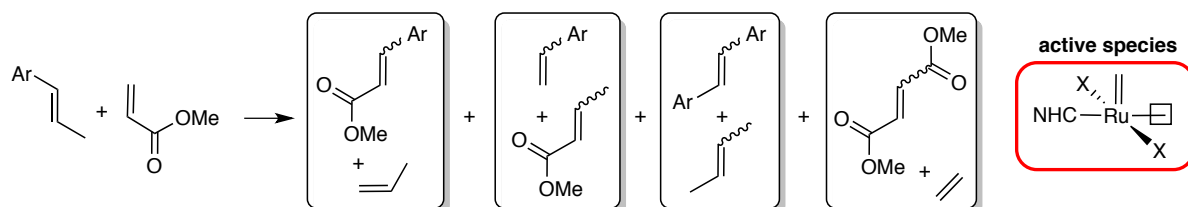
Irrespective of initiation mechanism, the first cycle of catalysis involves shuffling of the alkylidene substituent (typically a phenyl or aryl group) with substituents present on the olefinic bonds of the substrate. Metathesis cycling continues until the initially-displaced donor ligand successfully competes with olefin for binding to the metal, thus regenerating a five-coordinate, off-cycle species. The latter is the thermodynamic resting state, and builds up over time until it is the dominant ruthenium species present (**Scheme 1.11**). Understanding the deactivation chemistry of the resting-state species is thus crucial to understanding catalyst decomposition during catalysis.



Scheme 1.11. Chauvin mechanism for olefin metathesis, illustrated by cross-metathesis of a terminal alkene with a Grubbs-class catalyst. Off-cycle species are shown in blue.

1.5. Types of Metathesis Reactions

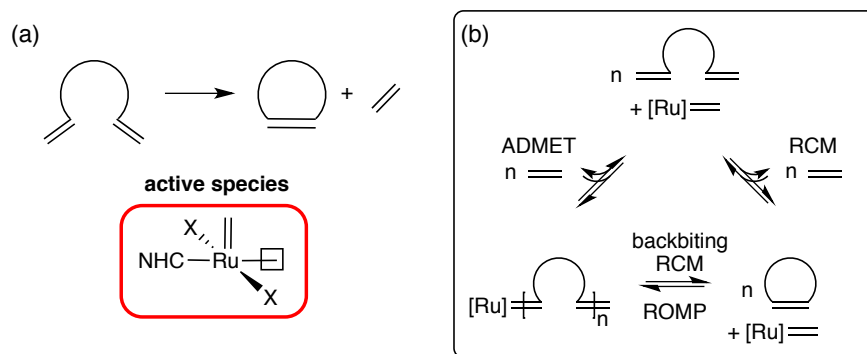
Olefin metathesis comprises a family of related reactions (**Scheme 1.12**–**Scheme 1.14**). The cross-metathesis (CM) reaction illustrated below is the intermolecular variant, which under non-ideal circumstances leads to a statistical mixture of all olefin substitution patterns (**Scheme 1.12**). General rules for controlling the selectivity of CM reactions have been outlined by Grubbs.⁴⁸ These rest on (a) a mismatch in reactivity between the reacting olefins, and (b) use of a catalyst with suitably curtailed reactivity. For example, a terminal olefin can often be selectively coupled with styrene using **GII**. Because CM lacks strong drivers that promote selectivity, it has seen relatively little industrial uptake in target-oriented synthesis, although its importance in the commodity SHOP process was noted above.



Scheme 1.12. Cross-metathesis reactions mediated by a Ru-methyldiene intermediate.

Ring-closing metathesis (RCM) is by far the most important application of metathesis in the production of specialty chemicals and APIs.^{32c} Here metathesis involves the intramolecular coupling of two olefinic sites in a diene. Cyclization competes with intermolecular metathesis (often termed acyclic diene metathesis, ADMET). In either case, a by-product is liberated: this is typically ethylene, the volatility of which helps drive the RCM reaction to completion. For macrocyclic or medium-sized rings, which are overwhelmingly

targeted in medicinal and fine-chemicals applications, high dilutions are normally required to favour RCM over oligomerization in the ring-chain equilibrium depicted (**Scheme 1.13**).^{49,50} The concentration-dependence of such equilibria have been recognized for more than 60 years.

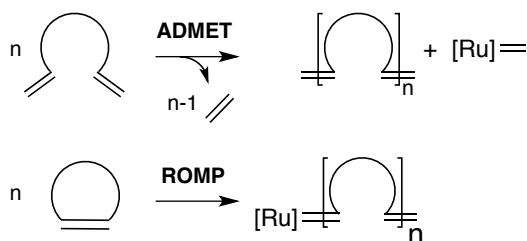


Scheme 1.13. (a) Simplified depiction of RCM, showing the Ru-methylidene intermediate. (b) Competing inter- and intramolecular metathesis, resulting in concentration-dependent formation of RCM or ADMET products.

In some instances, macrocyclic targets are conformationally restricted, and can be accessed at higher concentrations. A case in point is the tripeptide scaffold of Ciluprevir, which (after extensive optimization) could be obtained at substrate concentrations as high as 200 mM.⁴⁵ More typically, however, high dilutions are required. Indeed, this is a major difference between RCM and CM reactions, which otherwise proceed via identical inter- and/or intramolecular steps, and share many fundamental challenges. The requirement for high dilutions to favour cyclization over chain growth is a major issue for two reasons.⁵⁰ First, the added solvent costs add to the net economic burden on scale. Solvent consumption is already a major cost driver for pharmaceutical manufacturing gross margins, and an important indirect contributor via process costs for disposal.¹ Secondly, the slower rate of RCM reactions enables competing deactivation. In a recent comprehensive review, we summarized these and other obstacles and opportunities in the RCM assembly of cyclic olefins.⁵¹

While high-value specialty processes are the focus of this thesis, it should be noted that ADMET polymers are also of interest, and their formation can be favoured by carrying out diene metathesis at molar concentrations. Greater control over polymer molecular weights and microstructure, however, is attainable via ring-opening polymerization (ROMP). ROMP reactions are propagated by an alkylidene species (**Scheme 1.14**), which is less prone to

deactivation than the methyldiene species that enable CM and RCM processes. Specialty metathesis reactions that go beyond the scope of this thesis involve enyne metathesis (that is, alkene-alkyne coupling) and cyclopolymerization (alkyne-alkyne coupling). These processes generate molecular or polymeric 1,3-conjugated dienes. Both are carried by a conjugated alkylidene as the active species.^{52,53}

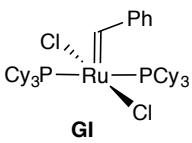
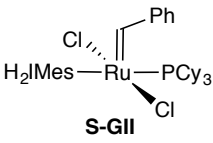


Scheme 1.14. Comparison of ADMET and ring-opening metathesis polymerization (ROMP). Variations in polymer microstructures and chain lengths are not depicted.

1.6. Commercially Available Pre-Catalysts

In contrast with rhodium and palladium catalysis, which frequently tolerate in situ catalyst generation, “prefabricated” catalysts are normally required in ruthenium chemistry. This is especially true for metathesis, in which installation of the alkylidene ligand is the major synthetic challenge.⁵⁴ The dominant catalysts in current use for olefin metathesis typically contain an *N*-heterocyclic carbene ligand (NHC; see **GII** in **Table 1.2**). These “second-generation” catalysts exhibit considerably higher activity than the original Grubbs catalyst **GI**, which contained two PCy₃ ligands. The difference is due in part to the higher “commitment” of the four-coordinate intermediate that carries catalysis: that is, its kinetic bias toward reaction with olefin, in preference for re-coordination of the ancillary ligand.⁴⁶ While the second-generation Grubbs catalysts exhibit slower initiation, and loss of the PCy₃ ligand is rate-limiting,^{46,55} they are much more reactive than **GI**, and exhibit a broader substrate scope in consequence.

Table 1.2. Kinetic Distinctions between First- and Second-Generation Grubbs Catalysts.

	Initiation	Preference for reaction with olefin vs re-uptake of PCy ₃	"Commitment"
 G-I	Faster	Weak	Low
 S-GII	Slower	Strong	High

The ligand sets present in the prototypical Grubbs complexes have undergone much fine-tuning, and a 2010 review described more than four hundred ruthenium metathesis catalysts.⁵⁶ The ancillary ligand trans to the NHC group (a placeholder for incoming olefin) has been varied to modulate initiation rates.^{46,57-59} The anionic ligands have also been varied, if less extensively: early work from the Fogg group explored such modifications with the intention of reducing the susceptibility to deactivation pathways.⁶⁰⁻⁶³ By far the greatest amount of effort, however, has gone into tuning the NHC ligand to increase activity: the capacity to generate bulky, tetrasubstituted olefins and *Z*-olefin products have seen much interest.⁶⁴⁻⁶⁷ Chiral NHC ligands have also been incorporated, with the goal of conferring enantioselectivity.⁶⁸⁻⁷¹ The alkylidene ligand has also been modified, largely in the course of developing alternative synthetic routes to active catalysts that circumvent the intellectual property restrictions associated with the benzylidene catalysts.^{58,72-74} Additional modification to achieve solid support and to improve catalyst removal have received significant attention.^{63,75,76} A recent review lists 46 commercially available catalysts of the second-generation type as of December 2013.^{32a} Despite this very large number of pre-catalysts, however, only modifications at the X or NHC ligands alter the active species. In many cases (**Figure 1.3**), different pre-catalysts funnel into the same active species. It should also be noted that despite the large number of catalysts available, **S-GII** is by far the dominant system used in RCM.

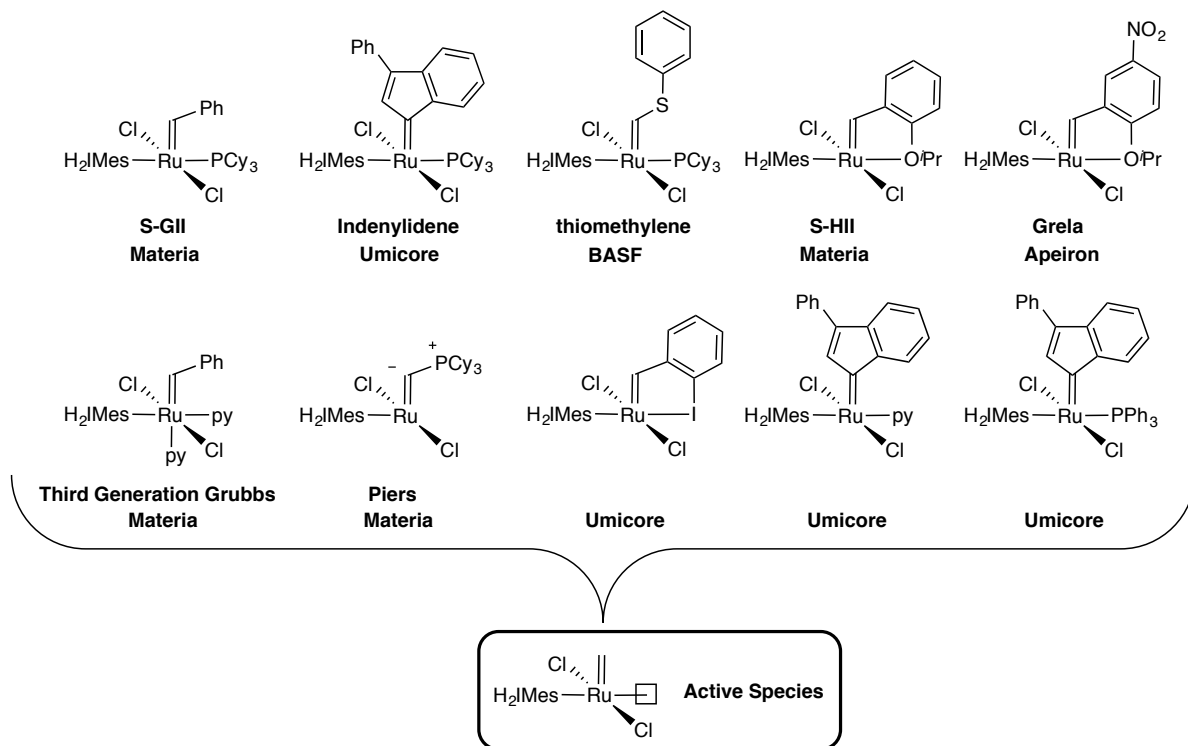


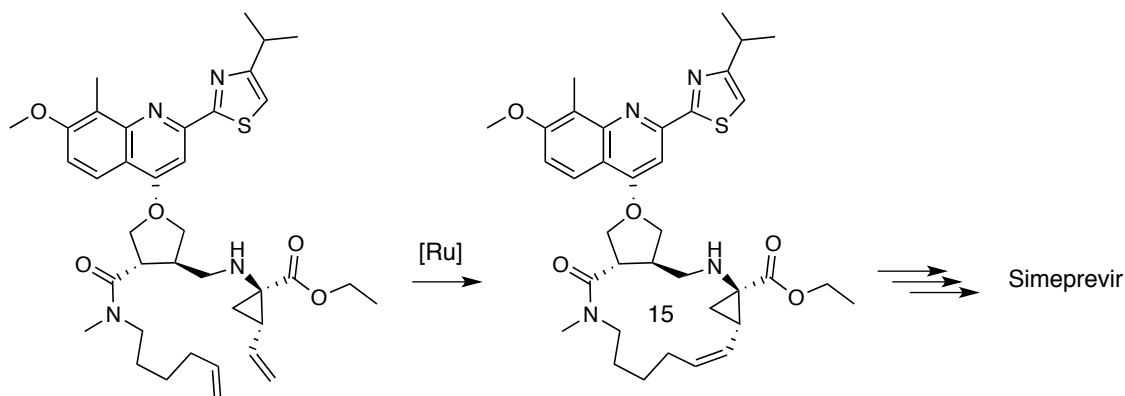
Figure 1.3. Many commercially available second-generation ruthenium metathesis catalysts ultimately lead to the same active species during catalysis.

1.7. Molecular Metathesis Comes of Age

Ring-closing metathesis, and particularly metathesis macrocyclization, is of keen interest in pharmaceutical manufacturing. The classic example cited for the last decade has been the Boehringer-Ingelheim synthesis of Ciluprevir, a protease inhibitor for Hepatitis C Virus (HCV) that was ultimately withdrawn from Phase 1 clinical trials due to cardiac toxicity.^{42,77} More recently, significant attention has focused on the development of stapled peptides by Aileron Technologies.⁷⁸ Stapled peptides incorporate metathesis-active olefinic amino acids into the peptide sequence: subsequent cyclization enforces an alpha-helical conformation in the peptide, which increases its cell permeability.

Both of these examples, however, pale in comparison to Simeprevir. This HCV protease inhibitor, co-developed by Medevir and Janssen Pharma (a subsidiary of Johnson & Johnson), bears a structural resemblance to Ciluprevir, and likewise utilizes RCM to generate the key macrocyclic structure (**Scheme 1.15**).⁷⁹ Having successfully passed clinical trials, Simeprevir was approved by the regulatory agencies of Japan (September 2013), the US (November 2013), and in Canada (November 2013). Approval in the EU and elsewhere

followed. Market uptake greatly exceeded projected sales: blockbuster status (annual sales of at least \$1B USD) was reached by the second quarter of 2014, with sales approaching \$2B by the end of Q3.⁸⁰



Scheme 1.15. RCM macrocyclization step in the synthesis of the breakthrough HCV inhibitor Simeprevir.

Breakthroughs in the industrial implementation of cross-metathesis have also emerged over the past year. These have been spearheaded by Elevance Renewable Sciences, created in 2007 as a joint venture between the metathesis catalyst company Materia (which holds the intellectual property for the Grubbs and Schrock catalysts, among many others: see **Figure 1.3**) and agribusiness giant Cargill. Elevance was established with the mandate of applying Materia's metathesis technology to the valorization of renewable feedstocks, particularly palm, soybean, and rapeseed oils. Metathesis "cracking" of the unsaturated oils affords desirable specialty olefins and oleochemicals, including C16-C18 fatty esters, and difunctional C10-C15 fatty ester building blocks.

In 2013, Elevance announced the commissioning of its first bio-refinery in Gresik, Indonesia, in a joint venture with Asian agribusiness leader Wilmar International. Although shipment scales were not disclosed, annual production capacity is reportedly 180 000 MT. First shipments were announced in July 2013, and a series of specialty products followed in a period of rapid commercial deployment in 2014. Novel product lines introduced to date include high-performance surfactants (Steposol MET-10U, a joint development with Stepan), and other degreasing solvents and lubricants. Additional bio-refineries are under development in Natchez, Mississippi and Lahad Datu, Malaysia.

The challenge lies in establishing profitability with the much narrower margins associated with these targets, relative to new blockbuster drugs. Nevertheless, the influential industry

analyst Biofuels Digest, which has monitored Elevance since its 2011 IPO,⁸¹ delivers a trenchant but positive assessment: “Investors will need to see a bunch of these applications in order to use the capacity built out at Gresik — but, an impressive win if the company has correctly targeted a sizable niche market where it can hit the price [and] performance mark with sustainable attributes.”⁸²

This returns us to the issue of economics. The high net costs of RCM are recouped in the case of Simeprevir by the high prices that can successfully be charged for breakthrough therapies (an issue of extreme controversy in both first-world and developing economies).⁸³ The US launch price for 12 weeks of treatment with Simeprevir is reportedly \$66,000 (USD).⁸⁴ In the case of Elevance, profitability remains to be established, but the presence of Materia as a parent company limits exposure to catalyst costs. If the potential of metathesis is to be realized more broadly, however, direct and indirect catalyst costs must come down. Here an improved understanding of the underlying organometallic chemistry has a key part to play.

1.8. Scope of This Thesis

As noted above, the need to retain the active site throughout the catalytic cycle differentiates olefin metathesis from other catalytic processes, and deactivation pathways that result in loss of the alkylidene are typically irreversible.⁸⁵⁻⁸⁸ Because loss of the alkylidene entity means loss of metathesis activity, understanding and preventing such deactivation pathways is critical to achieving high turnover numbers (TON) and process economy.

A major impediment to the industrial uptake of olefin metathesis has been the low turnover numbers, high catalyst costs, and the need for extensive purification to remove ruthenium residues. Ruthenium methylidene species are the most abundant, but also the most vulnerable, alkylidene intermediate in the catalytic cycle. While early results pointed toward the importance of studying and understanding the fundamental organometallic chemistry involved in deactivation, the technical challenges were significant. Studies of the methylidene complexes – and particularly key second-generation methylidene complexes – were restricted by the absence of a high-purity, high-yield route to these species. This problem is addressed in Chapter 2, as a prerequisite for subsequent mechanistic studies. Chapter 3 uses the methylidene complexes to examine the impact of switching from a saturated to an unsaturated N-heterocyclic carbene. This is a long-standing question in olefin

metathesis, with significant implications for catalyst design. Chapter 4 examines the role of adventitious nucleophiles in Grubbs-catalyzed olefin metathesis reactions. Finally, Chapter 5 examines the potential for the Hoveyda-type catalyst to overcome the shortcomings of the second-generation Grubbs catalyst identified in Chapters 3 and 4 for a commercially relevant cross-metathesis reaction.

From a catalyst design point of view, key comparisons built into this thesis are the effect of the NHC ligand (IMes vs. H₂IMes: Chapter 3), the effect of the alkylidene (benzylidene vs. methylidene vs. metallacyclobutane: Chapter 4), and the effect of the ancillary ligand (**S-GII** vs. **S-III**: Chapter 5). From a practical standpoint, Chapter 2 brings new *life* to metathesis with the high-yield synthesis of the resting-state species, Chapters 3 and 4 examine the deactivation, or *death*, of the methylidene complexes, and Chapter 5 establishes a new paradigm for olefin metathesis within the context of *sustainable* synthesis.

1.9. References

- (1) Federsel, H.-J. r. *Green Chem.* **2013**, *15*, 3105–3115.
- (2) Knowles W. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1999–2007.
- (3) Noyori, R. *Angew. Chem. Int. Ed.* **2002**, *41*, 2008–2022.
- (4) Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2024–2032.
- (5) Chauvin, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 3741–3747.
- (6) Grubbs, R. H. *Angew. Chem. Int. Ed.* **2006**, *45*, 3760–3765.
- (7) Schrock, R. R. *Angew. Chem. Int. Ed.* **2006**, *45*, 3748–3759.
- (8) Negishi, E.-i. *Angew. Chem., Int. Ed.* **2011**, *50*, 6738–6764.
- (9) Suzuki, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6722–6737.
- (10) de Vries, J. G., Palladium-Catalysed Coupling Reactions. In *Top. Organomet. Chem. (Organometallics as Catalysts in the Fine Chemical Industry)*, Beller, M.; Blaser, H.-U., Eds. Springer-Verlag Berlin, 2012; Vol. 42, pp 1–34.
- (11) Carlsson, A. *ChemBioChem* **2001**, *2*, 484–493.
- (12) Ngwuluka, N.; Pillay, V.; Toit, L. C. D.; Ndesendo, V.; Choonara, Y.; Modi, G.; Naidoo, D. *Expert Opin. Drug Deliv.* **2010**, *7*, 203–224.
- (13) Smith, S. W. *Toxicol. Sci.* **2009**, *110*, 4–30.
- (14) Brown, J. M. *Organometallics* **2014**, *33*, 5912–5923.
- (15) Etayoa, P.; Vidal-Ferran, A. *Chem. Soc. Rev.* **2013**, *42*, 728–754.
- (16) Zanolli-Gerosa, A.; Herns, W.; Groarke, M.; Hancock, F. *Platinum Met. Rev.* **2005**, *49*, 158–165.
- (17) The Platinum Metals Report (Price Report), Johnson Matthey, <http://www.platinum.matthey.com/prices/price-charts>.
- (18) Blaser, H.-U., Applications of Transition Metal Catalysis in Drug Discovery and Development: An Industrial Perspective. Crawley, M. L.; Trost, B. M., Eds. John Wiley & Sons, 2012.
- (19) Ager, D. J.; de Vries, A. H. M.; de Vries, J. G. *Chem. Soc. Rev.* **2012**, *41*, 3340–3380.

- (20) Moulijn, J. A.; van Leeuwen, P. W. N. M.; van Santen, R. A.; Editors, *Catalysis: An Integrated Approach to Homogeneous, Heterogeneous and Industrial Catalysis*. 1993; p 460 pp.
- (21) Breuer, M.; Ditrach, K.; Habicher, T.; Hauer, B.; Kessler, M.; Stuermer, R.; Zelinski, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 788–824.
- (22) Noe, M. C.; Letavic, M. A.; Snow, S. L., Asymmetric Dihydroxylation of Alkenes. In *Organic Reactions* Pfizer Global Research and Development, Groton Laboratories: Groton, Connecticut, 2005; Vol. 66, pp 109–625.
- (23) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417–1492.
- (24) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 5062–5085.
- (25) Fitton, P.; Johnson, M. P.; McKeon, J. E. *Chem. Commun.* **1968**, 6–7.
- (26) King, A. O.; Corley, E. G.; Anderson, R. K.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J.; Xiang, Y. B.; Belley, M.; Leblanc, Y.; et al. *J. Org. Chem.* **1993**, *58*, 3731–3735.
- (27) Camp, D.; Matthews, C. F.; Neville, S. T.; Rouns, M.; Scott, R. W.; Truong, Y. *Org. Process Res. Dev.* **2006**, *10*, 814–821.
- (28) Manley, P. W.; Acemoglu, M.; Marterer, W.; Pachinger, W. *Org. Process Res. Dev.* **2003**, *7*, 436–445.
- (29) Jacks, T. E.; Belmont, D. T.; Briggs, C. A.; Horne, N. M.; Kanter, G. D.; Karrick, G. L.; Krikke, J. J.; McCabe, R. J.; Mustakis, J. G.; Nanninga, T. N.; Risedorph, G. S.; Seamans, R. E.; Skeeane, R.; Winkle, D. D.; Zennie, T. M. *Org. Process Res. Dev.* **2004**, *8*, 201–212.
- (30) Anderson, A. W.; Merckling, N. G. Polymeric bicyclo[2.2.1]hept-2-ene. U.S. Patent No. 2721189, 1955.
- (31) Ivin, K. J.; Mol, J. C., *Olefin Metathesis and Metathesis Polymerization*. Academic Press: New York, 1997.
- (32) Mol, J. C. *J. Mol. Catal. A* **2004**, *213*, 39–45.
- (33) A recent book provides a comprehensive update on olefin metathesis. See: (a) Grela, K., *Olefin Metathesis—Theory and Practice*. Wiley: Hoboken, 2014. For a recent review highlighting the synthesis of biologically active molecules using RCM, see: (b) Fürstner, A. *Science* **2013**, *341*, 1229713, and Ref. 2. For a recent comprehensive review of RCM, including emerging applications in pharma, see: (c) van Lierop, B. J., Lummiss, J. A. M., Fogg, D. E. Ring-Closing Metathesis. In *Olefin Metathesis—Theory and Practice*, pp. 85–152. See also: (d) Fandrick, K. R.; Savoie, J.; Jinhua, N. Y.; Song, J. J.; Senanayake, C. H., Challenges and Opportunities for Scaling the Ring-Closing Metathesis Reaction in the Pharmaceutical Industry. In *Olefin Metathesis – Theory and Practice*, pp. 349–366. For a review of asymmetric catalysts for stereocontrolled olefin metathesis, see: (e) Kress, S.; Blechert, S. *Chem. Soc. Rev.* **2012**, *41*, 4389–4408, (f) Hoveyda, A. H.; Malcolmson, S. J.; Meek, S. J.; Zhugralin, A. R. *Angew. Chem. Int. Ed.* **2010**, *49*, 34–44.
- (34) Hérisson, J. L.; Chauvin, Y. *Makromol. Chem.* **1971**, *141*, 161–176.
- (35) Schrock, R. R. *J. Am. Chem. Soc.* **1974**, *96*, 6796–6797.
- (36) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. J. *Am. Chem. Soc.* **1990**, *112*, 3875–3886.
- (37) Fox, H. H.; Lee, J. K.; Park, L. Y.; Schrock, R. R. *Organometallics* **1993**, *12*, 759–768.
- (38) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100–110.
- (39) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.
- (40) Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 9858–9859.

- (41) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247–2250.
- (42) Nicola, T.; Brenner, M.; Donsbach, K.; Kreye, P. *Org. Process Res. Dev.* **2005**, *9*, 513–515.
- (43) Chatel-Chaix, L.; Baril, M.; Lamarre, D., Pharmacology and Mechanisms of Action of Antiviral Drugs: Protease Inhibitors. In *Advanced Therapy for Hepatitis C*, McCaughan, G. W.; McHutchison, J.; Pawlotsky, J.-M., Eds. Wiley-Blackwell: Toronto, 2011.
- (44) Kong, J.; Chen, C.-y.; Balsells-Padros, J.; Cao, Y.; Dunn, R. F.; Dolman, S. J.; Janey, J.; Li, H.; Zacuto, M. J. *J. Org. Chem.* **2012**, *77*, 3820–3828.
- (45) Farina, V.; Shu, C.; Zeng, X.; Wei, X.; Han, Z.; Yee, N. K.; Senanayake, C. H. *Org. Process Res. Dev.* **2009**, *13*, 250–254.
- (46) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543–6554.
- (47) Thiel, V.; Hendann, M.; Wannowius, K.-J.; Plenio, H. *J. Am. Chem. Soc.* **2012**, *134*, 1104–1114.
- (48) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.
- (49) Conrad, J. C.; Eelman, M. D.; Duarte Silva, J. A.; Monfette, S.; Parnas, H. H.; Snelgrove, J. L.; Fogg, D. E. *J. Am. Chem. Soc.* **2007**, *129*, 1024–1025.
- (50) Monfette, S.; Fogg, D. E. *Chem. Rev.* **2009**, *109*, 3783–3816.
- (51) van Lierop, B. J.; Lummiss, J. A. M.; Fogg, D. E., Ring-Closing Metathesis. In *Olefin Metathesis-Theory and Practice*, Grela, K., Ed. Wiley: Hoboken, NJ, 2014; pp 85–152.
- (52) Galan, B. R.; Giessert, A. J.; Keister, J. B.; Diver, S. T. *J. Am. Chem. Soc.* **2005**, *127*, 5762–5763.
- (53) Gregg, T. M.; Keister, J. B.; Diver, S. T. *J. Am. Chem. Soc.* **2013**, *135*, 16777–16780.
- (54) Fogg, D. E.; Foucault, H. M., Ring-Opening Metathesis Polymerization. In *Comprehensive Organometallic Chemistry III*, Crabtree, R. H.; Mingos, D. M. P., Eds. Elsevier: Oxford, 2007; Vol. 11, pp 623–652.
- (55) Adlhart, C.; Chen, P. *Helv. Chim. Acta* **2003**, *86*, 941–949.
- (56) Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Rev.* **2010**, *110*, 1746–1787.
- (57) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *Organometallics* **2001**, *20*, 5314–5318.
- (58) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791–799.
- (59) Love, J. A.; Morgan, J. P.; Trnka, T. M.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2002**, *41*, 4035–4037.
- (60) Conrad, J. C.; Parnas, H. H.; Snelgrove, J. L.; Fogg, D. E. *J. Am. Chem. Soc.* **2005**, *127*, 11882–11883.
- (61) Conrad, J. C.; Amoroso, D.; Czechura, P.; Yap, G. P. A.; Fogg, D. E. *Organometallics* **2003**, *22*, 3634–3636.
- (62) Halbach, T. S.; Mix, S.; Fischer, D.; Maechling, S.; Krause, J. O.; Sievers, C.; Blechert, S.; Nuyken, O.; Buchmeiser, M. R. *J. Org. Chem.* **2005**, *70*, 4687–4694.
- (63) Krause, J. O.; Nuyken, O.; Wurst, K.; Buchmeiser, M. R. *Chem. Eur. J.* **2004**, *10*, 777–784.
- (64) Stewart, I. C.; Douglas, C. J.; Grubbs, R. H. *Org. Lett.* **2008**, *10*, 441–444.
- (65) White, D. E.; Stewart, I. C.; Grubbs, R. H.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 810–811.

- (66) Stewart, I. C.; Ung, T.; Pletnev, A. A.; Berlin, J. M.; Grubbs, R. H.; Schrodi, Y. *Org. Lett.* **2007**, *9*, 1589–1592.
- (67) Berlin, J. M.; Campbell, K.; Ritter, T.; Funk, T. W.; Chlenov, A.; Grubbs, R. H. *Org. Lett.* **2007**, *9*, 1339–1342.
- (68) Funk, T. W.; Berlin, J. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 1840–1846.
- (69) Berlin, J. M.; Goldberg, S. D.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2006**, *45*, 7591–7595.
- (70) Fournier, P.-A.; Collins, S. K. *Organometallics* **2007**, *26*, 2945–2949.
- (71) Van Veldhuizen, J. J.; Garber, S. B.; Kingsbury, J. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 4954–4955.
- (72) Michrowska, A.; Bujok, R.; Harutyunyan, S.; Sashuk, V.; Dolgonos, G.; Grela, K. *J. Am. Chem. Soc.* **2004**, *126*, 9318–9325.
- (73) Wallace, D. J. *Adv. Synth. Catal.* **2009**, *351*, 2277–2282.
- (74) Puentener, K.; Scalone, M. Process for the preparation of 9,10-dehydro-12,13-desoxyepothilone derivatives. 2006-EP61527
2006111491, 20060411., 2006.
- (75) Michrowska, A.; Mennecke, K.; Kunz, U.; Kirschning, A.; Grela, K. *J. Am. Chem. Soc.* **2006**, *128*, 13261–13267.
- (76) Chen, S.-W.; Zhang, Z.-C.; Ma, M.; Zhong, C.-M.; Lee, S.-g. *Org. Lett.* **2014**, *16*, 4969–4971.
- (77) Hinrichsen, H.; Benhamou, Y.; Wedemeyer, H.; Reiser, M.; Sentjens Roel, E.; Calleja Jose, L.; Forns, X.; Erhardt, A.; Cronlein, J.; Chaves Ricardo, L.; Yong, C.-L.; Nehmiz, G.; Steinmann Gerhard, G. *Gastroenterology* **2004**, *127*, 1347–1355.
- (78) Chang, Y. S.; Graves, B.; Guerlavais, V.; Tovar, C.; Packman, K.; To, K.-H.; Olson, K. A.; Kesavan, K.; Gangurde, P.; Mukherjee, A.; Baker, T.; Darlak, K.; Elkin, C.; Filipovic, Z.; Qureshi, F. Z.; Cai, H.; Berry, P.; Feyfant, E.; Shi, X. E.; Horstick, J.; Annis, D. A.; Manning, A. M.; Fotouhi, N.; Nash, H.; Vassilev, L. T.; Sawyer, T. K. *Proc. Natl. Acad. Sci.* **2013**, *110*, E3445–E3454.
- (79) Rosenquist, Å.; Samuelsson, B.; Johansson, P.-O.; Cummings, M. D.; Lenz, O.; Raboisson, P.; Simmen, K.; Vendeville, S.; Kock, H. d.; Nilsson, M.; Horvath, A.; Kalmeijer, R.; Rosa, G. d. l.; Beumont-Mauviel, M. *J. Med. Chem.* **2014**, *57*, 1673–1693.
- (80) Medivir: Interim Report, January – September 2014, Marketwatch.
<http://www.marketwatch.com/story/medivir-interim-report-january-september-2014-2014-11-20>.
- (81) Elevance's \$100M IPO: The 10-Minute Version. *Biofuels Digest* 2011, pp
<http://www.biofuelsdigest.com/bdigest/2011/09/22/elevances-ipo-the-10-minute-version/>.
- (82) Lane, J., Elevance Clean 1200 degreaser launches: renewables titan packs a wallop into all that sustainability. *Biofuels Digest* 2014, pp
<http://www.biofuelsdigest.com/bdigest/2014/06/10/elevance-clean-1200-enters-degreasing-and-voc-exempt-solvent-market-as-fourth-commercial-product-launched-by-elevance/>.
- (83) Hill, A.; Cooke, G. *Science* **2014**, *345*, 141–142.
- (84) Hill, A.; Khoo, S.; Fortunak, J.; Simmons, B.; Ford, N. *Clinical Infectious Diseases* **2014**, *58*, 928–936.
- (85) Hong, S. H.; Wenzel, A. G.; Salguero, T. T.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2007**, *129*, 7961–7968.

- (86) Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160–17161.
- (87) Tsang, W. C. P.; Hultsch, K. C.; Alexander, J. B.; Bonitatebus, P. J., Jr.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 2652–2666.
- (88) Kreickmann, T.; Arndt, S.; Schrock, R. R.; Mueller, P. *Organometallics* **2007**, *26*, 5702–5711.

Chapter 2. Designing Routes to Catalysts and Intermediates Required for Subsequent Mechanistic Studies

2.1. Context, Objectives, and Overview of Content

As noted in the preceding Chapter, the second-generation Grubbs catalyst **GII** is the dominant catalyst currently used for RCM reactions. A clear mechanistic picture of its operation is thus important, and a number of studies have examined, for example, the initiation, commitment, and thermal robustness of the benzylidene precatalyst.¹⁻³ Less studied, though arguably more relevant to catalysis, is the methylidene derivative **GIIIm**. The latter represents the resting state of the catalyst for any metathesis reaction involving a terminal olefin. That is, because **GIIIm** is thermodynamically stable relative to both the benzylidene precatalyst **GII**, and other ruthenium species present in the catalytic cycle, its concentration builds up during metathesis.

Direct insight into **GIIIm**-mediated catalyst deactivation is particularly desirable given evidence that the methylidene complexes are much less thermally robust than their benzylidene parents.^{1,4} Investigations of this point have been impeded, however, by the absence of a straightforward, high-yield route to **GIIIm**. In consequence, prior to the advances described in this thesis, there were only two major experimental studies of the second-generation methylidene species (both from the Grubbs group).^{1,4,5} The first of these established that initiation (i.e. PCy₃ dissociation) is much slower for **GIIIm** than its benzylidene **GII** parent.¹ The second reported a key thermal decomposition pathway for the methylidene complex **GIIIm**, albeit in the absence of substrate.^{4,5} While these insights helped shape subsequent work in the field, a number of unanswered questions remain, particularly with respect to catalyst deactivation. Improved understanding is critical for researchers to design improved, “next-generation” catalysts, to establish guidelines for conditions that maximize catalyst productivity, and ultimately to develop rational strategies for recovery and recycling of spent catalyst post-metathesis (or indeed post-metathesis modification of spent catalyst; i.e. tandem catalysis by design). Unwanted tandem catalysis by catalyst deactivation products is also important, as product yields and selectivity can be eroded by adventitious chemistry catalyzed by spent catalyst. Fundamental to progress in this area is thus the

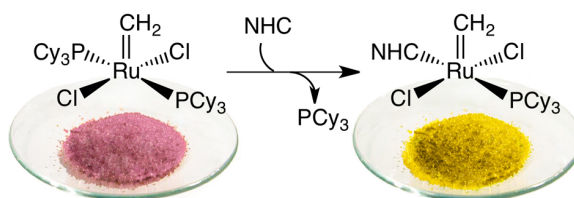
development of high-yield, high-purity routes to the second-generation methyldiene complexes **GIIIm**. Such routes are described in the first part of this chapter.

The second part builds on these advances to design high-purity routes to ^{13}C -labelled benzyldiene and methyldiene complexes, for both first- and second-generation Grubbs catalysts. Here the goal was incorporation of a ^{13}C -label at the key alkylidene site, to enable tracking of the alkylidene moiety. Despite the clear power of such labelled species to afford insight into catalyst initiation, speciation, and deactivation – and indeed, despite the demonstrated utility of isotopic probes in early mechanistic studies into metathesis⁶⁻⁸ – their synthesis has not previously been undertaken.

Both Parts 1 and 2 are published work. A final section covers advances not yet published, aimed at establishing routes to labelled **S-GIIIm** that circumvent the requirement for costly labelled ethylene.

2.1.1. Tables of Contents Entries (published work only)

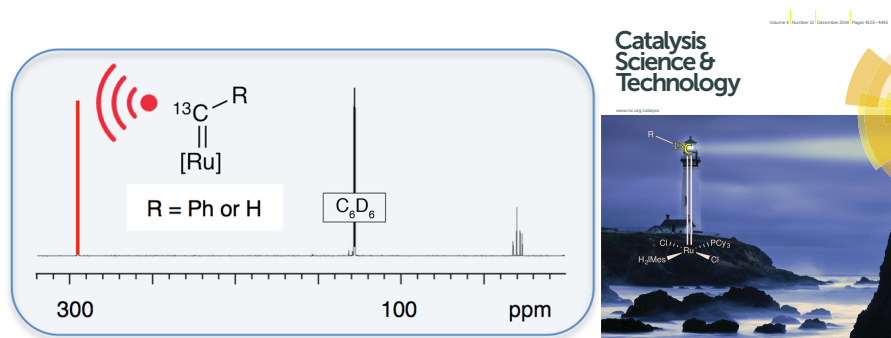
Targeting an Achilles Heel in Olefin Metathesis: A Strategy for High-Yield Synthesis of Second-Generation Grubbs Methyldiene Catalysts. Justin A.M. Lummiss, Nicholas J. Beach, Jeffrey C. Smith, and Deryn E. Fogg.* *Catal. Sci. Technol.* **2012**; 2, 1630–1632 (“Hot Article”).



The first clean, high-yield route is presented to methyldiene complexes $\text{RuCl}_2(\text{L})(\text{PCy}_3)(=\text{CH}_2)$ ($\text{L} = \text{H}_2\text{IMes}$ or IMes , **S-GIIIm** or **A-GIIIm** respectively), key vectors for catalysis and deactivation in many olefin metathesis reactions.

Author Contributions: The manuscript was written by JAML and DEF. The H_2IMes complex **S-GIIIm** was synthesized and characterized by JAML. The aromatic IMes analogue **A-GIIIm** was prepared by NJB, using analogous methods. JCS (Carleton University) identified impurities present in commercial H_2IMes by electrospray mass spectrometry. JAML developed a protocol for their removal.

Isotopic Probes for Ruthenium-Catalyzed Olefin Metathesis. Justin A.M. Lummiss, Adrian G.G. Botti, Deryn E. Fogg.* *Catal. Sci. Technol.* **2014**; 4, 4210–4218 (inside cover, “Hot Article”).



Routes are described to previously unreported first- and second-generation Grubbs metathesis catalysts bearing a ^{13}C label at the key benzyldiene or methyldiene site. Improved syntheses of the ^2H -labelled isotopologues are also presented. Labelling at the alkylidene position is important because it provides unique, direct information about changes at the active site of the catalyst, and the fate of the $[\text{Ru}]=\text{CHR}$ ligand during catalyst deactivation. A case study demonstrates the power of ^{13}C -labelling in tracking the methyldiene moiety in amine-induced decomposition of the second-generation complex $\text{RuCl}_2(\text{PCy}_3)(\text{H}_2\text{IMes})(=^{13}\text{CH}_2)$. Also reported is the solubility of ethylene in C_6D_6 and CD_2Cl_2 , measured at $296 \pm 1.5\text{K}$ and $101.0 \pm 0.8\text{ kPa}$.

Author Contributions: The manuscript was written by JAML and DEF; AGGB aided in establishing the relevant literature context, and wrote the experimental sections relating to the ^2H -labelled complexes. All ^{13}C -labelled experiments were performed by JAML; all ^2H -labelled experiments by AGGB. The solubility of ethylene in various solvents was measured by JAML.

2.2. High-Yield Routes to the Grubbs Methyldiene Complexes

2.2.1. Introduction

The high activity and ease of handling of "second-generation" ruthenium metathesis catalysts (e.g. **S-GII**, **A-GII**; **Figure 2.1**) have greatly expanded the scope of olefin metathesis methodologies.⁹ Mounting industrial interest underscores the need for more

detailed understanding of catalyst behaviour under planned conditions of implementation. Central in this context is the behaviour of the methyldene derivatives that represent the catalyst resting states in ring-closing metathesis (RCM) and cross-metathesis (CM) reactions of terminal olefins. These species have been identified as key vectors for both catalyst decomposition^{10,11} and metathesis. To date, difficulties encountered in synthesis of **S-GIIIm** (vide infra), compounded by the poor initiation efficiencies characteristic of the second-generation catalysts,^{1,12,13} have restricted direct study of these important intermediates.[†] Here we report the first clean, high-yield route to methyldene complexes **S-GIIIm** and **A-GIIIm**.

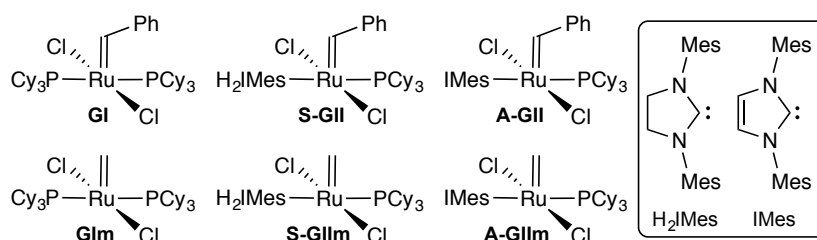
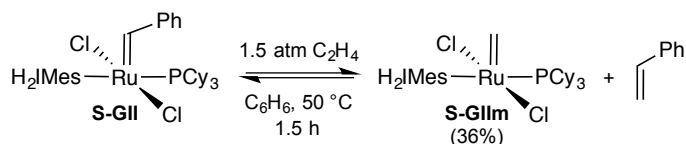


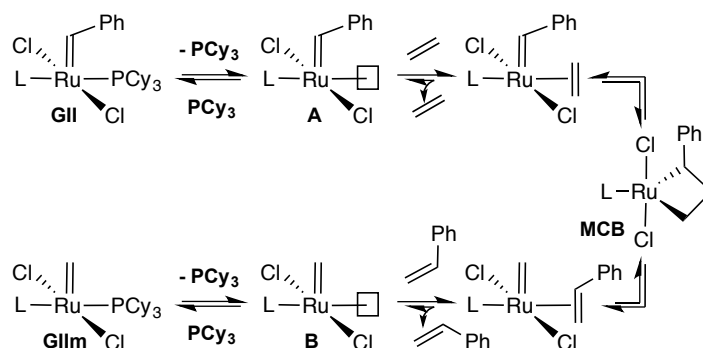
Figure 2.1. Metathesis catalysts discussed.

The literature route to **S-GIIIm** (involving CM of benzylidene **S-GII** with ethylene at 50 °C; **Scheme 2.1**)¹ affords the desired product in <40% yield, the balance being unidentified byproducts. The implied rapidity of decomposition is unexpected. The starting complex **S-GII** has a reported half-life of >1 month in benzene at 55 °C,⁴ and while the 5.7 h half-life found⁴ for the methyldene target is much shorter, this still exceeds the 1.5 h timescale of the CM reaction by a considerable margin. Of note, however, is the accelerated decomposition observed for various Ru metathesis catalysts in the presence of ethylene.^{4,14-16} We suspected that the low yield of **S-GIIIm** might originate in the vulnerability of intermediates formed during ethylene exchange, particularly four-coordinate $\text{RuCl}_2(\text{H}_2\text{IMes})(=\text{CH}_2)$ (**B**, **Scheme 2.2**), metallacyclobutane **MCB**, and – perhaps most susceptible¹⁴ – the unsubstituted metallacyclobutane formed via degenerate CM of **GIIIm** with ethylene.

[†] A rare exception involves a thermolysis study of $\text{GII}=\text{CH}_2$ in benzene, see Ref (4).



Scheme 2.1. Previously reported route to methyldene **S-GIIIm**.

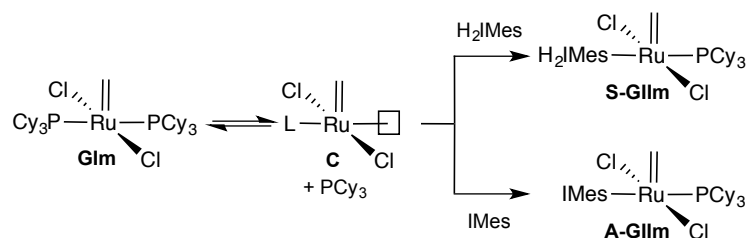


Scheme 2.2. Details of the synthetic sequence of Scheme 2.1 ($L = \text{H}_2\text{IMes}$), highlighting the high-commitment nature of **A** and **B** (see text). A parallel sequence involves degenerate exchange of **GIIIm** with ethylene via an unsubstituted metallacyclobutane analogous to **MCB**.

Kinetics studies by the groups of Grubbs¹ and Chen² indicate that four-coordinate **A** ($L = \text{H}_2\text{IMes}$) reacts preferentially with olefin, rather than free PCy_3 (a propensity that led Chen to classify the second-generation complexes as "high-commitment" catalysts).² Indeed, this bias is one factor underlying the exceptional metathesis activity of the *N*-heterocyclic carbene (NHC) catalysts. In the present context, however, high commitment is detrimental: the bias toward reaction with ethylene results in competitive inhibition of the desired ligand exchange, and prolongs the time that the catalyst spends in its least stable, phosphine-free states. The thermal sensitivity of **GII** in the presence of ethylene^{4,14,15,16c} (as in the synthesis shown in **Scheme 2.1**) is evidently much greater than that suggested by model studies in the absence of olefin.

The limitations intrinsic to ethenolysis led us to explore an alternative approach to the second-generation methyldene complexes, based on ligand exchange of **GIIIm** with free NHCs (H_2IMes , IMes ; **Scheme 2.3**). While this synthetic strategy may seem counter-intuitive, given that the half-life of **GIIIm** (40 min at 55 °C in C_6D_6)¹⁰ is much shorter than that of **GIIIm**, it is designed to exploit the *low*-commitment nature of the first-generation complex: that is, its propensity for rapid reaction with free PCy_3 ^{1,2} or, potentially, NHC donors. We considered that fast uptake of the Lewis base, coupled with elimination of the

vulnerable metallacyclobutane intermediate, could potentially improve reaction rates and yields.



Scheme 2.3. Ligand exchange route to second-generation methylidene complexes.

2.2.2. Results and Discussion

Access to the first-generation methylidene complex **GIm** in high purity is a prerequisite for the planned approach. In our hands, the reported¹⁷ synthesis of **GIm** via CM with ethylene resulted in persistent contamination by residual **GI**, consistent with the equilibrium nature of this reaction.[†] Essentially quantitative conversions could be readily attained, however, by washing the crude product with pentane to remove styrene, and re-subjecting it to the ethylene treatment. We obtained **GIm** free of **GI** after the second pass, in an overall isolated yield of 85%.

With clean **GIm** in hand, we turned to installation of the H₂IMes and IMes ligands. Earlier work described the efficiency with which **A-GII** can be obtained by treating **GI** with pure IMes.¹⁸⁻²⁰ Use of *isolated* IMes, in preference to the in situ-generated carbene, greatly simplified workup and purification, as PCy₃ was then the only adventitious species present at the end of reaction. Building on this precedent, we chose to use pure free IMes and H₂IMes to synthesize the methylidene complexes of interest. The free carbenes are readily accessible via the established procedures,^{21,22} and are now also commercially available (Strem).

A potential complication in our intended use of **GIm** as a precursor for ligand exchange is the low room-temperature lability of the PCy₃ ligand,¹ which necessitates use of elevated temperatures. While both free H₂IMes and free IMes show excellent thermal stability,[‡] the vulnerability of **GIm** is evident from the discussion above. On heating a benzene solution of

[†] In comparison, an equilibrium yield of just 20% **GI=CH₂** was reported on treating vinylalkylidene complex RuCl₂(PCy₃)₂(=CHCH=CPh₂) with 100 psi C₂H₄ at 50 °C in CD₂Cl₂. See Ref. (17).

[‡] ¹H NMR experiments showed no decomposition of H₂IMes or IMes over 10 h at 60 °C in C₆D₆, as indicated by integration against an internal standard.

GIm and free NHC at 60 °C, however, we found that ligand exchange out-competes decomposition. Thus, NMR-scale experiments in C₆D₆ revealed rapid formation of **S-GIm** (99% by 22 min; **Figure 2.2a**), with excellent agreement between conversions and in situ yields, as judged from integration against internal standard. Even on increasing reaction times to 45 min, to address any increase in timescale required for preparative-scale experiments, no decomposition was evident. It may be noted that this longer reaction period remains well within the nearly six-hour half-life of the product.⁴ **S-GIm** is obtained in 81% isolated yield, despite some losses incurred by its partial solubility in the cold pentane used to extract the PCy₃ co-product. The corresponding reaction with free IMes likewise enables quantitative formation of **A-GIm** (**Figure 2.2b**), which is isolated in similar yields (78%).

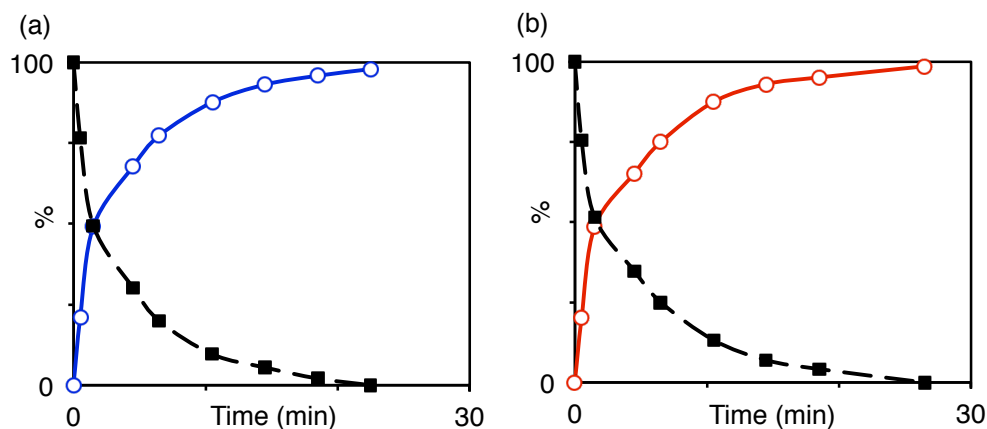


Figure 2.2. Kinetics of ligand exchange of **GIm** (black line) with isolated free NHCs to afford (a) H₂IMes derivative **S-GIm** (blue), or (b) IMes derivative **A-GIm** (red). Conditions: C₆D₆, 60 °C; conversion measured by integration vs. trimethoxybenzene.

2.2.3. Conclusions

The foregoing describes the first clean, high-yield route to the second-generation Grubbs methyldene complexes **S-GIm** and **A-GIm**. A strategy based on ligand exchange of RuCl₂(PCy₃)₂(=CH₂) with free H₂IMes or IMes eliminates the decomposition that severely limits the yields attainable in metathetical exchange of benzyldene **GII** with ethylene. Use of the isolated free NHCs (which are now commercially available) also contributes to high purity with minimal workup, as the only byproduct in the reaction is readily-removed PCy₃. Given the importance of these methyldene resting-state species as vectors for both metathesis and catalyst deactivation, we anticipate that these straightforward, high-yield

routes to **S-GIm** and **A-GIm** will aid significantly in clarifying key reaction pathways in olefin metathesis.

2.2.4. Experimental Details for Section 2.2

General Procedures

Reactions were carried out under N₂ using standard Schlenk and glove-box techniques. Dry, oxygen-free C₆H₆, CH₂Cl₂ and hexanes were obtained using a Glass Contour solvent purification system. Pentane was distilled over sodium benzophenone, acetone over calcium sulphate. All solvents were stored under N₂ over Linde 4 Å molecular sieves. C₆D₆ was purchased in 1-gram ampoules packed under N₂ (Cambridge Isotopes). Given the documented reactivity of free carbenes with even traces of water,^{23,24} NMR spectra of free carbenes were measured in C₆D₆ that had been dried over 4 Å molecular sieves in an N₂-filled glove box for at least 4 h. Ethylene (BOC Ultra-High Purity Grade 3.0; 99.9%) was used as received. Free IMes,²² H₂IMes•HBF₄,²⁵ and **GI**¹⁷ were prepared by literature methods. Free H₂IMes was obtained from Strem or prepared by literature methods.²¹ As a precautionary measure, all samples of free NHCs were dissolved in benzene and filtered through Celite to remove any potential contaminants (such as unconverted imidazolinium salt or residual base remaining from the deprotection procedure), prior to storage at -35 °C under N₂.

NMR spectra were recorded on a Bruker Avance 300 or 500 MHz spectrometer at 298 K, and referenced to the residual proton or carbon signals of the deuterated solvent (¹H, ¹³C NMR). Signals are reported in ppm, relative to TMS (¹H, ¹³C) or 85% H₃PO₄ (³¹P) at 0 ppm. The kinetics of ligand exchange between **GIm** and free H₂IMes or IMes were monitored in the NMR probe at 60 °C. ¹H NMR data (and ³¹P{¹H} NMR data, where applicable) for known compounds are provided for convenience; in some cases the NMR solvent differs from that in the literature report.

Identification of [H₂IMes•H]⁺. Traces of the unconverted imidazolinium salt were observed in one batch of free H₂IMes. Any such contaminant is readily removed by the protocol described in the General Procedures above. A sample of the salt was isolated for the purposes of identification by filtering a benzene solution of (predominantly) H₂IMes through a fine-frit filter. The identity of the cation was established by electrospray mass spectrometric (ESI-MS) analysis using a QSTAR XL hybrid quadrupole time-of-flight mass

spectrometer (AB Sciex, Framingham, MA) equipped with a nanoelectrospray ionization source, operating in positive ion mode. ESI-MS (aq. 33% MeCN + aq. 0.1% formic acid), m/z : Calcd $[\text{C}_{21}\text{H}_{27}\text{N}_2]^+$ ($\text{H}_2\text{IMes}\cdot\text{H}^+$), 307.2169; Found, 307.2177.

Synthesis of GIm. In a modified version of the reported procedure,¹⁷ a 100 mL Schlenk tube was charged with solid **GI** (1.00 g, 1.22 mmol) and 25 mL C_6H_6 in a glovebox, and equipped with a fritted gas-dispersion tube. (Benzene was chosen as reaction solvent, in preference to the CH_2Cl_2 used in the literature report, as we found that it afforded higher yields). To maintain saturation, a very slow flow of ethylene was passed through the stirred solution via the gas-dispersion frit, and vented to the box atmosphere through the open stopcock. A colour change from purple to brown was observed within 15 min. After 45 min, the solvent was stripped off under vacuum to afford a pink solid, which was washed with -35°C pentane (2×2 mL), cold acetone (2×1 mL), and again with cold pentane (2×2 mL). NMR analysis of the light pink powder revealed ca. 5% residual **GI**. The crude product was re-subjected to reaction with ethylene and isolated as before to afford clean **GIm** as a light pink powder. Yield: 769 mg (85%). NMR spectra were measured in C_6D_6 : signals are shifted slightly relative to the reported¹⁷ values in CD_2Cl_2 , but are otherwise in good agreement. $^{31}\text{P}\{^1\text{H}\}$ NMR (121.5 MHz, C_6D_6): δ 43.5 ppm (s, PCy_3). ^1H NMR (300.1 MHz, C_6D_6): δ 19.42 (s, 2H, $\text{Ru}=\text{CH}_2$), 2.77-2.61 (m, 6H, Cy), 2.08-1.88 (m, 12H, Cy), 1.85-1.49 (m, 30H, Cy), 1.38-1.13 (m, 18H, Cy).

Synthesis of S-GIm. In the glovebox, light pink **GIm** (150 mg, 0.200 mmol) was dissolved in 10 mL C_6H_6 in a 50 mL Schlenk tube. Free H_2IMes (75 mg, 0.245 mmol) was added as a white crystalline powder. The Schlenk tube was removed to a vacuum line and heated to 60°C for 45 min under Ar. The solution changed colour from pink to yellow-brown within 15 min. The solvent was removed under vacuum to yield a yellow solid, which was washed with cold pentane (3×2 mL; glovebox) to yield **S-GIm** as a fine yellow powder. Yield: 125 mg (81%). NMR spectra are in good agreement with the reported¹ values. $^{31}\text{P}\{^1\text{H}\}$ NMR (202.5 MHz, C_6D_6): δ 38.2 ppm (s, PCy_3). ^1H NMR (500.1 MHz, C_6D_6): δ 18.42 (s, 2H, $\text{Ru}=\text{CH}_2$), 6.93 (s, 2H, Mes *m-CH*), 6.75 (s, 2H, Mes *m-CH*), 3.30-3.18 (m, 4H, NCH_2CH_2), 2.78 (s, 6H, *o-CH}_3*), 2.56 (s, 6H *o-CH}_3*), 2.42-2.29 (m, 3H, Cy), 2.18 (s, 3H, *p-CH}_3*), 2.11 (s, 3H, *p-CH}_3*), 1.70-1.49 (m, 15H, Cy), 1.37-0.95 (m, 15H, Cy).

Synthesis of A-GIIIm. Prepared as in (C) above, but using free IMes (as a white crystalline powder). Yield 150 mg (78%) of **A-GIIIm**, a fine yellow powder. $^{31}\text{P}\{^1\text{H}\}$ NMR (202.5 MHz, C_6D_6): δ 40.9 ppm (s, PCy_3). ^1H NMR (500.1 MHz, C_6D_6): δ 18.77 (s, 2H, $\text{Ru}=\text{CH}_2$), 6.90 (s, 2H, Mes *m*-CH), 6.72 (s, 2H, Mes *m*-CH), 6.22 (d, $^3J_{\text{HH}} = 2$ Hz, 1H, $\text{NCH}=\text{}$), 6.13 (dd, $^3J_{\text{HH}} = 2$ Hz, $^5J_{\text{PH}} = 1$ Hz, 1H, $\text{NCH}=\text{}$), 2.60 (s, 6H, *o*- CH_3), 2.37 (s, 6H *o*- CH_3), 2.44-2.30 (m, 3H, Cy), 2.19 (s, 3H, *p*- CH_3), 2.12 (s, 3H, *p*- CH_3), 1.77-1.47 (m, 15H, Cy), 1.30-1.01 (m, 15H, Cy). $^{13}\text{C}\{^1\text{H}\}$ NMR (125.8 MHz, C_6D_6): δ 294.5 (d, $^2J_{\text{PC}} = 12$ Hz, $\text{Ru}=\text{CH}_2$), 191.6 (d, $^2J_{\text{PC}} = 79$ Hz, NCN), 139.4, 139.0, 138.4, 137.4, 137.0, 135.6, 129.8, 129.4, 124.1 (d, $^4J_{\text{PC}} = 3$ Hz, $\text{NCH}=\text{}$), 123.6 (s, $\text{NCH}=\text{}$), 30.9 (d, $J_{\text{PC}} = 19$ Hz, Cy), 29.4 (Cy), 28.2 (d, $J_{\text{PC}} = 10$ Hz, Cy), 26.8 (Cy), 21.34 (*p*- CH_3), 21.32 (*p*- CH_3), 19.8 (*o*- CH_3), 18.9 (*o*- CH_3). Anal. Calcd. for $\text{C}_{40}\text{H}_{61}\text{Cl}_2\text{N}_2\text{PRu}$: C, 62.16%; H, 7.96%; N, 3.62%. Found: C, 62.46%; H, 7.59%; N, 3.62%.

2.3. Incorporating a ^{13}C Isotopic Label into the Active Site for the Grubbs Benzylidene and Methyldiene Complexes

2.3.1. Introduction

Olefin metathesis is now a core tool in organic synthesis.²⁶⁻²⁹ With industrial applications of molecular metathesis catalysts now emerging,²⁶ improved understanding of their deactivation pathways is becoming increasingly urgent, particularly for the dominant ruthenium catalysts. Isotopic labelling has long been an important tool in organometallic chemistry, enabling direct insight into the rates and fates of bond-forming and bond-breaking reactions via NMR and mass spectrometric (MS) analysis.³⁰⁻³² Within the context of olefin metathesis, experiments with labelled olefins afforded key evidence for the Chauvin mechanism,⁶⁻⁸ for the chain-carrying role of metal alkylidene intermediates,³³ and for the relative competence of ring-closing^{34,35} or cross-metathesis^{36,37} relative to degenerate exchange. Deuterium-labelled *N*-heterocyclic carbene (NHC) ligands have also been used^{38,39} to probe C-H activation during catalyst deactivation and to track the release and return of solid-supported metathesis catalysts.⁴⁰

The present work was motivated by the potential offered by isotopic labelling for insight into the operation and decay⁴¹ of the Grubbs catalysts, which remain among the most

important catalyst systems used in olefin metathesis.^{26,27} We were particularly interested in accessing derivatives bearing a ^{13}C tag at the key $\text{Ru}=\text{CHR}$ site (**Figure 2.3a**). Labelling at the alkylidene position is of keen interest because this reports directly on changes at the active site. The diagnostic potency of the ^{13}C isotope, relative to the more routinely incorporated isotope ^2H , is a function of its order-of-magnitude expansion of the NMR chemical shift window, as well as elimination of potential scrambling pathways (a particular issue for catalytically promiscuous metals such as ruthenium). Also significant are the higher receptivity and slower T_2 relaxation relative to deuterium,[†] which significantly improve resolution, while drastically reducing acquisition time.

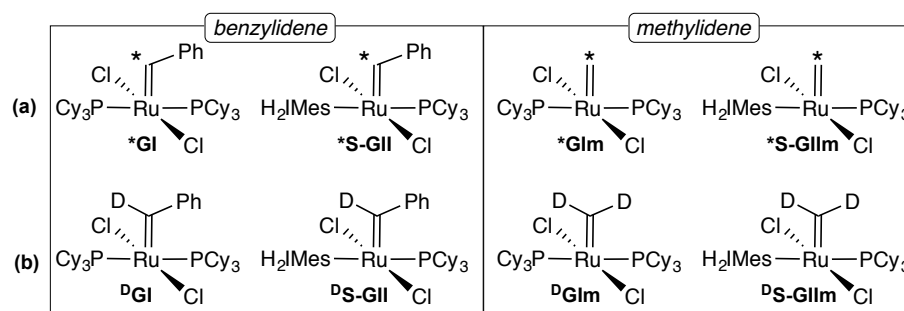


Figure 2.3. Isotopically labelled targets synthesized in this work. (a) ^{13}C -tagged (*) and (b) ^2H -tagged (D) first- and second-generation Grubbs catalysts, and their methyldiene resting states. (H_2IMes = $\text{N},\text{N}'\text{bis}(\text{mesityl})\text{imidazolin-2-ylidene}$).

Marciniec and co-workers recently reported successful ^{13}C -labelling of the Hoveyda catalyst at the benzylidene carbon, and use of the labelled complex to confirm catalyst anchoring on silica supports.⁴³ In subsequent studies, this compound was invaluable in affording unequivocal evidence for re-uptake of the styrenyl ether ligand during metathesis.⁴⁴ Similarly labelled Fischer carbene complexes earlier revealed transformation of the $[\text{Ru}] = ^{13}\text{CHOCH}_2\text{Ph}$ unit into a ruthenium hydridocarbonyl moiety.⁴⁵ To date, however, Grubbs catalysts bearing an isotopic label at the alkylidene site are limited to deuterated derivatives.^{15,41d,46-48} Here we report routes to the ^{13}C -labelled analogues, for both first- and second-generation Grubbs catalysts (**Figure 2.3a**). In the course of optimizing these syntheses with less costly ^2H -labelled reagents, we improved routes to the known^{15,41d,46,47}

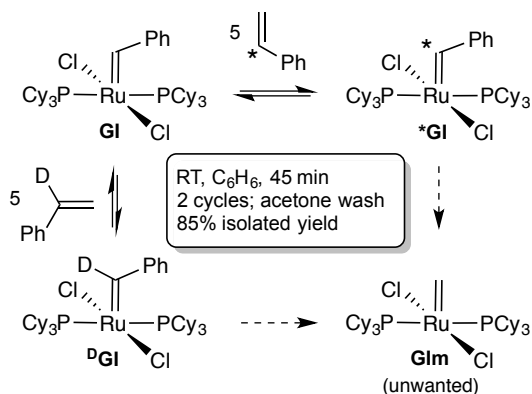
[†] The molar receptivity of ^{13}C is 4.4 times higher than that of deuterium at comparable levels of enrichment. Furthermore, spin-spin relaxation times (T_2) for deuterium nuclei are accelerated by quadrupolar relaxation, resulting in much broader signals, as line-widths at half-height are determined by $1/\pi T_2$. See Ref. (42).

deuterated isotopologues $^{\text{D}}\text{GI}$, $^{\text{D}}\text{GIm}$, and $^{\text{D}}\text{S-GIIm}$, and developed the first route to the deuterated second-generation Grubbs catalyst, $^{\text{D}}\text{S-GII}$ (Figure 2.3b).

2.3.2. Results and Discussion

First-Generation Catalysts via Labelled Styrenes

Cross-metathesis of **GI** with isotopically-labelled styrenes offers a convenient means of installing a *labelled* benzyldiene moiety on the first-generation Grubbs catalyst, as demonstrated by Dinger and Mol^{41d} in synthesis of $^{\text{D}}\text{GI}$. A challenge, however, lies in the selectivity for the labelled benzyldiene complex – that is, the kinetic product – relative to the unwanted thermodynamic product, methyldiene **GIm** (Scheme 2.4). Clean interception of labelled **GI** is especially important because the similar solubilities of these species hampers their separation.



Scheme 2.4. Kinetic vs. thermodynamic selectivity in synthesis of labelled **GI**.

We find that the timescale for degenerate exchange is much more readily established for ^{13}C -labelled $^*\text{GI}$ than ^2H -labelled $^{\text{D}}\text{GI}$. The doublet multiplicity of the ^1H NMR signal for the benzyldiene proton in $^*\text{GI}$ (Figure 2.4: δ_{H} 20.61 ppm; $^1J_{\text{CH}} = 146.6$ Hz) provides a unique, convenient means of simultaneously quantifying both formation of $^*\text{GI}$, and conversion of **GI**. This is especially useful in conjunction with use of an internal standard to detect net loss of $[\text{Ru}]=\text{CHR}$ species (that is, decomposition to non-alkylidene products). In the corresponding reactions with $\text{H}_2\text{C}=\text{CDPh}$, in contrast, the starting material and product cannot be simultaneously observed, and exchange is thus difficult to distinguish from decomposition.

To favour interception of the kinetic benzyldiene product, we carried out the exchange reaction at RT (glovebox; ca. 27 °C). We chose benzene in preference to dichloromethane as

the reaction medium, given the accelerating effect of aromatic solvents on metathesis.⁴⁹ On NMR scale, equilibration of **GI** with a five-fold excess of styrene- α - ^{13}C was complete within 45 min at RT. Neither **GI**^m nor decomposition was evident over 3 h (**Figure 2.4**), and the proportion of ***GI** present at equilibrium was 83%, as expected from the 1:5 stoichiometry of unlabelled vs. labelled styrene. Reactions on preparative scale (200 mg **GI**) involved two 45-minute cycles of reaction with styrene- α - ^{13}C . After each pass, the solvent was stripped off in the glovebox, and the styrene was extracted with acetone. This treatment gave clean, straightforward access to the previously unreported ^{13}C -labelled ***GI** in 85% yield, with an isotopic purity of 97%.

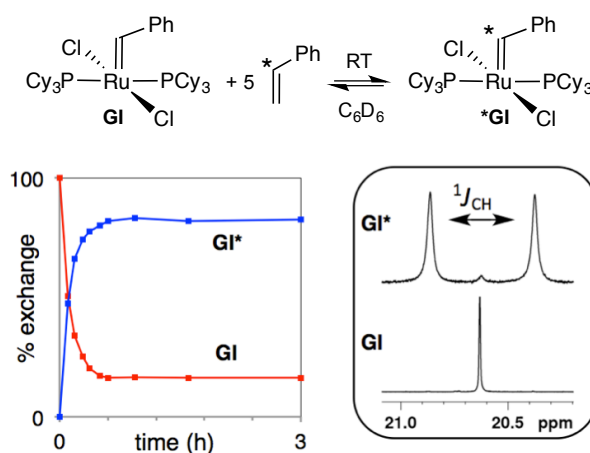


Figure 2.4. Formation and stability of ***GI** via the method of Scheme 1 (first pass). Inset: Benzylidene region of the ^1H NMR spectrum for isolated ***GI** (300.1 MHz, C_6D_6), illustrating the ease with which crossover can be measured. Lower trace: commercial starting **GI**. Upper trace: ***GI** with 2.2% residual **GI**.

Essentially identical yields and enrichment were obtained in the corresponding synthesis of **^DGI** via cross-metathesis of **GI** with styrene- α - D (400 mg scale). Dinger and Mol previously prepared this complex in 62% yield and 95% isotopic enrichment, via a similar sequence involving reaction with two successive portions of styrene (10 equivalents) in dichloromethane.^{41d,†} Superficially minor changes in workup led to a nearly 25% increase in isolated yield in the present work (despite the lower proportion of the styrene reagent). Specifically, use of acetone to extract residual styrene, rather than pentane, permitted us to

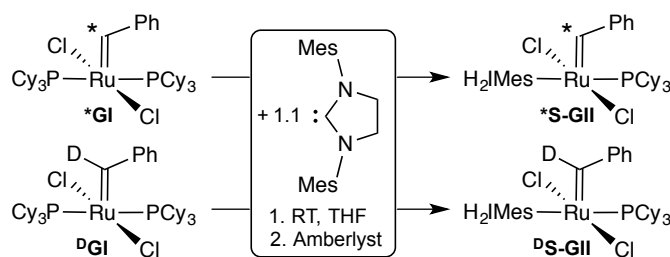
[†] A prior synthesis reported the $[\text{Ru}]=\text{CD}(\text{C}_6\text{D}_5)$ isotopologue of **^DGI**, albeit in 26% yield. See Ref. (48).

exploit the sparing solubility of **GI** in acetone.[†] The level of enrichment attainable for these benzyldiene targets is limited by (1) the isotopic purity of the styrene reagent; (2) the stoichiometry of the reaction: that is, the equilibrium ratio of unlabelled vs. labelled styrene; and (3) the number of reaction cycles, coupled with the efficiency with which the non-labelled styrene can be extracted.

Labelled Second-Generation Catalysts via Ligand Exchange

In sharp contrast, synthesis of the labelled second-generation benzyldienes via cross-metathesis of **S-GII** is unsatisfactory in both yield and purity. The non-lability of the phosphine ligand in **S-GII** renders exchange very slow (days) at RT, but efforts to accelerate reaction by heating result in co-formation of **S-GII_m**. As with the first-generation complexes, the benzyldiene and methyldiene complexes exhibit very similar solubilities, and are not readily separated.

More attractive as an entry point is therefore ligand exchange of labelled **GI** with free H₂IMes (**Scheme 2.5**). We previously described the efficiency of this route to **S-GII**, especially where combined with use of an ion-exchange resin to remove the phosphine co-product and excess NHC.⁵⁰ Accordingly, treating ***GI** and **^DGI** with free H₂IMes for 1 h in THF at RT, then stirring with Amberlyst resin, enabled access to clean ***S-GII** and **^DS-GII** in nearly 90% isolated yield (97% isotopic purity for ***S-GII**; 96% for **^DS-GII**). It should be noted, however, that the THF must be scrupulously dry to prevent hydrolysis of the free H₂IMes, which adversely affects the reaction stoichiometry, compromising product yields and/or purity.



Scheme 2.5. Successful ligand-exchange route to labelled second-generation benzyldiene complexes.

[†] Workup in the Mol route involved washing with pentane (in which **GI** is more soluble) and methanol. Probably also pertinent is the use of dichloromethane in the literature work, rather than benzene. The faster rate of metathesis in aromatic media was noted above. See Ref. (49) .

Methyldene Complexes: Additional Challenges

Synthesis of the labelled methyldene complexes is much more demanding, owing to the instability of these species. A half-life of 6 h has been reported⁴ for **S-GIIIm** at 55 °C in C₆D₆, and this figure drops to just 40 min for **GIm**.¹⁰ (For added data concerning the lifetimes of these species, see below). The first-generation methyldene complex **GIm** is nevertheless accessible in high yields and high purity via ethenolysis at RT.^{17,51} An alternative route utilizing reaction of RuH₂(N₂)₂(PCy₃)₂ with CH₂Cl₂ or CD₂Cl₂ is attractive for circumventing the need for a gaseous labelled reagent.⁴⁷ In situ yields of **GIm** or ^D**GIm** were limited to ca. 65%, however, and the product was contaminated with a RuHCl(H₂)(PCy₃)₂ by-product. Also examined in the present study was a potential route involving cross-metathesis with β-labelled styrenes. As this also proved less satisfactory (resulting in <60% ^{*}**S-GIIIm**, as a mixture with **S-GII**), it is briefly described in a closing section.

Our principal focus in this section is on adapting the successful ethenolysis route to permit efficient use of labelled ethylene gas. Sparging to maintain high ethylene concentrations is economically prohibitive, given the high prices of these reagents (\$550 or \$1400 CAD, respectively, for 1 L of C₂D₄ or ¹³C₂H₄ gas; Sigma-Aldrich). Instead, we carried out reactions in sealed vessels, and optimized procedures with deuterated ethylene, before proceeding to the more expensive ¹³C-labelled gas. As a first step, however, we measured the solubility of dissolved ethylene (a critical parameter in these sealed-tube experiments) in the proposed reaction solvents, using non-labelled ethylene.

Impact of Solvent on Ethylene Solubility and Methyldene Lifetime

The published data for the solubility of ethylene vary widely. The IUPAC-NIST Solubility Database cites no study as authoritative, although it excludes several values on the basis of unreliability.[†] Given the scatter in the data reported, we measured the solubility of ethylene

[†] A single entry for benzene in the IUPAC-NIST Solubility Data Series database corresponds to data for ethylene in the temperature and pressure regime used in our experiments, while no relevant entries exist for dichloromethane. Krauss and Gestrich reported a solubility in benzene of 140 mM at 298K, and 150 mM at 293K (see: Ref. (52)). A solubility of 32 mM was reported by the Diver group in CD₂Cl₂ at room temperature and balloon pressure (see: Ref. (53)). Our study, carried out at 296 ± 1.5 K and 1 atm (101.0 ± 0.8 kPa), yielded values of 89 ± 1 mM in C₆D₆, and 54 ± 3 mM in CD₂Cl₂. To rule out potential integration errors arising from differences in the *T*₁ relaxation of the ethylene protons, relative to TMB, we measured the ¹H NMR spectra at

in CD_2Cl_2 and C_6D_6 , at 23 ± 1.5 °C. In these experiments, we integrated the ^1H NMR singlet for dissolved C_2H_4 against that for a known concentration of trimethoxybenzene (TMB; **Figure 2.5**), after saturating the solution in ethylene by five sequential freeze-pump-thaw cycles. An equilibrium concentration of 89 mM was found in C_6D_6 , nearly double that in CD_2Cl_2 (54 mM), for experiments in triplicate, using independently-prepared stock solutions.

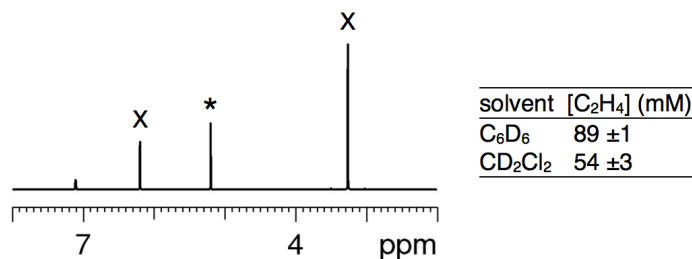


Figure 2.5. Measuring the solubility of ethylene in organic solvents by ^1H NMR analysis (300.1 MHz). Left: representative spectrum. Signal labelled (*) is due to C_2H_4 , (x) denotes TMB; C_6HD_5 signal not labelled. Right: tabulated data. Conditions: $296 \pm 1.5\text{K}$, 101.0 ± 0.8 kPa, 5 x freeze-pump-thaw cycles prior to equilibrating under ethylene; experiments in triplicate.

Notably, we also find that the highly sensitive methyldiene complex **GIm** is much longer-lived in benzene. These experiments were likewise carried out by integrating the signal of interest (in this case, the methyldiene singlet) against that for TMB. The half-life in CD_2Cl_2 or CDCl_3 was ca. 2.4 h at 35 °C, as compared to 6.6 h in C_6D_6 (**Figure 2.6**). Unexpectedly, THF is even more deleterious, with the half-life in this solvent dropping to ca. 1 h. On the basis of both ethylene solubility and product stability, therefore, benzene is preferred for the synthesis of **GIm**.

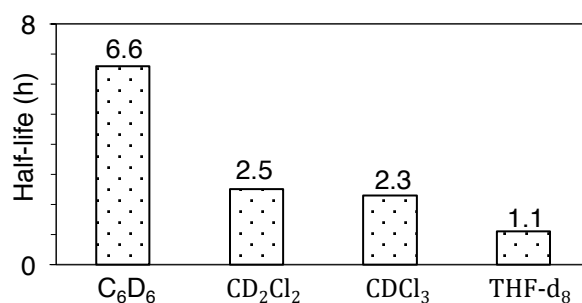
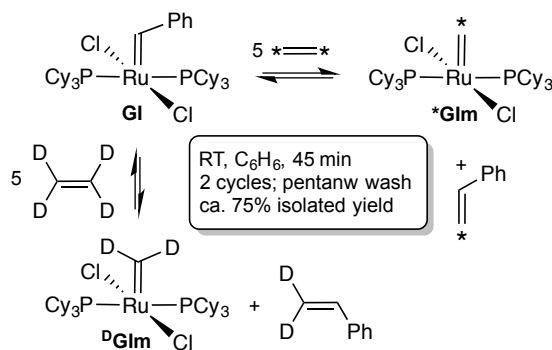


Figure 2.6. Impact of solvent on the lifetime of **GIm** (18 mM) at 35 °C. Assessed by ^1H NMR analysis; integration against TMB as internal standard. Cf. reported half-life at 55 °C in C_6D_6 40 min.¹⁰

different delay times. Minimal differences in relative integration (<3%) were apparent for single-pulse experiments, versus 16-scan experiments with an arbitrarily long D_1 relaxation delay

First-Generation Methylidenes via Labelled Ethylene

Following these probe experiments, synthesis of $^{\text{D}}\text{GIm}$ was undertaken on preparative scale (400 mg **GI**). For details of practical measures aimed at maximizing the efficiency of gas delivery from the lecture bottles, readers are referred to Appendix D. Cross-metathesis with C_2D_4 in benzene was conducted in two 45-minute cycles (**Scheme 2.6**). After each pass, the solvent was stripped off on the Schlenk line, and the styrene byproduct was extracted with pentane. (Pentane was used in preference to acetone because **GIm** – unlike **GI** – is very sparingly soluble in pentane: this is convenient as pentane residues are more readily removed under vacuum). The first cycle of treatment afforded $^{\text{D}}\text{GIm}$ in 85% isolated yield, with 5% **GI** remaining. A second treatment enabled isolation of $^{\text{D}}\text{GIm}$ in 75% total yield (>99% enrichment; no **GI** detected). The corresponding reaction with $^{13}\text{C}_2\text{H}_4$ afforded $^*\text{GIm}$ in 71% yield (99.5% enrichment). These isolated yields are well below the 85% level that we were able to attain for non-labelled **GIm**.⁵¹ The difference is due in part to the smaller scale for the labelling reactions (400 mg, vs. 1 g). Parallel experiments with C_2H_4 in sealed systems, however, also indicate consistently lower yields relative to the continuously-sparged reactions.



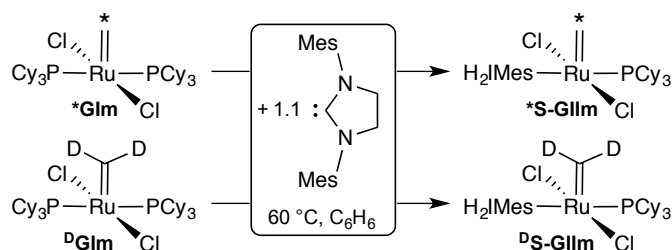
Scheme 2.6. Synthesis of $^*\text{GIm}$ and $^{\text{D}}\text{GIm}$ by ethenolysis.

Second-Generation Methylidenes via Ligand Exchange

Ethenolysis is impractical as a route to the second-generation methylidene complexes. Competing decomposition has been shown to limit isolated yields to 27–36% for **GIIIm** or its D-labelled isotopologue.^{1,15} More efficient is the “free-carbene” route developed by our group,⁵¹ in which **GIm** is treated with H_2IMes at 60 °C (cf. the corresponding synthesis of the benzylidene complex **S-GII** described above). The challenge in using this methodology to prepare the methylidene complexes lies in their thermal instability (see **Figure 2.6** and

discussion above). Nevertheless, $^{\text{D}}\text{S-GIIIm}$ could be obtained by heating $^{\text{D}}\text{GIIm}$ with free H_2IMes for 45 min (**Scheme 2.7**). Traces of the decomposition byproduct $[\text{MePCy}_3]\text{Cl}$ were extracted with degassed water (a technique used successfully to refine workup for the non-labelled target, which was obtained in 80% yield for reactions on 700 mg scale). Free PCy_3 and decomposed Ru were removed by successive extraction with acetone and cold pentane. The partial solubility of the product in these wash solvents limited isolated yields to 60% for reactions on ca. 200 mg scale: the >99% enrichment of the precursor was maintained. Purification with Amberlyst in THF was not feasible for these methylidene complexes, in contrast to the benzylidene analogues discussed above, owing to extensive decomposition.

Use of the same procedure, but omitting the acetone wash, enabled isolation of $^*\text{S-GIIIm}$ in 68% yield (160 mg scale), without any deleterious effect on purity.

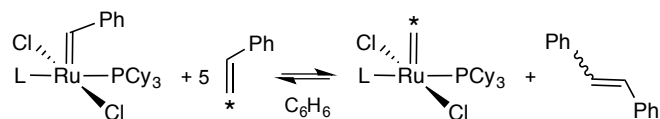


Scheme 2.7. Synthesis of $^*\text{S-GIIIm}$ and $^{\text{D}}\text{S-GIIIm}$ by ligand exchange.

Limitations in Ethylene-Free Access to Labelled Methylidenes

Given the cost and technical demands involved in handling the labelled gases, we also explored the potential accessibility of the labelled methylidene complexes by cross-metathesis with styrene- β - ^{13}C (**Scheme 2.8**). Here we hoped to exploit the thermodynamic preference for the methylidene species in metathesis of terminal olefins; see above. This approach failed for the synthesis of **GIIm**, however. Exchange of **GI** with 5 equiv of styrene at RT was far too slow: NMR-scale reactions proceeded to only 13% **GIIm** after 7 days, with 27% net loss of alkylidene (as judged by integration against internal standard). Increasing the temperature to 40°C caused catalyst degradation to dominate over the desired metathesis exchange: after 28 h at 40°C , just 4% **GIIm** was observed, accompanied by 43% decomposition. The corresponding reaction of **S-GII** with β - ^{13}C labelled styrene at 40°C resulted in a 60:40 mixture of **S-GII**: $^*\text{S-GIIIm}$ after 24 h. Longer reaction increased conversion of **GII**, but at the cost of competing decomposition of $^*\text{S-GIIIm}$. This route is therefore considerably less attractive than the ligand-exchange chemistry, where highly pure

S-GIIIm is desired. It offers advantages in other contexts, however, and will be treated in more detail in Section 2.4.



Scheme 2.8. Potential installation of ^{13}C -labelled methyldiene by cross-metathesis with $\beta\text{-}^{13}\text{C}$ -labelled styrene.

Case Study: Amine-Induced Deactivation of **GIIIm**

The ease with which these isotopically labelled complexes enable tracking of the methyldiene moiety during catalyst deactivation was tested in a study of the amine-induced decomposition of **S-GIIIm**. Amines have long been regarded as detrimental to ruthenium metathesis catalysts,[†] and have been flagged as problematic in reports from pharma.^{26a} We recently demonstrated that during catalysis, sterically accessible primary and secondary amines decompose **S-GIIIm** via a two-step mechanism, involving (1) replacement of the PCy_3 ligand by amine, and (2) abstraction of the methyldiene ligand by the released PCy_3 .³ Given the extreme vulnerability exhibited by **S-GIIIm** during catalysis, however, our original study focused on equimolar proportions of amine relative to catalyst.

Here we wished to examine the susceptibility of the methyldiene ligand to *direct* attack by amine. We therefore selected $\text{H}_2\text{N}^n\text{Bu}$, as the least bulky (i.e. most aggressive) of the amines originally tested, and added it in tenfold excess relative to ***S-GIIIm**. While ^1H NMR analysis of non-labelled **S-GIIIm** suffices to reveal loss of the methyldiene signal, which is complete within 10 min at RT, the ^{13}C label in ***S-GIIIm** proved invaluable in tracking the fate of the methyldiene moiety. Thus, $^{13}\text{C}\{^1\text{H}\}$ NMR analysis at 10 min revealed two dominant species in a ca. 70:30 ratio. These are $[\text{*MePCy}_3]\text{Cl}$, which appears as a doublet at 1.5 ppm ($^1J_{\text{CP}} = 47.9$ Hz), and $\text{NH}^n\text{Bu*Me}$, a singlet at 36.8 ppm (**Figure 2.7**, top).

The ratio of these two species, which reports on the propensity for nucleophilic attack by phosphine, vs. amine, is difficult to ascertain by any other method (including GC analysis, which is hampered by the involatility of the salt). In the absence of the label, $^{13}\text{C}\{^1\text{H}\}$ NMR analysis is of limited use: see inverted spectrum. The signal for the methyl carbon of

[†] Sterically accessible amines are most damaging, while α -substituted amines are relatively innocuous. For a lucid review, see Ref. (54). For studies of the decomposition of the Grubbs catalysts by primary amines, see Ref. (39) and (55).

$[\text{MePCy}_3]\text{Cl}$ (1.52 ppm) is lost in the baseline, and that for HN^nBuMe is obscured by $\text{H}_2\text{N}^n\text{Bu}$ present in excess. The longer acquisition time should also be noted: 5.5 h, vs. 20 min.

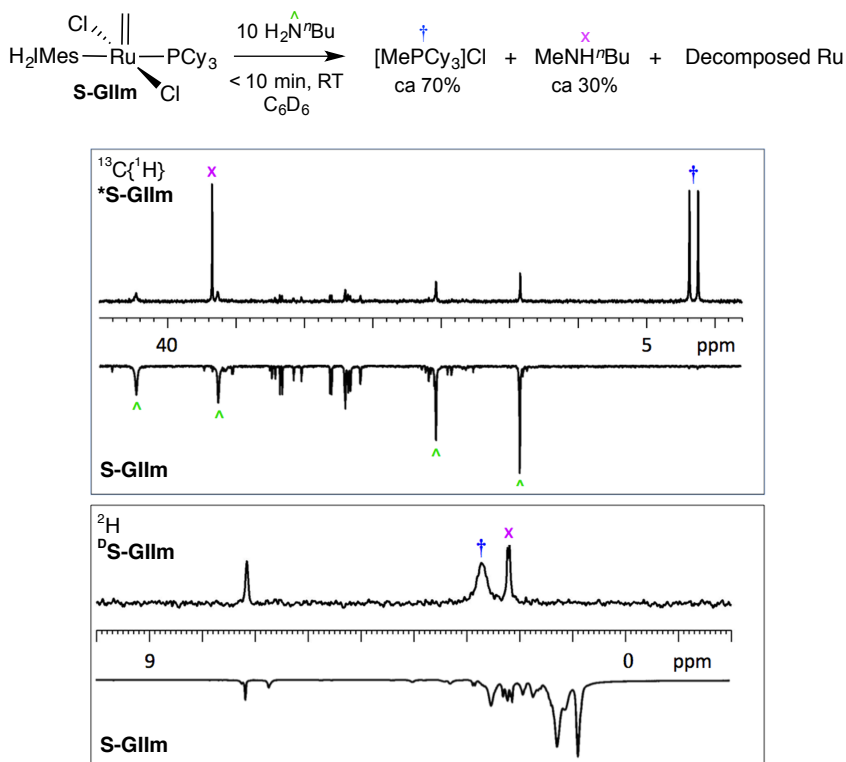


Figure 2.7. Spectra showing the superior rapidity and clarity with which ^{13}C -labelling enables tracking of the methylidene moiety during decomposition. Top: $^{13}\text{C}\{^1\text{H}\}$ NMR spectra; 20 min acquisition for $^*\text{S-GIIIm}$ and (inverted) 5.5 h acquisition for non-enriched **S-GIIIm**. Bottom: ^2H spectrum for $^d\text{S-GIIIm}$ and (inverted) ^1H NMR spectrum for **S-GIIIm** (2 h and 5 min acquisition, respectively).

The corresponding experiment with $^d\text{S-GIIIm}$ supported the inference from the $^*\text{GIIIm}$ experiment, but was less diagnostic. While the methyl signals for $[\text{MePCy}_3]\text{Cl}$ and HN^nBuMe can be observed at 2.8 and 2.2 ppm, respectively, assignment is hampered by the poor resolution of the $^2J_{\text{DP}}$ signal, and the narrow chemical shift window (**Figure 2.7**, bottom). It should be noted that neither $[\text{MePCy}_3]\text{Cl}$ nor HN^nBuMe can be readily identified by ^1H NMR analysis of the non-labelled **S-GIIIm** reaction, as their methyl resonances are obscured by overlapping signals (see inverted spectrum).

These results indicate a surprising bias toward nucleophilic attack by phosphine, relative to amine, even where amine is present in tenfold excess. While the origin of this effect is under further study, the data above illustrate the power of these isotopically labelled

complexes, and particularly ^{13}C -labelling at the $[\text{Ru}]=\text{CHR}$ center, in enabling rapid, quantitative insight into transformations that involve the active site.

2.3.3. Conclusions

The foregoing describes the first synthesis of Grubbs metathesis catalysts bearing a ^{13}C label at the key alkylidene site, as well as improved routes to their ^2H -labelled isotopologues. Both first- and second-generation Grubbs catalysts (that is, the benzyldiene precatalysts) were prepared, as were their resting-state methyldiene complexes. A case study was presented that demonstrates the ease with which the methyldiene label can be tracked via the ^{13}C label. This study revealed an unexpected, profound bias for abstraction of the methyldiene moiety by phosphine, relative to amine. While the basis for this phenomenon is the subject of ongoing study, the data above illustrate the power of these isotopically labelled complexes for insight into catalyst activation and deactivation, and their potential to expand understanding of the behaviour of the important Grubbs metathesis catalysts.

2.3.4. Experimental Details for Section 2.3

General Procedures

Reactions were carried out under N_2 using standard Schlenk and glovebox techniques. Dry, oxygen-free C_6H_6 and CH_2Cl_2 were obtained using a Glass Contour solvent purification system. Pentane was distilled over sodium benzophenone, acetone over calcium sulphate. All solvents were stored under N_2 over Linde 4 Å molecular sieves. C_6D_6 and CD_2Cl_2 (Cambridge Isotopes) were degassed by five successive freeze/pump/thaw cycles and stored over 4 Å molecular sieves under N_2 for at least 6 h prior to use. Ethylene (BOC Ultra-High Purity Grade 3.0; 99.9%) was used as received from Linde. The first-generation Grubbs catalyst (**GI**, 97% purity), styrene- α - ^{13}C (98% purity, 99% ^{13}C -enrichment, 4-*tert*-butylcatechol as a stabilizer), styrene- α - d_1 (98% purity, 98% ^2H -enrichment, hydroquinone as stabilizer), styrene- β - ^{13}C (99% ^{13}C -enrichment, 4-*tert*-butylcatechol as stabilizer), $^{13}\text{C}_2\text{H}_4$ (99% ^{13}C -enrichment), and 1,3,5-trimethoxybenzene (TMB, >99%) were obtained from Sigma-Aldrich, C_2D_4 (99.8% ^2H -enrichment) from C/D/N Isotopes. Free H_2IMes was prepared by the literature method.²¹

NMR spectra were recorded on a Bruker Avance 300 NMR at 296 ± 1.5 K, and referenced to the residual proton/deuteron or carbon signals of the solvent (^1H , ^2H , ^{13}C). Signals are

reported in ppm, relative to TMS (^1H , ^{13}C) or 85% H_3PO_4 (^{31}P) at 0 ppm. The number of intervening bonds for J_{PC} coupling constants is omitted for cyclohexyl carbons, for which specific assignments were not attempted.

Synthesis of Isotopically Labelled Ru Complexes

$\text{RuCl}_2(\text{PCy}_3)_2(=^{13}\text{CHPh})$, *GI. In the glovebox, styrene- α - ^{13}C (144 μL , 1.26 mmol, 5.0 equiv) was added to a purple solution of **GI** (208 mg, 0.253 mmol) in C_6H_6 (20 mL) in a 100 mL Schlenk tube. The reaction was stirred at RT for 45 min. The solvent was removed under vacuum to yield a purple solid, which was washed with acetone (3 x 2 mL) to remove excess styrene. The crude product (196 mg, 83% ^{13}C -enriched) was then re-subjected to styrene- α - ^{13}C (146 μL , 1.28 mmol, 5.0 equiv) as before. Work-up afforded *GI as a dark purple powder. Yield: 177 mg (85%, 97% ^{13}C -enriched). NMR shifts are in good agreement with those reported^{41d} for **$^{\text{D}}\text{GI}$** in C_6D_6 , barring those due to the alkylidene proton/deuteron. ^{13}C -coupling adds complexity to the splitting patterns observed. $^{31}\text{P}\{^1\text{H}\}$ NMR (121.5 MHz, C_6D_6): δ 36.9 (d, $^2J_{\text{PC}} = 8.0$ Hz, PCy_3). ^1H NMR (300.1 MHz, C_6D_6): δ 20.61 (d, $^1J_{\text{HC}} = 146.6$ Hz, 1H, $\text{Ru}=\text{CHPh}$), 8.72 (br s, 2H, Ph *o*-CH), 7.40-7.00 (m, 3H, Ph *p*-CH, *m*-CH; overlaps with solvent $\text{C}_6\text{D}_5\text{H}$), 2.87 (m, 6H, Cy), 2.10-1.85 (m, 12H, Cy), 1.83-1.41 (m, 30H, Cy), 1.38-1.05 (m, 18H, Cy). $^{13}\text{C}\{^1\text{H}\}$ NMR (C_6D_6 , 75.5 MHz) δ 295.0 (t, $^2J_{\text{CP}} = 8.0$ Hz, Ru), 153.4 (d, $J_{\text{CC}} = 44.6$ Hz, Ph *i*-C) 131.5 (d, $J_{\text{CC}} = 2.2$ Hz, Ph *o*-CH) 129.4 (d, $J_{\text{CC}} = 4.0$ Hz, Ph *m*-CH), 129.3 (*p*-CH), 32.5 (t, $J_{\text{CP}} = 9.1$ Hz, Cy), 30.2 (s, Cy), 28.2 (t, $J_{\text{CP}} = 5.0$ Hz, Cy), 27.0 (s, Cy).

$\text{RuCl}_2(\text{PCy}_3)_2(=\text{CDPh})$, $^{\text{D}}\text{GI}$. Prepared as for *GI above, but using styrene- α - d_1 (247 μL , 2.37 mmol, 5 equiv) and **GI** (390 mg, 0.474 mmol). Yield: 330 mg (85%, 96% ^2H -enriched). NMR data agree with those reported;^{41d} they are reproduced here for convenience. Resolution is slightly improved relative to *GI above. $^{31}\text{P}\{^1\text{H}\}$ NMR (121.5 MHz, C_6D_6): δ 36.7 (PCy_3). ^1H NMR (300.1 MHz, C_6D_6): 8.77 (d, $^3J_{\text{HH}} = 7.8$ Hz, 2H, Ph *o*-CH), 7.31 (t, $^3J_{\text{HH}} = 7.4$ Hz, 1H, Ph *p*-CH), 7.18-7.12 (m, 2H, Ph *m*-CH; overlaps with solvent $\text{C}_6\text{D}_5\text{H}$), 2.91 (m, 6H, Cy), 2.10-1.93 (m, 12H, Cy), 1.86-1.50 (m, 30H, Cy), 1.44-1.12 (m, 18H, Cy). ^2H NMR (46.1 MHz, C_6H_6): δ 20.61 ppm (br s, $\text{Ru}=\text{CD}_2$).

$\text{RuCl}_2(\text{H}_2\text{IMes})(\text{PCy}_3)(=^{13}\text{CHPh})$, *S-GII. In the glovebox, a 50 mL round-bottomed flask was charged with pink *GI (174 mg, 0.211 mmol) and THF (4.5 mL). To the stirred solution was added free H_2IMes (71 mg, 0.233 mmol, 1.1 equiv). The reaction was stirred at

ambient temperature (27 °C) for 1 h, at which point an aliquot removed for ^1H NMR analysis revealed ca. 1% ***GI** remaining, owing to hydrolysis of H_2IMes by trace water. A further 7.0 mg H_2IMes (0.023 mmol, 0.1 equiv) was added, and stirring was continued for 30 min, at which point conversion was complete (^1H NMR analysis). Off-the-shelf Amberlyst 15 exchange resin (180 mg, 4.0 equiv) was added and the suspension was stirred vigorously for 1 h to sequester free PCy_3 (confirmed by ^{31}P NMR analysis). The resin was filtered off and rinsed with THF (3 x 1 mL). The filtrate was stripped to dryness to yield ***S-GII** as a pink powder. Yield: 155 mg (87%, 97% ^{13}C -enriched). ^1H NMR analysis indicated the presence of ca. 2% of the H_2IMes hydrolysis product *N,N'*-dimesityl-*N*-formylethylenediamine.⁵⁰ This impurity was removed from an 18 mg portion of the product by washing with cold pentane (3 x 1 mL): catalyst purity increased to >98%, albeit to the detriment of the isolated yield (13 mg; 72%). NMR chemical data agree well with the values reported²⁵ for non-labelled **S-GII**, with the addition of ^{13}C splitting. $^{31}\text{P}\{^1\text{H}\}$ NMR (C_6D_6): δ 30.2 (d, $^2J_{\text{PC}} = 8.3$ Hz, PCy_3). ^1H NMR (300.1 MHz, C_6D_6): δ 19.64 (d, $^1J_{\text{HC}} = 147.9$ Hz, 1H, $\text{Ru}=\text{CHPh}$), 9.49 (br s, 1H, Ph *o*-CH), 7.45-5.30 (m, 8H, Ph, Mes *m*-CH; overlaps with solvent $\text{C}_6\text{D}_5\text{H}$), 3.68-0.74 (m, 55H, Cy and CH_2 , CH_3 of H_2IMes). $^{13}\text{C}\{^1\text{H}\}$ NMR (C_6D_6 , 75.5 MHz): δ 294.8 (d, $^2J_{\text{CP}} = 8.3$ Hz, Ru), 221.5 (d, $^2J_{\text{CP}} = 77.3$ Hz, C_{NHC}), 152.0 (d, $^1J_{\text{CH}} = 45.9$ Hz, Ph *i*-C), 139.4 (br s), 138.3, 137.8, 137.6, 137.3 (br, s), 135.9, 130.3, 129.4, 52.2 (d, $^4J_{\text{CP}} = 3.3$ Hz, NHC CH_2), 51.2 (d, $^4J_{\text{CP}} = 2.0$ Hz, NHC CH_2), 32.0 (d, $J_{\text{CP}} = 16.5$ Hz, Cy), 29.7 (s, Cy), 28.2 (d, $J_{\text{CP}} = 10.0$ Hz, Cy), 26.6 (s, Cy), 21.2 (s, *p*- CH_3), 21.1 (s, *p*- CH_3), 20.5 (s, *o*- CH_3), 19.0 (br s, *o*- CH_3). Swivelling about the $\text{Ru}=\text{CHPh}$ bond prevents observation of all phenyl carbons except the *ipso*-carbon, and broadens the corresponding ^1H NMR signals.

$\text{RuCl}_2(\text{H}_2\text{IMes})(\text{PCy}_3)(=\text{CDPh})$, $^{\text{D}}\text{S-GII}$. Prepared as for ***S-GII** above, but using $^{\text{D}}\text{GI}$ (275 mg, 0.334 mmol), H_2IMes (113 mg, 0.367 mmol, 1.1 equiv), and Amberlyst 15 resin (284 mg, 1.34 mmol, 4 equiv). Yield: 244 mg (86%, 96% ^2H -enriched). NMR chemical shifts are in excellent agreement with the values reported²⁵ for non-labelled **S-GII**, barring those due to the alkylidene proton/deuteron. ^2H NMR (46.1 MHz, C_6H_6): δ 19.64 ppm (br s, $\text{Ru}=\text{CDPh}$).

$\text{RuCl}_2(\text{PCy}_3)_2(=^{13}\text{CH}_2)$, *GI_m**.** In the glovebox, a 50 mL round-bottom flask equipped with a Kontes valve was charged with purple **GI** (403 mg, 0.490 mmol) and C_6H_6 (20 mL). The flask was removed to a Schlenk line, degassed by five consecutive freeze/pump/thaw

cycles, and connected via a T-valve to the $^{13}\text{C}_2\text{H}_4$ lecture bottle and a Schlenk line. Ethylene was introduced from a lecture bottle (for details, see SI). Once a positive pressure was achieved, the reaction vessel was sealed and allowed to stir at RT. A colour change from deep purple to red, then brown, was evident within 10 min. The flask was then briefly opened to re-establish positive pressure, and resealed. The reaction was stirred for 45 min, after which the flask was returned to the glovebox and solvent was removed under vacuum. Styrene and ruthenium decomposition products were extracted with cold pentane (5 x 1.5 mL; $-35\text{ }^\circ\text{C}$) to afford a pink solid consisting of ***GIm** and **GI** in 95:5 ratio (310 mg). Following a second pass of reaction with ethylene, clean ***GIm** was isolated as a pink solid. Yield 259 mg (71%, 99.5% ^{13}C -enriched). NMR data agree with those reported for **GIm**,⁵¹ with the addition of ^{13}C splitting. $^{31}\text{P}\{^1\text{H}\}$ NMR (121.5 MHz, C_6D_6): δ 43.4 ppm (d, $^2J_{\text{PC}} = 8.4\text{ Hz}$, PCy_3). ^1H NMR (300.1 MHz, C_6D_6): δ 19.41 (d, $^1J_{\text{HC}} = 156.7\text{ Hz}$, 2H, $\text{Ru}=\text{CH}_2$), 2.80-2.55 (m, 6H, Cy), 2.10-1.88 (m, 12H, Cy), 1.85-1.44 (m, 30H, Cy), 1.38-1.10 (m, 18H, Cy). $^{13}\text{C}\{^1\text{H}\}$ NMR (C_6D_6 , 75.5 MHz) δ 294.7 (t, $^2J_{\text{CP}} = 8.4\text{ Hz}$, $\text{Ru}=\text{CH}_2$), 31.1 (t, $J_{\text{CP}} = 9.6\text{ Hz}$, Cy), 29.7 (s, Cy), 28.1 (t, $J_{\text{CP}} = 5.3\text{ Hz}$, Cy), 26.9 (s, Cy).

$\text{RuCl}_2(\text{PCy}_3)_2(=\text{CD}_2)$, $^{\text{D}}\text{GIm}$. Prepared as for ***GIm**, but using C_2D_4 and **GI** (400 mg, 0.486 mmol). Yield: 272 mg (75%, >99% ^2H -enriched). NMR chemical shifts are in excellent agreement with the values reported⁵¹ for non-labelled **GIm**, barring those due to the alkylidene proton/deuteron. ^2H NMR (46.1 MHz, C_6H_6): δ 19.44 ppm (br s, $\text{Ru}=\text{CD}_2$).

$\text{RuCl}_2(\text{H}_2\text{IMes})(\text{PCy}_3)(=^{13}\text{CH}_2)$, *S-GIm**.** In the glovebox, light pink ***GIm** (202 mg, 0.270 mmol) was dissolved in 12 mL C_6H_6 in a 100 mL Schlenk tube. White crystalline H_2IMes (91 mg, 0.297 mmol, 1.1 equiv) was added. The flask was removed to a Schlenk line and immersed in a $60\text{ }^\circ\text{C}$ oil bath. A colour change from pink to yellow-brown was observed within 15 min, and heating was continued for a total of 45 min. The solvent was then removed under vacuum at room temperature to yield a brown residue. This brown tar was transformed into a well-behaved yellow powder by suspending in pentane in the glovebox, scratching with a spatula, and stripping off the pentane (3x). Yield 179 mg (86%) of a crude yellow solid; ^{31}P NMR analysis indicated contamination with $[\text{MePCy}_3]\text{Cl}$. Dissolving 161 mg of crude product in 8 mL benzene and washing with water (2 x 1.5 mL) removed the $[\text{MePCy}_3]\text{Cl}$ impurity. The benzene was then removed under vacuum and the yellow solid was washed with cold pentane (3 x 1.5 mL) to give ***S-GIm** as a fine yellow powder. Yield:

127 mg (68%, 99.5% ^{13}C -enriched). NMR chemical shifts are in excellent agreement with the values reported for the non-labelled isotopologue,⁵¹ although ^{13}C coupling adds further complexity. $^{31}\text{P}\{^1\text{H}\}$ NMR (121.5 MHz, C_6D_6): δ 38.3 ppm (d, $^2J_{\text{PC}} = 8.5$ Hz, PCy_3). ^1H NMR (300.1 MHz, C_6D_6): δ 18.42 (d, $^1J_{\text{HC}} = 158.6$ Hz, 2H, $\text{Ru}=\text{CH}_2$), 6.92 (s, 2H, Mes *m*-CH), 6.75 (s, 2H, Mes *m*-CH), 3.35-3.15 (m, 4H, NHC CH_2), 2.78 (s, 6H, *o*- CH_3), 2.55 (s, 6H *o*- CH_3), 2.44-2.25 (m, 3H, Cy), 2.18 (s, 3H, *p*- CH_3), 2.11 (s, 3H, *p*- CH_3), 1.70-1.45 (m, 15H, Cy), 1.30-0.95 (m, 15H, Cy). $^{13}\text{C}\{^1\text{H}\}$ NMR (C_6D_6 , 75.5 MHz) δ 294.4 (d, $^2J_{\text{CP}} = 8.5$ Hz, $\text{Ru}=\text{CH}_2$), 222.2 (d, $^2J_{\text{CP}} = 79.8$ Hz, C_{NHC}) 139.3 (s, Mes-A *o*-C), 138.6 (s, Mes-A *p*-C), 138.1 (s, Mes-B *p*-C), 137.8 (s, Mes-B *o*-C), 137.4 (s, Mes-B *i*-C), 135.0 (s, Mes-A, *i*-C), 130.2 (s, Mes-A, *m*-CH), 129.7 (s, Mes-B, *m*-CH), 51.6 (d, $^4J_{\text{CP}} = 3.5$ Hz, NHC CH_2), 50.0 (d, $^4J_{\text{CP}} = 1.7$ Hz, NHC CH_2), 30.7 (d, $J_{\text{CP}} = 17.8$ Hz, Cy), 29.2 (s, Cy), 28.0 (d, $J_{\text{CP}} = 10.4$ Hz, Cy), 26.7 (s, Cy), 21.22 (s, Mes *p*- CH_3), 21.20 (s, Mes *p*- CH_3), 20.1 (s, Mes-A *o*- CH_3), 19.1 (s, Mes-B *o*- CH_3). *Note*: Mes-A and Mes-B denote the two unique mesityl groups.

$\text{RuCl}_2(\text{H}_2\text{IMes})(\text{PCy}_3)(=\text{CD}_2)$, $^{\text{D}}\text{S-GIIIm}$. Prepared as for $^*\text{S-GIIIm}$ above, but using $^{\text{D}}\text{GIIm}$ (210 mg, 0.280 mmol) and free H_2IMes (94 mg, 0.308 mmol). Instead of dissolving the crude product in benzene and extracting with water (an improved work-up developed with $^*\text{S-GIIIm}$), the crude product was washed with H_2O (1 x 2 mL), then washed with acetone to remove residual water (1 x 1 mL), and finally pentane (3 x 1 mL), yielding a yellow solid. Yield: 131 mg (63%, >99% ^2H -enriched). $^{31}\text{P}\{^1\text{H}\}$ and ^1H NMR chemical shifts are in excellent agreement with the values reported for the non-labelled isotopologue,⁵¹ barring those due to the alkylidene proton/deuteron. ^2H NMR (46.1 MHz, C_6H_6): δ 18.43 ppm (br s, $\text{Ru}=\text{CD}_2$).

Representative Procedure for C_2H_4 Solubility Measurements. A sample of TMB (11.2 mg, 0.066 mmol) was weighed out using an analytical balance inside the glovebox, transferred to a J. Young NMR tube, and dissolved in C_6D_6 (750 μL). The solution was degassed via five consecutive freeze/pump/thaw cycles, then opened to an atmosphere of C_2H_4 (oil-bubbler pressure) for ca. 0.5 min. The concentration of dissolved C_2H_4 was established by ^1H NMR analysis by comparing the integration of the C_2H_4 singlet at 5.25 ppm (4H) against the TMB aromatic singlet at 6.25 ppm (3H). A recycle delay (D_1) of 20.0 s was used to ensure accurate integration and the reported numbers are the average of three trials. The same procedure was used to measure the solubility of ethylene in CD_2Cl_2 .

Representative Procedure for Half-life Measurements. In the glovebox, a J. Young NMR tube was charged with **GIm** (10 mg, 0.013 mmol), TMB (ca. 1 mg), and THF-d₈ (0.75 mL). The initial ratio of **GIm** to TMB was measured by ¹H NMR analysis. The NMR probe was heated to 35 °C and ¹H NMR spectra were collected to 95% consumption of the starting methyldiene. The half-life of **GIm** in CD₂Cl₂, CDCl₃, and C₆D₆ was determined similarly.

Representative Procedure for Amine-Induced Deactivation of **GIIIm.** In the glovebox, ***S-GIIIm** (9.8 mg, 0.013 mmol) was dissolved in C₆D₆ (633 μL) in a J Young NMR tube, and treated with H₂NⁿBu (12.5 μL, 0.13 mmol; 10 equiv). The NMR tube was shaken vigorously for 10 minutes, after which ¹³C NMR spectra were collected. Loss of the methyldiene signal was accompanied by the emergence of new peaks for [^{*}MePCy₃]Cl (1.5 ppm; d, ¹J_{CP} = 47.9 Hz) and NHⁿBu^{*}Me (36.8 ppm; s), with an integration ratio of 69:31.

2.4. Ethylene-Free Synthesis of ***GIIIm**

2.4.1. Introduction

The objective of the preceding Section was access to the labelled methyldiene complexes in high yields and purity. An alternative route via cross metathesis of **GI** and **S-GII** with β-¹³C-styrene (see **Scheme 2.8** above) was briefly mentioned, but was not developed. This route failed for **GIm** (for which decomposition proved faster than exchange), and afforded **S-GIIIm** only as a mixture with **S-GII**. The great advantage of the styrene exchange route, however, is the potential to circumvent the cost and technical demands associated with handling a ¹³C-labelled gas. Additionally, using styrene instead of ethylene reduces the proportion of the unsubstituted MCB intermediate formed. The vulnerability of this intermediate was identified in Section 2.2. In some contexts, moreover – notably, ¹³C NMR analysis – intermediate levels of purity and isotopic enrichment can be adequate. Synthesis of ***S-GIIIm** via cross metathesis of **S-GII** with β-¹³C-styrene was therefore examined more closely, as described below.

2.4.2. Results and Discussion

Optimizing the Temperature of Styrene Exchange

Given the susceptibility of the methyldiene target to thermal degradation, we sought to establish the minimum temperature at which ***GIIIm** could be obtained. These temperature

effects are most clearly revealed by cross-metathesis of **GII** with the α -labelled styrene, which permits tracking of both kinetic and thermodynamic products: that is, ***GII** and **GII_m**, respectively (**Figure 2.8a**). Use of the β -labelled styrene, in contrast, can reveal only the rate of formation of ***GII_m**, as the **GII** formed by degenerate exchange cannot be distinguished from that initially present (**Figure 2.8b**). Insight into this point is important to clarify whether low yields of **GII_m** are due simply to slow initiation of **GII**, or to slow formation and competing decomposition of **GII_m**.

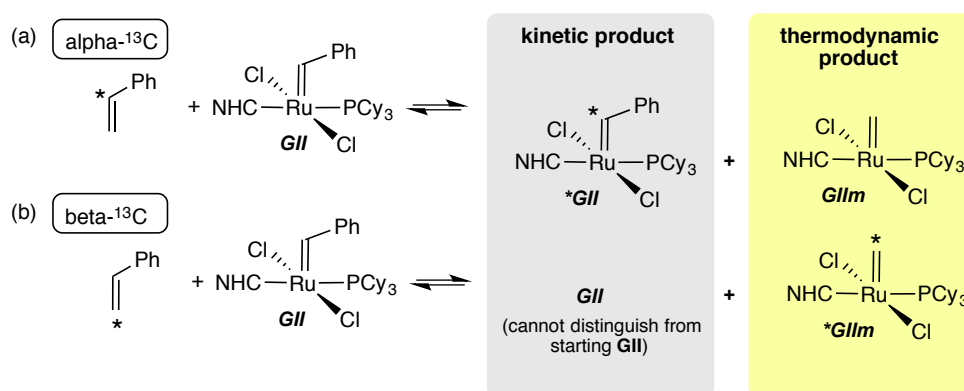


Figure 2.8. Products observed from reaction of **GII** with: (a) α - ^{13}C -labelled styrene; (b) β - ^{13}C -labelled styrene.

An NMR-scale probe reaction was therefore carried out, in which **S-GII** was treated with five equivalents of styrene- α - ^{13}C . At RT, formation of **S-GII_m** was extremely slow (**Figure 2.9a**). The problem is not initiation: after 8 h, the proportion of unreacted **S-GII** was 37%, but the yield of **S-GII_m** was just 2%, indicating that at this stage, the reaction was limited to the kinetic regime. More seriously, decomposition outstrips conversion to **S-GII_m**: loss of the alkylidene signal reaches 6% at 8 h, as determined by integration against internal standard. These data underscore the very slow turn-on efficiency of **S-GII** at room temperature. (Interestingly, this implies that where metathesis via **S-GII** is rapid at room temperature, a small portion of the catalyst charge is responsible: ca. 15% at 1 h).

At 40 °C, in contrast, just 7% unreacted **S-GII** remained at ca. 8 h. While the dominant species present remained the kinetic product ***S-GII** (41%; **Figure 2.9b**), formation of **S-GII_m** here outpaced decomposition (26%, vs. 19%). Some of the decomposition, moreover, is almost certainly due to retention of ethylene in the NMR tube, which results in formation of the unprotected metallacyclobutane (**MCB**). Preparative-scale reactions at 40 °C were therefore pursued.

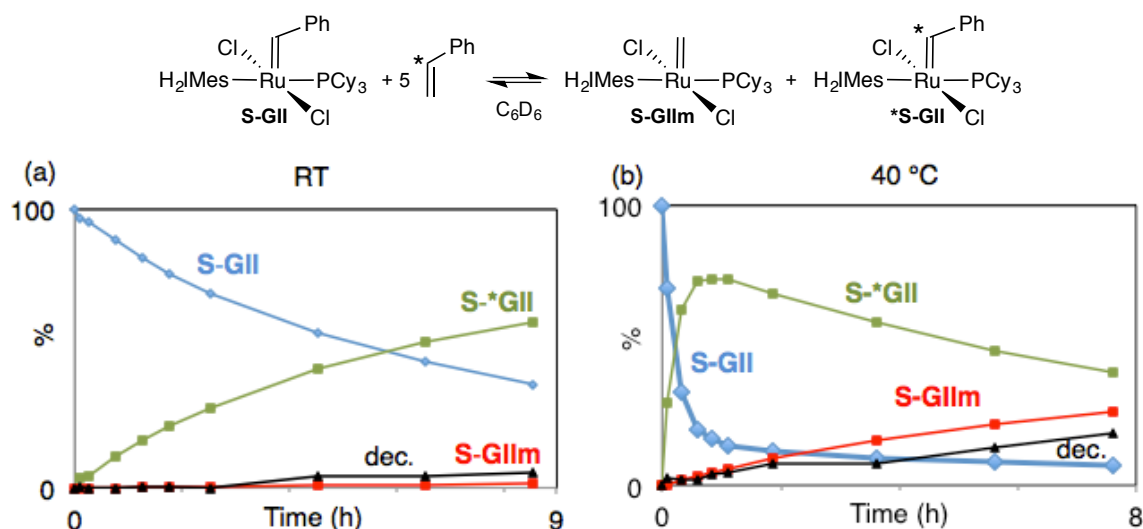


Figure 2.9. Impact of temperature on the rates of formation of methylidene **S-GIIIm** (red) by reaction of **S-GII** (blue) with ^{13}C -labelled styrene. Degenerate metathesis results in co-formation of $^*\text{S-GII}$ (green); decomposition (black) to non-alkylidene species is also detected. Reactions carried out in a sealed J. Young NMR tube, with integration against TMB as internal standard.

Synthesis of ^{13}C -Enriched $^*\text{GIIIm}$

Reaction of **S-GII** with five equivalents of β - ^{13}C -labelled styrene was carried out on 200 mg scale at 40 °C. The proportion of $^*\text{S-GIIIm}$ reached 40% after 24 h. Longer reaction was not attempted, to limit decomposition. The mixture of **S-GII** and $^*\text{S-GIIIm}$ was isolated in 67% yield after extracting the decomposition products and styrene with pentane. The proportion of $^*\text{S-GIIIm}$ increased slightly (to 47%) following workup, owing to the higher solubility of **S-GII** in pentane. While substantially less pure than the **S-GIIIm** prepared via the ethenolysis–ligand exchange route (Section 2.2), the material obtained by this route is nonetheless of value for solid-state ^{13}C NMR studies of **S-GIIIm**. Although the benzyldiene complex **S-GII** is present in essentially equal proportions, enrichment is selective for the methylidene species. The 1.1% natural abundance of ^{13}C in the contaminating **S-GII** thus renders this species spectroscopically insignificant.

Interestingly, the IMes analogue was less amenable to synthesis via this route. Initiation (i.e. loss of PCy_3) is dramatically slower for **A-GII** than **S-GII**, a point discussed in more detail in Chapter 3. Uptake of the label therefore proved very slow. In NMR-scale reactions of **A-GII** with styrene at 40 °C, yields of the desired **A-GIIIm** reached just 9% after 6 h, with 11% decomposition. Increasing the temperature of the reaction would undoubtedly accelerate

formation of **A-GIIIm**, although it remains unclear whether the extent of decomposition would then be prohibitive. In the present work, optimization of the styrene route for the synthesis of **A-GIIIm** was not pursued.

2.4.3. Conclusions

The synthesis of ***S-GIIIm** described above, involving cross-metathesis of **S-GII** with labelled styrenes (Route B), is complementary to the approach of Section 2.2 (Route A), in which **S-GIIIm** was prepared by ethenolysis of **GI**, followed by ligand exchange. The key difference lies in the nature of the metallacyclobutane intermediate. Route A exploits the low-commitment nature of the **GI** system to minimize the time spent as the unsubstituted metallacyclobutane. In Route B, a substituted metallacyclobutane intermediate is present, and the greater stability of this species is exploited to gain access to **S-GIIIm** in one step from **S-GII**. This direct route to **S-GIIIm** is useful where lower enrichment is sufficient, but its utility is limited by the poor yields and purity relative to Route A.

The success of route B highlights the important connection between catalyst commitment and **MCB** substitution. Specifically, high-commitment catalysts are vulnerable to decomposition when an unsubstituted **MCB** intermediate is anticipated. This suggests that low-commitment catalysts should out-perform high-commitment catalysts when high concentrations of ethylene are present, for example during ethenolysis of bio-renewables.

2.4.4. Experimental Details for Section 2.4

General Procedures

Reactions were carried out using standard glovebox techniques at ambient temperature (RT; 25–27 °C). Literature procedures were used to prepare the second-generation complexes $\text{RuCl}_2(\text{PCy}_3)(\text{H}_2\text{IMes})(=\text{CHPh})$ (**GII**). NMR spectra were recorded at 23 °C, and referenced to the residual proton or carbon signals of the deuterated solvent (^1H , ^{13}C), or external 85% H_3PO_4 (^{31}P). Signals are reported relative to TMS (^1H and ^{13}C) or 85% H_3PO_4 (^{31}P) at 0 ppm.

Synthesis of ^{13}C -enriched GIIIm by CM of GII with $^{13}\text{CH}_2=\text{CHPh}$. In the glovebox, a 100 mL Kontes flask was charged with **GII** (200 mg, 0.236 mmol) and 20 mL C_6H_6 . Neat styrene- β - ^{13}C (135 μL , 1.18 mmol, 5.0 equiv) was added, after which the flask was sealed and the reaction was stirred at 40 °C. Aliquots were removed periodically for ^1H NMR

analysis. At 24 h, ca. 40% conversion to ***GIIIm** was evident. The reaction was arrested at this stage, as parallel experiments indicated that higher conversions were offset by increased decomposition. The solvent was removed under vacuum to yield a brown residue, from which styrene was extracted with pentane (4 x 1.5 mL), and the [MePCy₃]Cl decomposition product was extracted with water (1 x 1.5 mL). Washing with pentane (2 x 1.5 mL) afforded 47% enriched **GIIIm** as a fine brown powder. Yield 129 mg (67%). ³¹P{¹H} NMR (121.5 MHz, C₆D₆): δ 38.3 ppm (d, ²J_{PC} = 8.2 Hz, ***GIIIm**PCy₃), 30.1 ppm (s, **GII**PCy₃). ¹H NMR (300.1 MHz, C₆D₆): δ 19.65 ppm (s: 52% **GII** Ru=CHPh), δ 18.42 ppm (d, ¹J_{HC} 158.6 Hz : 47% ***GIIIm** Ru=CHPh), 17.53 (d, ¹J_{HC} 176.1 Hz 1% unidentified Ru=***CHR**).

2.5. Subsequent Advances

Chapters 3 and 4 of this thesis will present studies of catalyst deactivation enabled by access to **S-GIIIm** and **A-GIIIm**, and their labelled isotopologues. Briefly noted here are two studies not included in this thesis, aimed at expanding insight into the fundamental behaviour of methyldiene complexes using non-routine spectroscopic methods: X-ray absorption fine structure (EXAFS) spectroscopy and solid-state NMR spectroscopy.

Solution-state EXAFS experiments were carried out at the Advanced Photon Source (Argonne National Laboratories) to monitor the kinetics of thermolysis for methyldiene **S-GIIIm** at ppm levels of ruthenium. These experiments focused on the first-generation complex, the symmetry of which facilitated data analysis aimed at identifying the products of methyldiene deactivation. The preliminary data were featured in a 2012 perspective article written by our co-workers R.C. Nelson and J.T. Miller, entitled “An introduction to X-ray absorption spectroscopy and its in situ application to organometallic compounds and homogeneous catalysts.”⁵⁶ Of particular note was the apparent isosbestic point seen in the decay curves, established by monitoring the Ru K-edge (Figure 2.10). This is of keen interest in suggesting that, notwithstanding the multiple Ru species reported as decomposition products, a single deactivated intermediate is responsible.

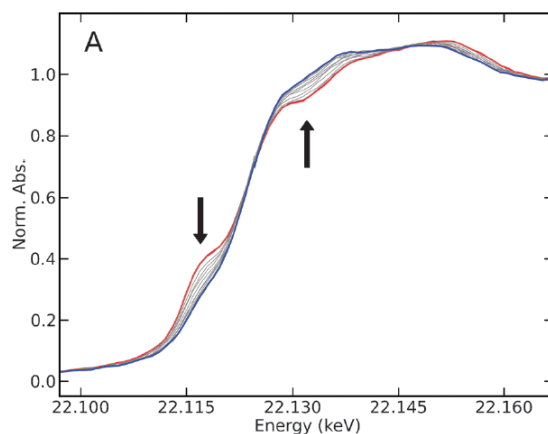


Figure 2.10. Ru K-edge XANES spectra obtained for the thermolysis of **GIm** at 50°C in toluene.

A key question, unanswered at the time the study was suspended, is whether XAFS is indeed capable of distinguishing between different organometallic Ru species present in these solutions. The X-ray absorption near-edge spectroscopy (XANES) region, which extends 50 eV on either side of the edge energy, reports on oxidation state for classical inorganic complexes. Whether this is also true for organometallic complexes, in which oxidation states are less clear-cut, has not been established. To examine this point, we analyzed a Ru(II) dihydrogen complex $\text{RuBr}_2(\text{H}_2)(\text{PCy}_3)_2$, and its Ru(IV) dihydride isomer $\text{RuBr}_2(\text{H})_2(\text{PCy}_3)_2$ (**Figure 2.11**). Only subtle differences were observed in the XANES spectra. Contributions from changes in the coordination number and the ligand set also contribute, complicating analysis and rendering definitive assignment of change in oxidation state challenging. A comprehensive study that establishes the feasibility and limitations of EXAFS for organometallic species would be of significant value to the community.

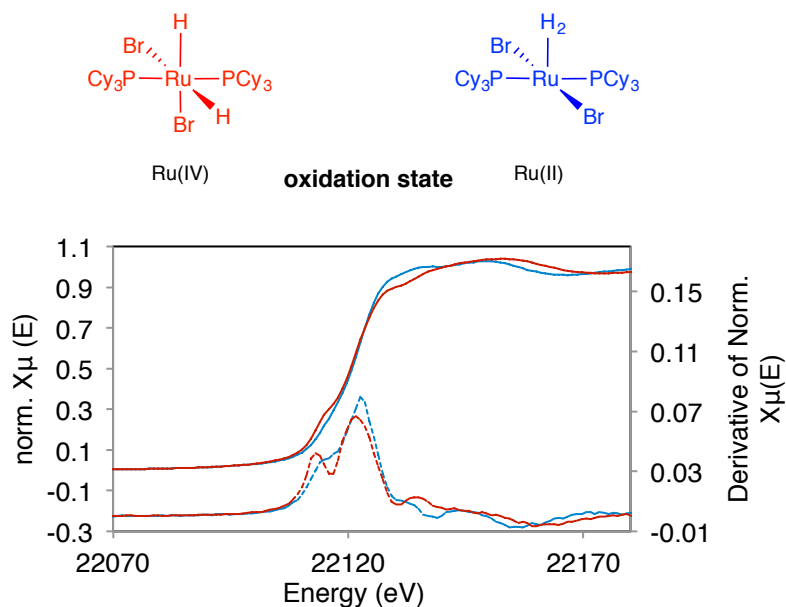


Figure 2.11. Ru K-edge XANES spectra for dihydride and dihydrogen isomers of ruthenium.

A long-standing question in the chemistry of **GII**m centers on the origin of the low phosphine lability of this species, relative to its benzylidene parent. In collaboration with Prof. David Bryce of this department, we undertook a solid-state NMR study to gain insight into this issue. Examination of the ³¹P chemical shift tensors revealed an increased Ru–P orbital interaction. This work is the subject of a manuscript now in preparation;⁵⁷ see List of Contributions (p. 156).

The success of the “free-carbene” ligand exchange reaction used to synthesize **GII**m in this chapter caused us to re-examine the classical routes to the second-generation Grubbs catalyst **S-GII**. Free H₂IMes was used to develop clean, high-yield, room-temperature routes to the three key, commercially available second-generation metathesis catalysts: that is, the second-generation Grubbs, Hoveyda and indenylidene catalysts (Figure 1.3). This chemistry was described in the M.Sc. thesis of Amy M. Reckling,⁵⁸ and as a 2012 cover article in a leading catalysis journal.⁵⁰

2.6. References

- (1) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543–6554.
- (2) Adlhart, C.; Chen, P. *Helv. Chim. Acta* **2003**, *86*, 941–949.
- (3) Lummiss, J. A. M.; Ireland, B. J.; Sommers, J. M.; Fogg, D. E. *ChemCatChem* **2014**, *6*, 459–463.

- (4) Hong, S. H.; Wenzel, A. G.; Salguero, T. T.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2007**, *129*, 7961–7968.
- (5) Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2004**, *126*, 7414–7415.
- (6) Grubbs, R. H.; Carr, D. D.; Hoppin, C.; Burk, P. L. *J. Am. Chem. Soc.* **1976**, *98*, 3478–3483.
- (7) Pietraszuk, C.; Fischer, H.; Rogalski, S.; Marciniec, B. *J. Organomet. Chem.* **2005**, *690*, 5912–5921.
- (8) Grubbs, R. H.; Burk, P. L.; Carr, D. D. *J. Am. Chem. Soc.* **1975**, *97*, 3265–3267.
- (9) For recent leading reviews, see: (a) X. Miao, P. H. Dixneuf, C. Fischmeister and C. Bruneau, *Green Chem.*, 2011, **13**, 2258–2271; (b) G. C. Vougioukalakis and R. H. Grubbs, *Chem. Rev.*, 2010, **110**, 1746–1787; (c) M. Mori, *Materials*, 2010, **3**, 2087–2140; (d) C. Samojlowicz, M. Bieniek and K. Grela, *Chem. Rev.*, 2009, **109**, 3708–3742; (e) S. Monfette and D. E. Fogg, *Chem. Rev.*, 2009, **109**, 3783–3816.
- (10) Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 7202–7207.
- (11) Chadwick, J. C.; Duchateau, R.; Freixa, Z.; van Leeuwen, P. W. N. M., Alkene Metathesis. In *Homogeneous Catalysts: Activity – Stability – Deactivation*, Wiley-VCH: Weinheim, 2011; pp 347–396.
- (12) Fogg, D. E.; Foucault, H. M., Ring-Opening Metathesis Polymerization. In *Comprehensive Organometallic Chemistry III*, Crabtree, R. H.; Mingos, D. M. P., Eds. Elsevier: Oxford, 2007; Vol. 11, pp 623–652.
- (13) Cavallo, L. *J. Am. Chem. Soc.* **2002**, *124*, 8965–8973.
- (14) van der Eide, E. F.; Piers, W. E. *Nature Chem.* **2010**, *2*, 571–576.
- (15) van Rensburg, W. J.; Steynberg, P. J.; Meyer, W. H.; Kirk, M. M.; Forman, G. S. *J. Am. Chem. Soc.* **2004**, *126*, 14332–14333.
- (16) For studies demonstrating the detrimental effect of ethylene on the rates and yields of Ru-catalyzed cross-metathesis and ring-closing metathesis of olefins, see: (a) K. A. Burdett, L. D. Harris, P. Margl, B. R. Maughon, T. Mokhtar-Zadeh, P. C. Saucier and E. P. Wasserman, *Organometallics*, 2004, **23**, 2027–2047; (b) Z. Lysenko, B. R. Maughon, T. Mokhtar-Zadeh and M. L. Tulchinsky, *J. Organomet. Chem.*, 2006, **691**, 5197–5203; (c) S. Monfette, M. Eyholzer, D. M. Roberge and D. E. Fogg, *Chem. Eur. J.*, 2010, **16**, 11720–11725. In contrast, initiation rates for the Piers phosphonium alkylidene catalysts are dramatically increased by addition of a catalytic amount of ethylene. See: (d) E. M. Leita, E. F. van der Eide, P. E. Romero, W. E. Piers and R. McDonald, *J. Am. Chem. Soc.*, 2010, **132**, 2784–2794.
- (17) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100–110.
- (18) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247–2250.
- (19) Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674–2678.
- (20) Bantreil, X.; Nolan, S. P. *Nature Protoc.* **2011**, *6*, 69–77.
- (21) Arduengo, A. J.; Krafczyk, R.; Schmutzler, R.; Craig, H. A.; Goerlich, J. R.; Marshall, W. J.; Unverzagt, M. *Tetrahedron* **1999**, *55*, 14523–14534.
- (22) Arduengo, A. J.; Dias, H. V. R.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1992**, *114*, 5530–5534.
- (23) Denk, M. K.; Rodezno, J. M.; Gupta, S.; Lough, A. J. *J. Organomet. Chem.* **2001**, *617–618*, 242–253.

- (24) Arduengo, A. J.; Davidson, F.; Dias, H. V. R.; Goerlich, J. R.; Khasnis, D.; Marshall, W. J.; Prakasha, T. K. *J. Am. Chem. Soc.* **1997**, *119*, 12742–12749.
- (25) Jafarpour, L.; Hillier, A. C.; Nolan, S. P. *Organometallics* **2002**, *21*, 442–444.
- (26) A recent book contains comprehensive updates on ring-closing metathesis (RCM) and cross-metathesis, RCM in pharma, and metathesis of renewable resources. (a) B. J. van Lierop, J. A. M. Lummiss and D. E. Fogg, in *Olefin Metathesis-Theory and Practice*, ed. K. Grela, Wiley, Weinheim, 2014, ch. 3, pp. 85-152. (b) K. Zukowska and K. Grela, in *Olefin Metathesis-Theory and Practice*, ed. K. Grela, Wiley, Weinheim, 2014, ch. 2, pp. 39-84. (c) K. R. Fandrick, J. Savoie, N. Y. Jinhua, , J. J. Song, C. H. Senanayake, ch. 12, pp. 349-366. (d) A. Nickel and R. L. Pederson, in *Olefin Metathesis-Theory and Practice*, ed. K. Grela, Wiley, Weinheim, 2014, ch. 11, pp. 335-348.
- (27) Kress, S.; Blechert, S. *Chem. Soc. Rev.* **2012**, *41*, 4389-4408
- (28) Biermann, U.; Bornscheuer, U.; Meier, M. A. R.; Metzger, J. O.; Schafer, H. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 3854–3871.
- (29) Hoveyda, A. H.; Malcolmson, S. J.; Meek, S. J.; Zhugralin, A. R. *Angew. Chem. Int. Ed.* **2010**, *49*, 34–44.
- (30) Lloyd-Jones, G. C.; Munoz, M. P. *J. Labelled Compd. Radiopharm.* **2007**, *50*, 1072–1087.
- (31) Schroder, D. *Acc. Chem. Res.* **2012**, *45*, 1521-1532.
- (32) Adlhart, C.; Hinderling, C.; Baumann, H.; Chen, P. *J. Am. Chem. Soc.* **2000**, *122*, 8204–8214.
- (33) Casey, C. P.; Tuinstra, H. E. *J. Am. Chem. Soc.* **1978**, *100*, 2270-2272.
- (34) Stewart, I. C.; Keitz, B. K.; Kuhn, K. M.; Thomas, R. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2010**, *132*, 8534–8535.
- (35) Fürstner, A.; Ackermann, L.; Beck, K.; Hori, H.; Koch, D.; Langemann, K.; Liebl, M.; Six, C.; Leitner, W. *J. Am. Chem. Soc.* **2001**, *123*, 9000–9006.
- (36) McGinnis, J.; Katz, T. J.; Hurwitz, S. *J. Am. Chem. Soc.* **1976**, *98*, 605-606.
- (37) Tanaka, K.; Tanaka, K.-I.; Takeo, H.; Matsumura, C. *J. Am. Chem. Soc.* **1987**, *109*, 2422-2425.
- (38) Leitao, E. M.; Dubberley, S. R.; Piers, W. E.; Wu, Q.; McDonald, R. *Chem. Eur. J.* **2008**, *14*, 11565–11572.
- (39) Curchay, F. C.; Sworen, J. C.; Ghiviriga, I.; Abboud, K. A.; Wagener, K. B. *Organometallics* **2006**, *25*, 6074–6086.
- (40) Kingsbury, J. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 4510–4517.
- (41) For a review describing NHC-mediated decomposition pathways, see Ref. 9b. Theoretical studies of such intrinsic deactivation pathways have been reviewed: (a) R. Credendino, A. Poater, F. Ragone and L. Cavallo, *Catal. Sci. Technol.*, 2011, **1**, 1287-1297. Decomposition can also be mediated by unintended contaminants. Alkoxide salts are particularly aggressive, even at RT. See: (b) N. J. Beach, J. A. M. Lummiss, J. M. Bates and D. E. Fogg, *Organometallics*, 2012, **31**, 2349–2356. Alcohols in the presence of NEt₃ also promote decomposition, albeit under more forcing conditions. For leading references, see: (c) N. J. Beach, K. D. Camm and D. E. Fogg, *Organometallics*, 2010, **29**, 5450–5455, and references therein; (d) M. B. Dinger and J. C. Mol, *Organometallics*, 2003, **22**, 1089–1095; (e) S. Manzini, A. Poater, D. J. Nelson, L. Cavallo, A. M. Z. Slawin and S. P. Nolan, *Angew. Chem. Int. Ed.*, 2014, **53**, 8995-8999. In the absence of base, reaction with methanol is slow, even for **GI**: see Ref. (d). For decomposition by primary and secondary amines, see discussion below.

- (42) Corporation, B., *NMR properties of selected isotopes in*. 2013.
- (43) Marciniec, B.; Rogalski, S.; Potrzebowski, M. J.; Pietraszuk, C. *ChemCatChem* **2011**, *3*, 904–910.
- (44) Bates, J. M.; Lummiss, J. A. M.; Bailey, G. A.; Fogg, D. E. *ACS Catal.* **2014**, *4*, 2387–2394.
- (45) Wu, Z.; Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1995**, *117*, 5503–5511.
- (46) Dinger, M. B.; Mol, J. C. *Organometallics* **2003**, *22*, 1089–1095.
- (47) Oliván, M.; Caulton, K. G. *J. Chem. Soc., Chem. Commun.* **1997**, 1733.
- (48) Pietraszuk, C.; Fischer, H. *Organometallics* **2001**, *20*, 4641–4646.
- (49) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204–2207.
- (50) van Lierop, B. J.; Reckling, A. M.; Lummiss, J. A. M.; Fogg, D. E. *ChemCatChem* **2012**, *4*, 2020–2025.
- (51) Lummiss, J. A. M.; Beach, N. J.; Smith, J. C.; Fogg, D. E. *Catal. Sci. Technol.* **2012**, *2*, 1630–1632.
- (52) Krauss, W.; Gestrich, W. *Chem.-Tech.* **1977**, *6*, 513–516.
- (53) Smulik, J. A.; Diver, S. T. *J. Org. Chem.* **2000**, *65*, 1788–1792.
- (54) Compain, P. *Adv. Synth. Catal.* **2007**, *349*, 1829–1846.
- (55) Wilson, G. O.; Porter, K. A.; Weissman, H.; White, S. R.; Sottos, N. R.; Moore, J. S. *Adv. Synth. Catal.* **2009**, *351*, 1817–1825.
- (56) Nelson, R. C.; Miller, J. T. *Catal. Sci. Technol.* **2012**, *2*, 461–470.
- (57) J.A.M. Lummiss, F. A. P., D.L. Bryce, D.E. Fogg *Organometallics* **2015**, Manuscript in preparation.
- (58) Reckling, A. Synthetic and Mechanistic Studies in Ruthenium-Catalyzed Olefin Metathesis. M.Sc. Dissertation, University of Ottawa, Ottawa, ON, 2012.

Chapter 3. Effect of NHC Saturation on Lifetime and Activity in Olefin Metathesis

3.1. Context, Objectives, and Overview of Content

A long-standing, contentious issue in olefin metathesis is the impact of NHC backbone saturation. The performance of Grubbs-class catalysts bearing saturated H₂IMes and unsaturated IMes ligands has been compared, and an early study demonstrated that the H₂IMes catalyst **S-GII** exhibits higher phosphine lability than its IMes analogue.¹ No such comparison, however, has been carried out for the resting-state methyldiene complexes RuCl₂(NHC)(PCy₃)(=CH₂) **GIIIm**. Given that these species are the thermodynamic resting states during catalysis, an improved understanding of their behaviour is critical to an appreciation of their roles in both propagation and deactivation. The previous Chapter described high-yield, high-purity routes to both the IMes and H₂IMes methyldiene complexes. With these species in hand, we sought to assess the impact of NHC backbone unsaturation on the lifetime, lability, and stability of the resting-state species.

An important early study by Grubbs established that decreasing alkylidene bulk correlates with increasing susceptibility to decomposition (that is, loss of the ruthenium alkylidene to generate unknown products).² In thermolysis studies at 55 °C in benzene, the first generation methyldiene complex **GIm** was shown to have a half-life of only 40 min. Its benzyldiene parent, in comparison, had a half-life of 8 days. The methyldiene species is thus the most abundant, but also the most vulnerable, alkylidene intermediate in the catalytic cycle.

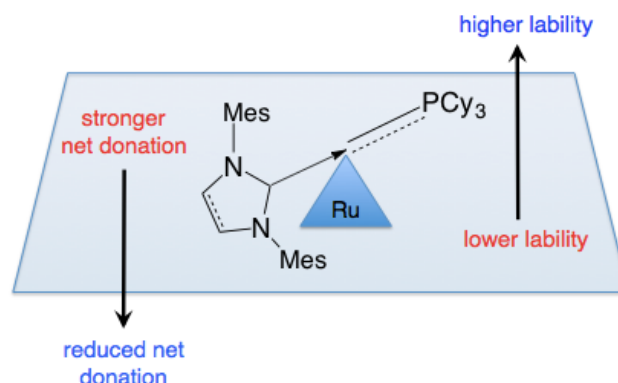
The greater vulnerability of the methyldiene complex underscores the importance of understanding its behaviour. As well, the faster deactivation of the methyldiene complexes offers new opportunities to directly assess differences in catalyst lifetime that are relevant on the timescale of catalysis. An important insight from the solid-state NMR study described in Chapter 2 (**Section 2.5**), is the role of the phenyl substituent in aiding release of the PCy₃ ligand. Interactions of the NHC with the benzyldiene moiety have also been reported.³ These perturbations are absent in the methyldiene. By limiting the factors that contribute to phosphine lability, it becomes easier to identify the source of the difference.

As noted in Chapter 1, the NHC ligand is retained throughout the catalytic cycle for metathesis. As such, it has a potentially significant impact not only on initiation, but also on selectivity and activity. The capacity of this ligand to modulate charge donation may have a

profound influence on reaction rates, depending on the rate-limiting step. Appropriate choice of the ligand, or combination of ligands, is crucial to maximizing efficiency. The primary focus of this chapter is therefore gaining a greater understanding of the impact of the NHC ligand on the behaviour of the methylenes species.

3.1.1. Table of Contents Entries (published work only)

Paradoxically Inhibiting Effect of Strong NHC Donation on Catalyst Initiation: A Showcase Example in Olefin Metathesis. Justin A. M. Lummiss, Carolyn S. Higman, Devon L. Fyson, Robert McDonald,[†] and Deryn E. Fogg.* *Chemical Science*. Submitted.



The influence of NHC saturation (NHC = *N*-heterocyclic carbene) on lifetime and phosphine lability is explored for the methylenide species $\text{RuCl}_2(\text{NHC})(\text{PCy}_3)(=\text{CH}_2)$. This complex is the resting state for the second-generation Grubbs catalysts during ring-closing or cross-metathesis reactions; that is, the most abundant form of the catalyst present during metathesis. The NHC ligands examined are H_2IMes (**S-GIIIm**) and its unsaturated analog IMes (**A-GIIIm**; IMes = 1,3-dimesityl-4,5-imidazol-2-ylidene). The IMes complex is found to exhibit much higher resistance to thermolytic decomposition in all solvents studied ($\text{C}_7\text{D}_8 \sim \text{C}_6\text{D}_6 > \text{CD}_2\text{Cl}_2 \sim \text{CDCl}_3 \gg \text{THF-d}_8$). At 40 °C in C_6D_6 , its lifetime is nearly ten times longer than that of **S-GIIIm**. For both complexes, stability drops by two orders of magnitude at 80 °C, but the half-life for **A-GIIIm** remains significantly longer (2.9 h, vs. 0.4 h for **S-GIIIm**). Key to this difference is the lower lability of the PCy_3 ligand in **A-GIIIm**. Crystallographic analysis of **A-GIIIm** and **S-GIIIm**, and of the structures reported for the parent benzylidene precatalysts (**A-GII**, **S-GII**) reveals no statistical distinction in the Ru–P bond distances to account for the stronger phosphine binding in the IMes system. Greater insight is afforded by a molecular dynamics study, which reveals much faster Ru–C_{NHC} rotation for the IMes ligand, relative to H_2IMes , in both **GII** and **GIIIm**. Greater single-bond

character in the Ru–IMes bond (i.e. reduced Ru–C_{NHC} π -backbonding) is consistent with the poorer π -acceptor capacity elsewhere reported for unsaturated NHC ligands. A compensating increase in Ru–P back-donation is proposed to account for the attenuated lability of the PCy₃ ligand in the IMes derivatives, and hence the slower decomposition observed for **A-GIIIm**. Because phosphine loss is also essential for metathesis, however, the advantage of longer lifetime for the IMes derivative is offset by slower uptake into the active cycle for catalysis.

Author Contributions: The manuscript was written by JAML and DEF. Complexes **S-GIIIm** and **A-GIIIm** were characterized by JAML. Thermolysis studies were carried out by JAML, DLF and CSH. Key control experiments were performed by CSH. Molecular dynamics studies were performed by JAML. X-ray quality crystals were grown by JAML and analyzed by RM.

3.2. N-Heterocyclic Carbenes in Olefin Metathesis: Assessing and Understanding lifetime and stability of the resting-state methylenes

3.2.1. Introduction

The extraordinary utility of *N*-heterocyclic carbenes (NHC) in transition-metal catalysis⁴⁻⁶ is due in large part to the strong σ -donor character of these ligands.⁷⁻⁹ The contributions of π -backbonding to metal–NHC interaction have won increasing acceptance.^{10,11} Even for saturated NHCs, however (which are proposed to be stronger π -acids),^{12,13} such effects are generally regarded as a minor perturbation. An alternative view emerges from a recent computational study by Belpassio, Zuccaccia and co-workers, in which the extent of back-donation was found to be strongly dependent on the ancillary ligands present.¹⁴ In a striking demonstration of the relevance of this issue to catalysis, the Furstner group showed that the outcome of gold-catalyzed reactions was closely tied to the π -acceptor properties of NHC ligands.¹⁵

The impact of NHC π -acidity on olefin metathesis is less clear-cut. Comparative studies of “second-generation” Grubbs catalysts bearing saturated H₂IMes or unsaturated, partially aromatic⁴ IMes (**S-GII** and **A-GII**, respectively; **Chart 3.1**) have not yielded a consensus opinion.¹⁶⁻¹⁹ Superior activity was described for **S-GII** in early work,^{1,20,21} but scattered subsequent reports indicated dramatically better performance for **A-GII**.^{20,22} To date, these

contradictions have not been reconciled, and even the most up-to-date theoretical comparisons²³ do not account for distinctions between the two complexes. Unsurprisingly, given this ambiguity, no correlation has been established between performance and NHC π -acceptor capacity.

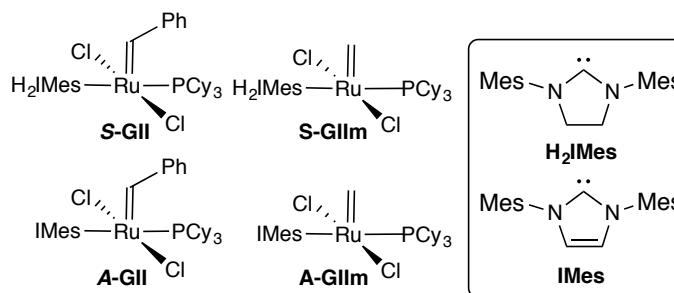


Chart 3.1. The second-generation Grubbs catalysts **S-GII** and **A-GII**, and their methyldiene resting states.

The present study was motivated by the desire to establish whether fundamental differences exist between the IMes and H₂IMes systems, and (if so) to understand their basis. Where prior work has centered on the benzyldiene precatalysts, here we focus more particularly on the methyldiene complexes **GIIIm** (**Chart 3.1**).²⁴ The latter are important players in catalyst performance because they represent the resting state during metathesis. That is, because **GIIIm** is thermodynamically stable relative to both the benzyldiene precatalyst **GII**, and other ruthenium species present in the catalytic cycle, its concentration builds up during metathesis.

A potentially key distinction between **S-GIIIm** and **A-GIIIm** lies in their susceptibility to decomposition. Recently-developed²⁴ routes to these species enable appropriately detailed study. Here we show that **A-GIIIm** is much longer-lived than **S-GIIIm** at all temperatures and in all solvents tested, and we relate this stability to increased Ru–P back-donation in **A-GIIIm**. Stronger phosphine binding limits PCy₃ lability, improving stability, but also impeding uptake into the productive cycle for olefin metathesis.

3.2.2. Results and Discussion

The thermodynamic stability of **GIIIm** relative to **GII** and other species in the catalytic cycle does not confer stability against non-metathetical reactions. Indeed, the relative steric accessibility of the methyldiene moiety renders it more vulnerable than its benzyldiene precursor. Hong and Grubbs demonstrated the susceptibility of isolated **S-GIIIm** to

nucleophilic attack by free PCy₃ at 55 °C in benzene,²⁵ while we recently reported that donors able to displace the PCy₃ ligand promote such behaviour.²⁶ In comparing the behaviour of **S-GII** and **A-GII** under conditions relevant to catalysis, we began by establishing baseline rates of decomposition for the methyldiene complexes at a range of temperatures.

Thermolytic Degradation

Initial experiments focused on the thermal stability of **S-GIIIm** and **A-GIIIm** at 60 °C in C₆D₆. Decreases in the proportion of **GIIIm** over time were established by integrating the [Ru]=CH₂ singlet relative to that for the unsaturated proton of 1,3,5-trimethoxybenzene (TMB; 6.26 ppm), used as an internal standard. The half-life of **A-GIIIm** exceeds that of its H₂IMes analog by nearly an order of magnitude, as shown by the rate curves for decomposition in **Figure 3.1**. A comparable difference was observed at 40 °C (see tabulated data at right). The difference dropped to seven-fold at 80 °C, but **A-GIIIm** remains significantly longer-lived.

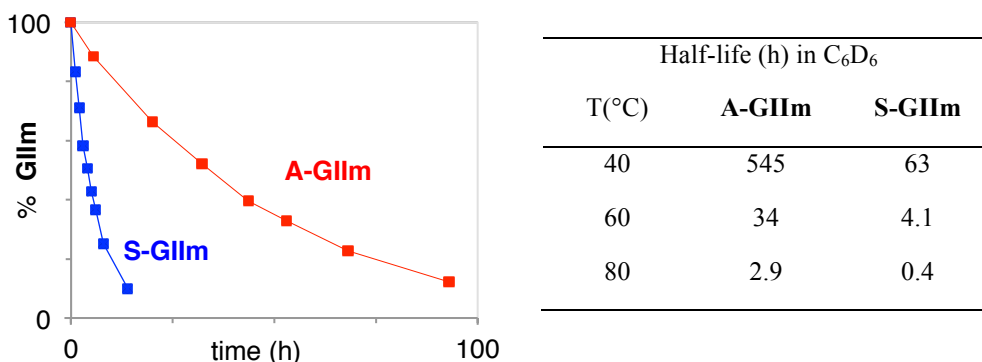


Figure 3.1. Assessing the stability of **S-GIIIm** and **A-GIIIm** at 60 °C (left); half-lives at various temperatures in C₆D₆ (right). NMR experiments: 300 MHz; TMB used as internal standard.

We next examined the impact of solvent on decomposition rates. This is of particular interest because initiation of the precatalyst **S-GII** (for which the rate-determining step is PCy₃ loss) has been shown to increase in the order toluene < CH₂Cl₂ < THF,¹ but metathesis activity follows no consistent trend.¹⁷ One probable complicating factor is a solvent-dependence in the competition for binding between olefin and free PCy₃ (for which Chen advanced the useful unifying term “commitment”).²⁷ Also plausible, however, is a solvent-dependent susceptibility to decomposition. In exploring the latter possibility, our chief interest lay in the solvents most widely used in metathesis (i.e., dichloromethane, toluene,

and benzene). Also considered were CDCl_3 and THF-d_8 , given the convenience of the former for NMR measurements, and the impressive initiation efficiency noted above for the latter. In these experiments, the proportion of **GIIIm** present after heating for 6 h at 60 °C[†] was measured by ^1H NMR analysis (**Figure 3.2**). As in the thermolysis experiments of **Figure 3.1**, TMB was used as an internal integration standard.

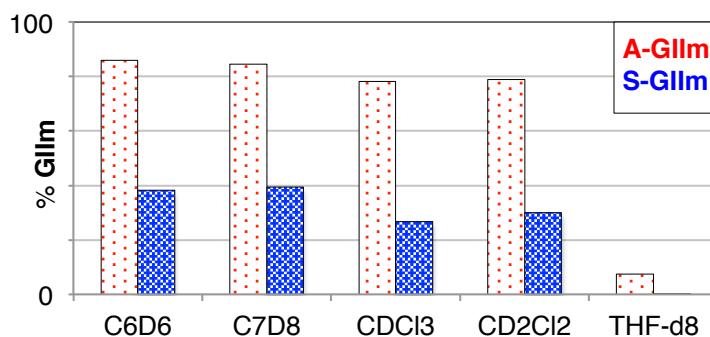


Figure 3.2. Assessing the thermal stability of **A-GIIIm** and **S-GIIIm** in common solvents (6 h, 60 °C; ^1H NMR integration vs. TMB).

For both the IMes and the H_2IMes complexes, no distinction in stability was apparent between toluene and benzene, although **S-GIIIm** was again much shorter-lived (ca. 38% remaining after 6 h, versus ca. 86% for **A-GIIIm**). Likewise, minimal differentiation emerged between CD_2Cl_2 and CDCl_3 (ca. 78% remaining for **A-GIIIm**; ca. 28% for **S-GIIIm**). Decomposition was only marginally faster in chlorinated media than in the aromatic solvents. This is notable in light of early work by Furstner and co-workers demonstrating faster olefin isomerization during RCM by **A-GII** in toluene, relative to CH_2Cl_2 , over a similar timescale and lower temperatures (6.5 h at 40 °C).²⁸ As the potential inference of faster methylidene decomposition in toluene is evidently unwarranted, the reduced tendency toward isomerization in chlorinated solvents may instead result from transformation of isomerization-active Ru-H species into the corresponding Ru-Cl complexes.²⁹

By far most aggressive of the solvents studied was THF, with just 7% **A-GIIIm** remaining at 6 h, and no remaining **S-GIIIm**. The dramatically higher susceptibility to decomposition in THF implies that the high initiation efficiencies reported in this solvent (approximately double those in toluene)¹ are offset by rapid deactivation. Several reports indeed describe

[†] The bath temperature was 60 °C. Thermolysis experiments in CD_2Cl_2 (b.p.₇₆₀ 39.8 °C) were carried out in thick-walled J. Young NMR tubes.

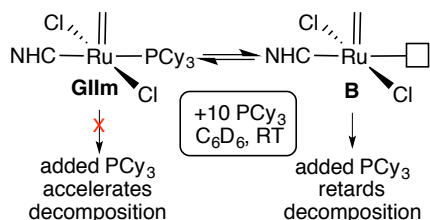
low or zero productivity in THF for metathesis reactions mediated by **GIIIm**.³⁰⁻³³ (In sharp contrast, Choi and co-workers reported that use of THF as solvent, in place of CH₂Cl₂, greatly improved the rates and yields of cyclopolymerization for the related catalyst RuCl₂(H₂IMes)(py)₂(=CHPh).^{34,35} We attribute the difference to the intermediacy of [Ru]=CHR species in the Choi chemistry: these alkylidene species are sterically protected from deactivation pathways mediated by nucleophilic attack at the [Ru]=CH₂ center).³⁶

Faster loss of PCy₃ in THF undoubtedly contributes to decomposition of **GIIIm**, for reasons examined in more detail below. This is insufficient, however, to account for the dramatically faster decomposition in THF evident in **Figure 3.2**. We suggest that the deactivation step itself is also accelerated in the higher-dielectric medium. This is consistent with formation of a charge-separated Ru species during decomposition of **GIIIm**.²⁵ We recently demonstrated that attack of free PCy₃ at the methyldiene to form a zwitterionic intermediate is the “trigger event” in decomposition of **S-GIIIm**.²⁶

Given that attack by free PCy₃ is one of the major decomposition routes for the methyldiene complexes, we speculated that the longer lifetime of **A-GIIIm** might reflect an attenuated PCy₃ lability in this complex. Direct examination of lability has not borne fruit to date, but indirect evidence points toward more facile loss of PCy₃ from the H₂IMes complexes.[†] We therefore sought to establish whether decomposition is indeed mediated by four-coordinate **B**, or whether five-coordinate **GIIIm** is also vulnerable. To that end, we assayed the impact of added PCy₃ (10 equiv) on the rate of decomposition of **A-GIIIm** and **S-GIIIm** at ambient temperatures (**Scheme 3.1**). Under these conditions, the equilibrium loss of phosphine is strongly inhibited, and five-coordinate **GIIIm** is favoured. No increase in the rate of decomposition was observed for either the IMes or the H₂IMes systems, despite the high concentration of free PCy₃ present. Clearly, phosphine attack on the methyldiene ligand does not involve five-coordinate **GIIIm**, presumably owing to steric constraints. We infer that

[†] The initiation efficiency of **S-GIIIm** and **A-GIIIm** has not been explicitly compared. Sanford, Love and Grubbs attempted to measure rates of PCy₃ exchange for **S-GIIIm** and related methyldiene complexes by magnetization transfer, but were thwarted by sample decomposition at the temperatures required. For corresponding benzylidene complexes **GII**, some evidence for reduced phosphine lability in the IMes complex comes from the fact that the rate constant for PCy₃ loss from **A-GII** at 50 °C was comparable with that measured for **S-GII** at a temperature 15 °C lower ($5 \times 10^{-4} \text{ s}^{-1}$ and $4.6 \times 10^{-4} \text{ s}^{-1}$, respectively. See Ref. (1) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543–6554.

the greater resistance of **A-GIIIm** to thermolytic decomposition, relative to **S-GIIIm**, is indeed the result of a higher barrier to loss of PCy₃ from the IMes derivative.



Scheme 3.1. Evaluating the possibility of PCy₃ attack on five-coordinate **GIIIm**. 20 mM **GIIIm**; extent of decomposition at 24 h ($\leq 2\%$) unchanged from that in the absence of added phosphine.

We conclude this section with a practical note of broader relevance. Reported NMR data for **S-GIIIm** and **A-GIIIm** are to date confined to values in C₆D₆. To facilitate identification and assignment of these key methyldiene complexes in future studies, Table 2 collects the diagnostic ¹H and ³¹P{¹H} NMR chemical shifts in a range of NMR solvents. Also tabulated, for convenience, are values for the corresponding benzyldiene complexes, for which literature ³¹P{¹H} NMR chemical shifts vary considerably. Referencing each sample externally against 85% H₃PO₄ standard ensured accurate referencing of the latter.

Table 3.1. Key NMR data for **GIIIm** and **GII** derivatives.^a

Solvent	d _H (Ru=CHR)		d _p (Ru-PCy ₃)	
	R = H			
	A-GIIIm	S-GIIIm	A-GIIIm	S-GIIIm
C ₆ D ₆	18.77	18.42	40.8	38.2
C ₇ D ₈	18.65	18.29	40.7	38.0
CD ₂ Cl ₂	18.09	17.73	39.9	37.1
CDCl ₃	18.15	17.78	39.2	36.2
THF-d ₈	18.21	17.86	40.3	37.6
	R = Ph			
	A-GII	S-GII	A-GII	S-GII
C ₆ D ₆	19.94	19.65	32.0	30.1
C ₇ D ₈	19.84	19.55	32.0	30.0
CD ₂ Cl ₂	19.38	19.08	32.1	29.9
CDCl ₃	19.43	19.13	31.8	29.6
THF-d ₈	19.55	19.25	31.9	29.9

^a 300.1 MHz (¹H NMR) or 121.6 MHz (³¹P{¹H} NMR); 22 °C.

Crystallographic Study

In the hope of gaining insight into the difference in lability between **A-GIIIm** and **S-GIIIm**, we examined their solid-state structures. The instability of these complexes in solution²⁵ can be retarded by low-temperature handling, and storage at $-35\text{ }^{\circ}\text{C}$ resulted in deposition of X-ray quality crystals over a period of days for both **A-GIIIm** and **S-GIIIm**• C_6D_6 (from concentrated solutions in toluene or benzene–pentane, respectively). The ORTEP plots are shown in **Figure 3.3**.

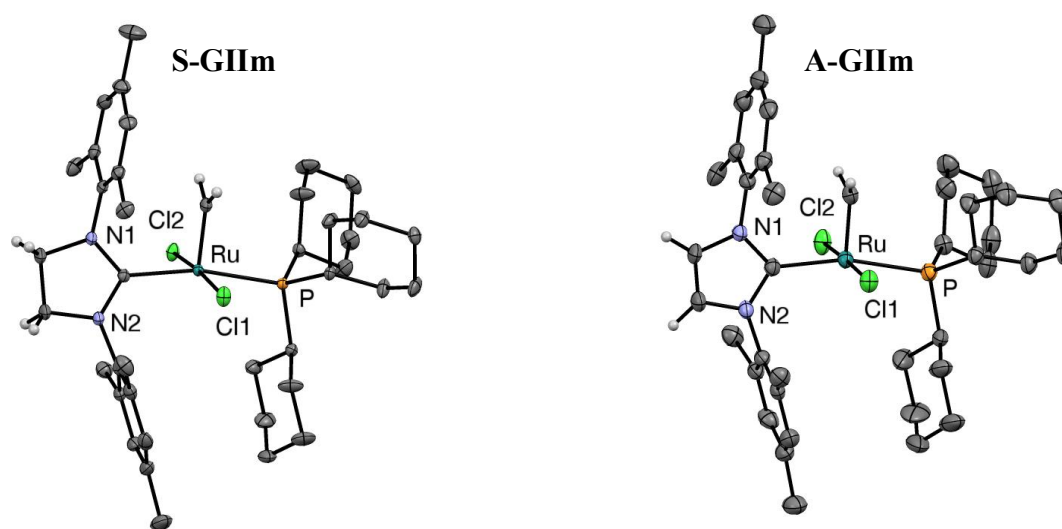


Figure 3.3. Perspective view of (left) **A-GIIIm**; (right) **S-GIIIm**• C_6D_6 . Non-hydrogen atoms are represented by Gaussian ellipsoids at the 30% probability level. Hydrogen atoms on methylidene and NHC backbone carbons are shown with arbitrarily small thermal parameters; other hydrogens are not shown.

Table 3.2. Key metrical parameters for the **GIIIm** complexes.

	A-GIIIm	S-GIIIm	
		non-solvated	• C_6H_6
τ parameter	0.19	0.19	0.13
Bond lengths (Å)			
Ru–P	2.4174(16)	2.427(1)	2.4224(4)
Ru=C	1.797(7)	1.800(2)	1.7952(19)
Ru–C _{NHC} _{NHC}	2.077(5)	2.065(2)	2.0679(16)
Ru–Cl(1)	2.389(2)	2.393(1)	2.3819(4)

Ru–Cl(2)	2.381(2)	2.379(1)	2.3870(4)
Bond angles (°)			
Cl–Ru–Cl	176.99(6)	177.05(2)	174.22(2)
P–Ru–C(NHC)	165.63(16)	165.81(5)	166.31(5)
P–Ru=C	97.2(2)	96.90(7)	95.76(6)
Cl(1)–Ru=C	93.1(2)	92.89(7)	94.11(6)
Cl(2)–Ru=C	89.9(2)	89.77(7)	91.59(7)
C(NHC)–Ru=C	97.2(3)	97.29(8)	97.86(7)

While neither structure emerged in searching the Cambridge Crystallographic Data Center database, a substructure search revealed non-solvated **S-GIIIm**.³⁷ The three datasets are therefore compared in **Table 1**. All three complexes are unequivocally square pyramidal, as indicated by their τ values (ranging from 0.19 to 0.13; cf. $\tau = 0$ for a perfect square pyramid, and $\tau = 1$ for a perfect trigonal bipyramid).^{38†} No statistical difference in Ru–C_{NHC} or Ru–P or bond distances is evident (**Table 1**). The latter is especially notable, given the marked difference in phosphine lability noted above. In prior work, Nolan and co-workers found systematically slightly shorter M–NHC bond distances for saturated NHCs in the Cp*RuCl(NHC) system.³⁹ Key bond angles are likewise statistically indistinguishable between **A-GIIIm** and **S-GIIIm**. A greater difference (approaching 3° for the Cl–Ru–Cl angle) is seen for solvated and non-solvated **S-GIIIm**. This perturbation of the solid-state structure by co-crystallized benzene is a harbinger of the potential impact of solvent on the structural conformation in solution

Molecular Dynamics

In a recent study of NHC-phosphenidene complexes, Bertrand and co-workers reported faster rotation for the unsaturated IPr ligand than its saturated analog (IPr = 1,3-bis(2,6-*i*Pr₂C₆H₃)-4,5-imidazol-2-ylidene), from which they inferred reduced P=C double-bond character in the former.⁴⁰ Thiele et al. similarly estimated rotational barriers in bis-NHC

[†] Notwithstanding its slightly lower τ value, the benzyliidene structure **GII** exhibits greater distortion. Its smaller tau value is an artifact of compensating distortion in the bond angles under comparison. In each of **GIIIm** and **GII**, the Cl–Ru–Cl angle is largest, and the C–Ru–P angle second-largest. Both angles for **S-GIIIm** (174.2° and 166.3°, respectively) are less distorted from the 180 ° ideal than those for **S-GII** (167.7° and 164.3°, respectively).

metathesis catalysts via a molecular dynamics study.⁴¹ Here we use exchange spectroscopy to compare the ease of rotation about the Ru–C_{NHC} bond in **A-GIIIm** and **S-GIIIm**, and relate this to the extent of Ru–C_{NHC} back-donation.

The IMes backbone carbons appear as two unique signals in room-temperature ¹³C{¹H} NMR spectra of **A-GIIIm** (**Figure 3.4a**), indicating that rotation of the IMes ligand about the Ru–C_{IMes} bond is slow on the timescale of these experiments. Similarly, four unique CH₃ singlets, and two unique aryl-CH singlets, are observed for the mesityl groups above and below the basal plane. It will be noted that each *o*-Me and *m*-CH site within a *given* mesityl ring is equivalent, owing to the presence of a mirror plane along the C_{NHC}–Ru–P axis. The same symmetry (and absence of rotation) is found for the H₂IMes complex **S-GIIIm** at RT in C₆D₆.

One-dimensional NOESY experiments, however, reveal exchange between the unique mesityl groups of **S-GIIIm** on a 2.0 s mixing time at RT (**Figure 3.4b**). No such exchange was evident for **S-GIIIm**, although exchange could be observed by raising the temperature to 40 °C (**Figure 3.4c**). Rotation about the Ru–C_{NHC} bond is evidently much slower for the saturated H₂IMes ligand, as also found in the Bertrand phosphinidene study.

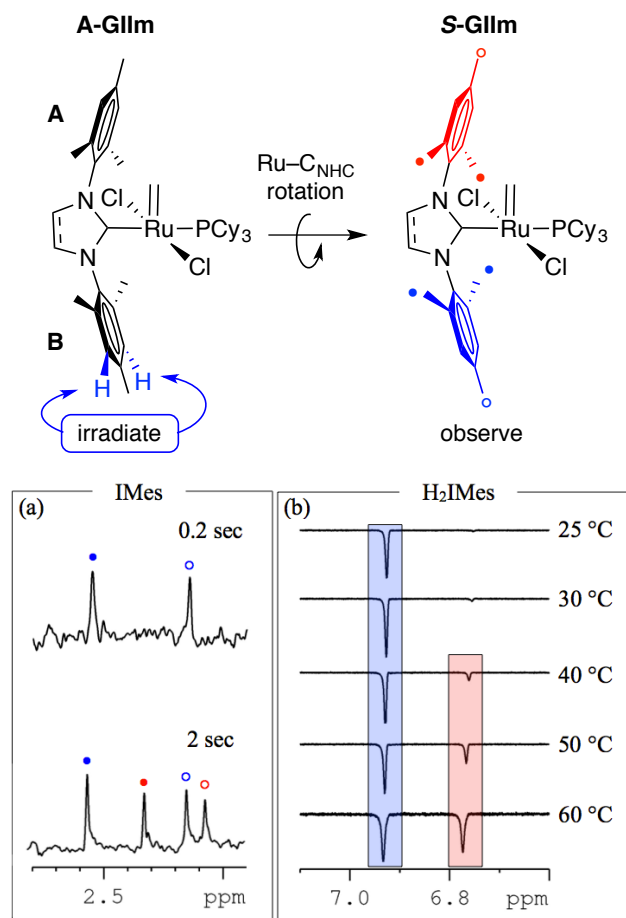


Figure 3.4. Rotational exchange of Mes rings **A** and **B** in **GIIIm**. 1D spectra (500 MHz, C_6D_6) after selective irradiation. (a) **A-GIIIm**: NOE enhancement of Me signals in **B** at RT, with slower EXSY enhancement of those in **A**. (b) **S-GIIIm**: Onset of EXSY enhancement of CH signals in **A** at 40 °C (2-s mixing).[†]

The corresponding 2D NOESY correlation spectra for **A-GIIIm** and **S-GIIIm**, and for their benzyldiene parents **A-GII** and **S-GII**, are provided in **Figure 3.5**. While acquisition is more time-consuming (requiring hours instead of minutes), these two-dimensional spectra enable simultaneous assessment of all exchange correlations. On the basis of the off-diagonal correlations observed, all NHC protons could be unequivocally assigned to sites above or below the basal plane of these square pyramidal complexes.

Lower resolution is apparent in the 1D 1H NMR spectra for **A-GII** and **S-GII**, relative to their methyldiene derivatives. This may reflect the lower symmetry of the complexes,

[†] The initiation efficiency of **S-GIIIm** and **A-GIIIm** has not been explicitly compared. Sanford, Love and Grubbs attempted to measure rates of PCy_3 exchange for **S-GIIIm** and related methyldiene complexes by magnetization transfer, but were thwarted by sample decomposition at the temperatures required. See ref. (1) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, 123, 6543–6554.

compounded by swiveling of the benzylidene unit. Nevertheless, cross-peaks for exchange correlations are seen for **A-GII**, confirming rotation about the Ru-IMes bond at room temperature (**Figure 3.5a**; 1.5 sec timescale). No such cross-peak is observed for **S-GII**. Rotation is evidently slower for the H₂IMes ligand (**Figure 3.5b**). Observation of this behaviour for both **GII** and **GIIIm** is important in indicating that NHC rotation is unrelated to the steric demand of the [Ru]=CHR substituent. Rather, this behavior is general to both the Grubbs precatalysts and their resting-state species.

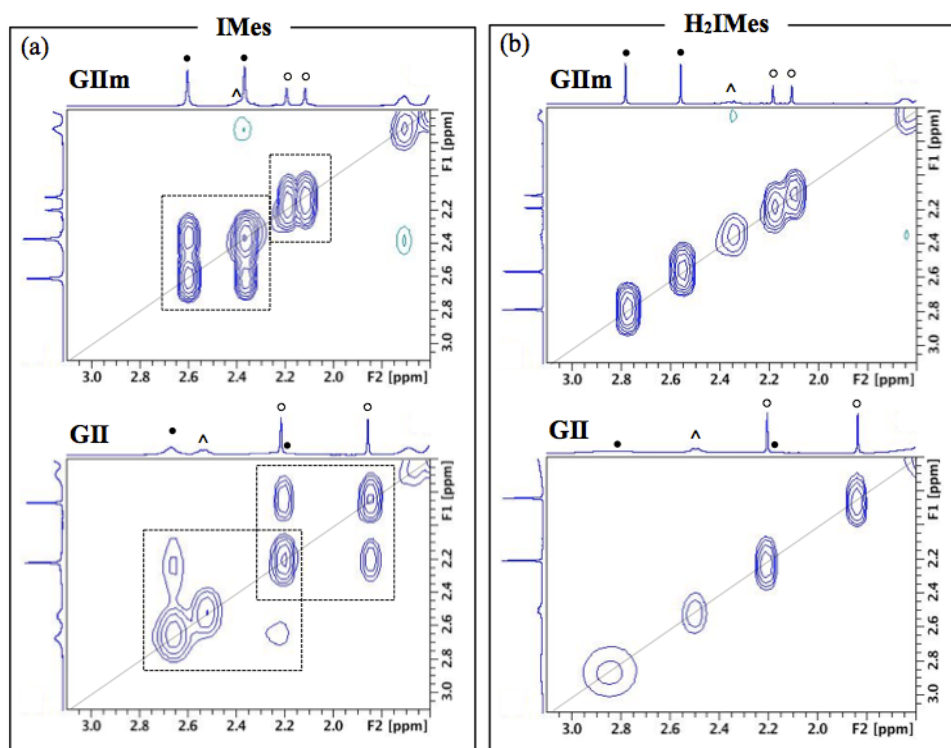


Figure 3.5. Determining exchange correlations for methyldene and benzylidene complexes. 2D NOESY spectra (¹H–¹H NMR; C₆D₆, 500.1 MHz, 25 °C, 1.5 s relaxation delay). (a) For the IMes complexes **A-GIIIm** and **A-GII**. (b) For the H₂IMes complexes **S-GIIIm** and **S-GII**, showing the alkyl region (• indicates *p*-Me, ° indicates *o*-Me, ^ indicates PCy₃).

Faster rotation of the IMes ligand implies less double-bond character in the Ru-C_{NHC} bond for the IMes ligand, relative to saturated H₂IMes. This is consistent with prior work showing that the unsaturated NHCs are poorer π -acceptors.¹² Of particular interest in the present context is an energy decomposition analysis of **S-GIIIm** by Poblet and co-workers, which demonstrated the π -acidity of the H₂IMes ligand.¹³ (Also of importance, this study suggested that the total charge donation to the metal is hence reduced for **S-GIIIm** relative to its IMes analog).

We propose that the poorer π -acceptor character of the IMes ligand in **S-GIIIm** is compensated for by greater back-donation from the metal onto phosphorus, as illustrated in **Figure 3.6**. Harvey and co-workers demonstrated that π -backbonding from the metal atom onto the P–R σ^* -antibonding orbitals can represent a significant component of metal–phosphine bonding, including for trialkylphosphine complexes.⁴² A leading recent review of computational approaches to the understanding of metal–phosphorus bonding likewise emphasizes that calculated ligand descriptors for phosphine ligands must consider their π -acceptor character.⁴³ In light of these developments, we suggest that a significant, overlooked contribution to the reduced Ru–PCy₃ lability in the second-generation Grubbs catalysts originates in the potent σ -donor properties of the NHC ligand, which constrains back-donation onto any π -acceptor ligands present.

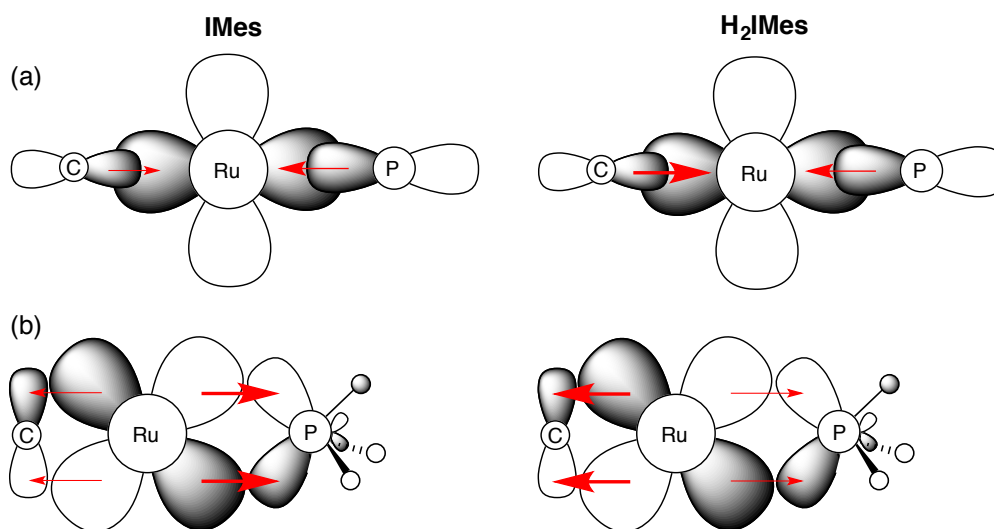


Figure 3.6. Illustration of the π -acidity of the H2IMes ligand relative to IMes, and its impact on PCy₃ lability: (a) σ bonding interactions (b) π bonding interactions. Perspective is looking down the ruthenium alkylidene bond.

Two key consequences can be envisaged. Most obviously, stronger Ru–P backbonding in the IMes complexes would account for the reduced lability of the PCy₃ ligand. Slower loss of PCy₃ would in turn account for the longer lifetime for **A-GIIIm** than **S-GIIIm**. Because phosphine dissociation is also required for entry into the active catalytic cycle, however, the advantage of longer lifetime is offset by slower initiation for **A-GII**, and slower re-entry for its methyldiene resting state.

The comparative stereochemical rigidity of the H₂IMes ligand, which enhances steric pressure exerted by the mesityl ring on the PCy₃ ligand, may also contribute to the greater lability of the PCy₃ ligand in **S-GII** and **S-GIIIm**. For the IMes system, such pressure can be relieved by rotation. Correspondingly, use of an unsaturated NHC ligand may be desirable for the metathesis of sterically encumbered olefins, owing to this steric adaptability.

3.2.3. Conclusions

The foregoing reveals a fundamental difference in Ru-C_{NHC} bonding between the IMes and H₂IMes ligands, with important implications for catalyst design. The poor π -acceptor character of the unsaturated NHC ligand results in stronger back-donation from the metal onto the PCy₃ ligand in the IMes complex, greatly reducing the lability of the PCy₃ ligand in both **A-GII** and its methyldiene resting state **A-GIIIm**. This accounts for the longer lifetime for **A-GIIIm**, relative to its H₂IMes analog **S-GIIIm**. Because phosphine dissociation is also required for entry into the active catalytic cycle, however, the advantage of longer lifetime is offset by slower initiation and re-entry.

The capacity of the IMes ligand to increase π -backbonding onto a trans-disposed ligand has important implications for catalyst design. If high initiation efficiency is desired, the “placeholder” ligand sited trans to the NHC group should be a pure σ -donor. The profoundly inhibiting effect of a π -acceptor ligand in this site is illustrated above: even for the second-generation Grubbs catalyst **S-GII**, this results in PCy₃ loss being rate-determining, while it results in strikingly low lability for the IMes derivatives. On the other hand, combining the non- π -acidic IMes ligand with a pure σ -donor in the trans position would result in higher total charge donation to the metal. This should relieve constraints on initiation, while also accelerating propagation, owing to stabilization of the four-coordinate intermediate RuCl₂(NHC)(=CHPh). Thus, the limiting effects of an unsaturated NHC ligand in the second-generation Grubbs complexes may be an artifact resulting from the choice of PCy₃ as an ancillary ligand.

3.2.4. Experimental Details for Section 3.2

General Procedures

Reactions were carried out using standard glovebox techniques at ambient temperature (RT; 25–27 °C). Dry, oxygen-free C₆H₆ and C₇H₈ were obtained using a Glass Contour

solvent purification system. Pentane was distilled over sodium benzophenone. All NMR solvents (Cambridge Isotopes) were stored under N₂ over Linde 4 Å molecular sieves for at least 6 h prior to use. Internal standards used for ¹H NMR quantification were obtained from Sigma-Aldrich: dimethyl terephthalate (DMT, >99%), 1,3,5-trimethoxybenzene (TMB, >99%). The methyldiene complexes **A-GIIIm** and **S-GIIIm** were prepared by literature methods.^{44,45}

NMR spectra were recorded on a Bruker Avance 300 and 500 NMR at 296 ± 1.5 K (unless otherwise noted), and referenced to the residual proton/deuteron of the solvent. Signals are reported in ppm, relative to TMS (¹H) or 85% H₃PO₄ (³¹P) at 0 ppm. X-ray quality crystals of **A-GIIIm** were grown from toluene-pentane at -35 °C over 48 h, while **S-GIIIm** were from benzene-pentane at -35 °C over weeks.

Representative Procedure for Half-Life Measurements. In the glovebox, a J. Young NMR tube was charged with **GIIIm** (10.2 mg, 0.0132 mmol), TMB (ca 0.5 mg), and C₆D₆ (660 µL). The sample was removed from the glovebox and a ¹H NMR spectrum measured to establish the **GIIIm**: TMB ratio at *t*₀. The NMR sample was then placed in a 40 °C oil bath (thermocouple-equipped; ±1.5 °C). The half-life (i.e. the time to reach 50% loss in total alkylidene signal) was determined by collecting ¹H NMR spectra at regular intervals until >50% decomposition had occurred. For representative rate profiles for **A-GIIIm** and **S-GIIIm** at 40 °C, 60 °C, and 80 °C, see the Supporting Information.

Representative Procedure for Thermolysis of **GIIIm in Typical Metathesis Solvents.** In the glovebox, a J. Young NMR tube was charged with **GIIIm** (10.8 mg, 0.015 mmol), DMT (ca 1.5 mg), and THF-d₈ (750 µL). The sample was removed from the glovebox and a ¹H NMR spectrum measured to establish the ratio of **GIIIm** to DMT at *t*₀. The NMR sample was then placed in a 60 °C oil bath (thermocouple-equipped; ±1.5 °C). After 6 h, the ¹H and ³¹P NMR spectra were collected and the total alkylidene integration was measured relative to internal standard.

3.3. Subsequent Advances

Important further advances in this chemistry have been made by Adrian Botti of this research group. Outstanding questions and opportunities will be discussed in Chapter 6 (Conclusion and Future Work).

3.4. References

- (1) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543–6554.
- (2) Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 7202–7207.
- (3) Gallagher, M. M.; Rooney, A. D.; Rooney, J. J. *J. Organomet. Chem.* **2008**, *693*, 1252–1260.
- (4) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. *Nature* **2014**, *510*, 485–496.
- (5) Nolan, S. P., *N-Heterocyclic Carbenes: Effective Tools for Organometallic Synthesis*. Wiley: Weinheim, 2014.
- (6) Cazin, C. S. J., *N-Heterocyclic Carbenes in Transition Metal Catalysis and Organocatalysis*. Springer 2011; Vol. 32.
- (7) Arduengo, A. J. *Acc. Chem. Res.* **1999**, *32*, 913–921.
- (8) Bourissou, D.; Guerret, O.; Gabbai, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39–91.
- (9) Herrmann, W. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1290–1309.
- (10) Diez-Gonzalez, S.; Nolan, S. P. *Coord. Chem. Rev.* **2007**, *251*, 874–883.
- (11) Jacobsen, H.; Correa, A.; Poater, A.; Costabile, C.; Cavallo, L. *Coord. Chem. Rev.* **2009**, *253*, 687–703.
- (12) Fantasia, S.; Petersen, J. L.; Jacobsen, H.; Cavallo, L.; Nolan, S. P. *Organometallics* **2007**, *26*, 5880–5889.
- (13) Antonova, N. S.; Carbo, J. J.; Poblet, J. M. *Organometallics* **2009**, *28*, 4283–4287.
- (14) Marchione, D.; Belpassi, L.; Bistoni, G.; Macchioni, A.; Tarantelli, F.; Zuccaccia, D. *Organometallics* **2014**, *33*, 4200–4208.
- (15) Alcarazo, M.; Stork, T.; Anoop, A.; Thiel, W.; Fürstner, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 2542–2546.
- (16) Selected recent reviews: (a) Vougioukalakis, G.C.; Grubbs, R.H. *Chem. Rev.* **2010**, *110*, 1746–1787. (b) Lozano-Vila, A. M.; Monsaert, S.; Bajek, A.; Verpoort, F. *Chem. Rev.* **2010**, *110*, 4865–4909. (c) Monfette, S.; Fogg, D. E. *Chem. Rev.* **2009**, *109*, 3783–3816. (d) Samojlowicz, C.; Bieniek, M.; Grela, K. *Chem. Rev.* **2009**, *109*, 3708–3742.
- (17) van Lierop, B. J.; Lummiss, J. A. M.; Fogg, D. E., Ring-Closing Metathesis. In *Olefin Metathesis-Theory and Practice*, Grela, K., Ed. Wiley: Hoboken, NJ, 2014; pp 85–152.
- (18) Fürstner, A. *Science* **2013**, *341*, 1229713.
- (19) Fandrick, K. R.; Savoie, J.; Jinhua, N. Y.; Song, J. J.; Senanayake, C. H., Challenges and Opportunities for Scaling The Ring-Closing Metathesis Reaction In The Pharmaceutical Industry. In *Olefin Metathesis – Theory and Practice*, Grela, K., Ed. 2014; pp 349–366.
- (20) Ritter, T.; Hejl, A.; Wenzel, A. G.; Funk, T. W.; Grubbs, R. H. *Organometallics* **2006**, *25*, 5740–5745.
- (21) Schramm, M. P.; Reddy, D. S.; Kozmin, S. A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4274–427.
- (22) Fürstner, A.; Ackermann, L.; Gabor, B.; Goddard, R.; Lehmann, C. W.; Mynott, R.; Stelzer, F.; Thiel, O. R. *Chem. Eur. J.* **2001**, *7*, 3236–3253.
- (23) Minenkov, Y.; Occhipinti, G.; Jensen, V. R. *Organometallics* **2013**, *32*, 2099–2111.
- (24) Lummiss, J. A. M.; Beach, N. J.; Smith, J. C.; Fogg, D. E. *Catal. Sci. Technol.* **2012**, *2*, 1630–1632.
- (25) Hong, S. H.; Wenzel, A. G.; Salguero, T. T.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2007**, *129*, 7961–7968.
- (26) Lummiss, J. A. M.; McClennan, W. L.; McDonald, R.; Fogg, D. E. *Organometallics* **2014**, *33*, 6738–6741.

- (27) Adlhart, C.; Chen, P. *Helv. Chim. Acta* **2003**, *86*, 941–949.
- (28) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204–2207.
- (29) Bo, G. D.; Markó, I. E. *Eur. J. Org. Chem.* **2011**, 1859–1869.
- (30) Rountree, S. M.; Lagunas, M. C.; Hardacre, C.; Davey, P. N. *Applied Catal. A* **2011**, *408*, 54–62.
- (31) El-azizi, Y.; Schmitzer, A.; Collins, S. K. *Angew. Chem. Int. Ed.* **2006**, *45*, 968–973.
- (32) Stark, A.; Ajam, M.; Green, M.; Raubenheimer, H. G.; Ranwell, A.; Ondruschka, B. *Adv. Synth. Catal.* **2006**, *348*, 1934–1941.
- (33) Schulz, M. D.; Wagener, K. B. *ACS Macro Lett.* **2012**, *1*, 449–451.
- (34) Kang, E.-H.; Yu, S. Y.; Lee, I. S.; Park, S. E.; Choi, T.-L. *J. Am. Chem. Soc.* **2014**, *136*, 10508–10514.
- (35) Kang, E.-H.; Lee, I. S.; Choi, T.-L. *J. Am. Chem. Soc.* **2011**, *133*, 11904–11907.
- (36) Lummiss, J. A. M.; Ireland, B. J.; Sommers, J. M.; Fogg, D. E. *ChemCatChem* **2014**, *6*, 459–463.
- (37) Trnka, T. M.; Day, M. W.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2001**, *40*, 3441–3444.
- (38) Addison, A. W.; Rao, T. N.; Reedijk, J.; Van Rijn, J.; Verschoor, G. C. *J. Chem. Soc., Dalton Trans.* **1984**, 1349–1356.
- (39) Hillier, A. C.; Sommer, W. J.; Yong, B. S.; Petersen, J. L.; Cavallo, L.; Nolan, S. P. *Organometallics* **2003**, *22*, 4322–4326.
- (40) Back, O.; Henry-Ellinger, M.; Martin, C. D.; Martin, D.; Bertrand, G. *Angew. Chem. Int. Ed.* **2013**, *52*, 2939–2943.
- (41) Kolmer, A.; Kaltschnee, L.; Schmidts, V.; Peeck, L. H.; Plenio, H.; Thiele, C. M. *Magn. Reson. Chem.* **2013**, *51*, 695–700.
- (42) Leyssens, T.; Peeters, D.; Orpen, A. G.; Harvey, J. N. *New J. Chem.* **2005**, *29*, 1424–1430.
- (43) Fey, N.; Orpen, A. G.; Harvey, J. N. *Coord. Chem. Rev.* **2009**, *253*, 704–722.
- (44) Beach, N. J.; Lummiss, J. A. M.; Bates, J. M.; Fogg, D. E. *Organometallics* **2012**, *31*, 2349–2356.
- (45) Lummiss, J. A. M.; Botti, A. G. G.; Fogg, D. E. *Catal. Sci. Technol.* **2014**, *4*, 4210–4218.

Chapter 4. Donor-Induced Deactivation of the Grubbs Catalysts

4.1. Context, Objectives, and Overview of Content

The functional-group tolerance of metathesis catalysts is an important issue, particularly for the commercial applications, which are the ultimate proving ground for any synthetic methodology. An important early review by Armstrong examined the functional-group tolerance of the Schrock molybdenum catalyst **Mo-1** and the first-generation Grubbs catalyst **GI** (**Chart 4.1**).¹ Subsequent reviews by Eustache² and Verpoort³ considered the second-generation Grubbs and Hoveyda catalysts, **S-GII** and **S-HII**. We recently published a comprehensive overview in which functional-group tolerance was considered from a new perspective, defined by the proximity of the functional group to the metal.⁴ Directly-functionalized olefins (an area of increasing interest from the perspective of reaction scope, including tandem catalysis) were treated as one category, given the significant influence of substitution on the reactivity of the double bond, and olefins bearing allylic, homoallylic, or more remote functionalities were treated as another. The latter group was further divided into two major classes: Bronsted acids and Lewis bases. In general, the molybdenum catalyst **Mo-1** (**Chart 4.1**) was shown to tolerate Lewis donors to a greater extent than has been appreciated, but poor tolerance for Bronsted acids. The dominant ruthenium catalysts exhibited the opposite pattern of behaviour. They proved vulnerable to a wide range of donor groups (sulfides, amides, amines, ethers, carbonyls, etc.) The capacity for chelation was a strong correlative for problems, particularly for weak oxygen donors, which were otherwise well tolerated. The work described in this Chapter focused on amines, as the most problematic of the Lewis donors encountered, and as a key structural element in many metathesis targets.

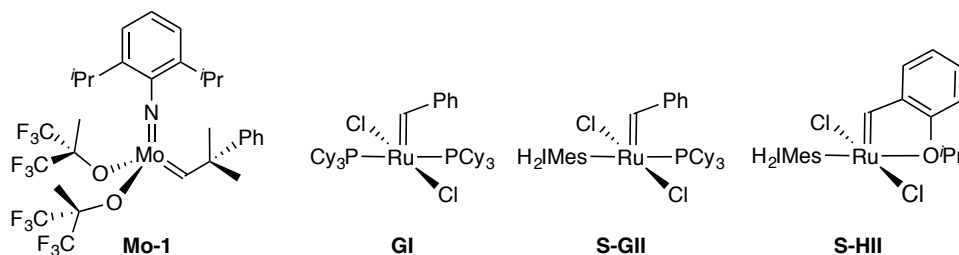


Chart 4.1. Key metathesis catalysts.

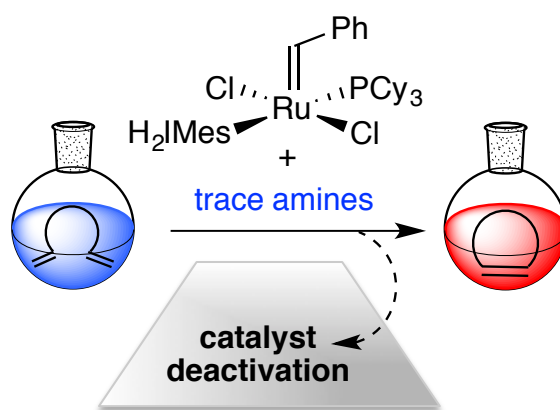
Amine groups are ubiquitous in biologically- and medically-relevant compounds, and are therefore widespread in target-driven metathesis. Recent reports from pharma, however, highlight NH-containing contaminants as problematic for metathesis.^{5,6} The success and failure of metathesis reactions involving amine-bearing substrates was analyzed by Compain in a seminal 2007 review.⁷ He pointed out that bulky amines,^{8,9} or ones in which adjacent electron-withdrawing groups attenuate basicity,¹⁰ are in fact generally well tolerated in Ru-catalyzed metathesis. From an inorganic perspective, this suggests that binding to the metal may be the underlying problem, but it is unclear whether this impedes catalysis because of (e.g.) competition with olefin for binding, or base-enabled catalyst deactivation. A deeper understanding of the organometallic chemistry of amines with the Grubbs catalysts was therefore sought.

It should be noted that this approach complements current strategies focusing on protection of the amine group using Lewis¹¹ or Bronsted^{12,13} acids, or (ideally) as the ammonium salts.¹⁴⁻¹⁷ Protection as amide, carbamate, or sulfonamide derivatives is also common but often less effective, owing to the potential for carbonyl chelation. All such protection /deprotection approaches, however, require additional steps, which add to solvent and reagent costs, among others, and degrade yields. An improved understanding of the limiting effect of amines on catalyst performance can thus be regarded as an investment in rational design of next-generation catalysts with improved functional-group tolerance.

With these goals in mind, Section 4.2 of this Chapter examines whether amine-induced deactivation in the second-generation Grubbs system involves attack on the methyldiene complex **S-GII_m**, its metallacyclobutane derivative, or the benzyldiene precatalyst **S-GII**. These findings highlight the methyldiene species as the Achilles heel. Section 4.3 explores the underlying mechanistic behaviour, identifies the kinetically relevant step, and proposes “donor-induced deactivation” as a potentially general pathway. The initial findings with pyridine and **GIm** are expanded in Section 4.4, which demonstrates the relevance of this deactivation pathway for other amines, including those discussed in Section 4.2.

4.1.1. Table of Contents Entries (published work only)

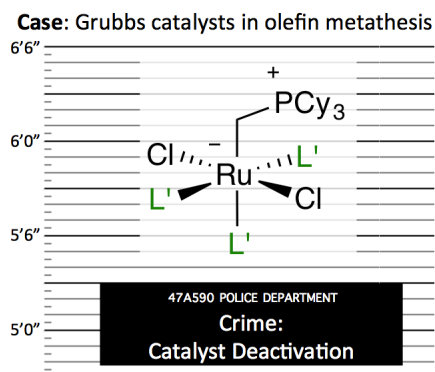
Amine-Mediated Degradation in Metathesis via the Second-Generation Grubbs Catalyst.
Justin A.M. Lummiss, Benjamin J. Ireland, Jacob M. Sommers, and Deryn E. Fogg.*
ChemCatChem **2014**; 2, 459–463.



Amine-mediated decomposition during metathesis reactions promoted by the second-generation Grubbs catalyst is studied. For most amines, the dominant deactivation pathway involves ejection of the PCy₃ ligand by amine, followed by abstraction of the methyldiene moiety from the resting-state species RuCl₂(H₂IMes)(PCy₃)(=CH₂) as [MePCy₃]Cl. An exception is highly basic DBU, which is slow to degrade the resting-state methyldiene complex, and for which the phosphonium byproduct is not observed. However, DBU is shown to rapidly attack a species generated during catalysis, most probably the metallacyclobutane intermediate.

Author Contributions: BJI carried out all experiments with the benzylidene precatalysts. BJI (with DEF) wrote the sections of the manuscript relating to these compounds; the remainder of the manuscript was written by JAML and DEF. All reactions involving the methyldiene complex **S-GII**m and the in situ-generated metallacyclobutane intermediate were performed by JAML. JMS aided BJI and JAML with replication of data for publication. Of the benzylidene derivatives, the DBU adduct of **S-GII** was prepared and characterized by JAML, the pyrrolidine and morpholine adducts by BJI.

Donor-Induced Decomposition of the Grubbs Catalysts: An Intercepted Intermediate. Justin A.M. Lummiss, William L. McClennan, Robert McDonald, and Deryn E. Fogg.*
Organometallics. **2014**; 33, 6738-6741.



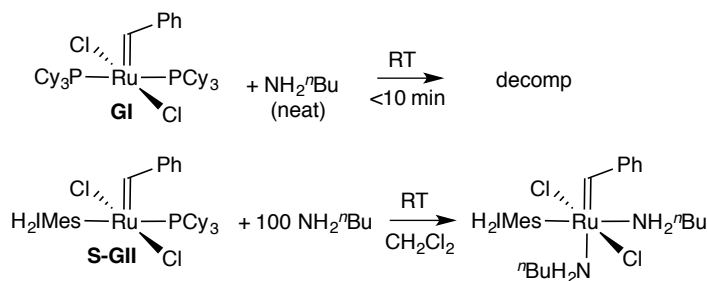
σ -Alkyl species $\text{RuCl}_2(\text{CH}_2\text{PCy}_3)(\text{py})_3$ **Ru-6** is intercepted on adding pyridine to the first-generation Grubbs catalyst **GI** during RCM, or to the isolated resting-state species **GIm**. Complex **Ru-6** is formed by pyridine-induced displacement of PCy_3 , and nucleophilic attack of the liberated PCy_3 on the methyldiene carbon. The rapid, near-quantitative conversion of **GIm** into **Ru-6** indicates that nucleophilic attack by PCy_3 is the primary deactivating event. Once formed, **Ru-6** decomposes more slowly via several competing pathways. One such pathway involves elimination of the σ -alkyl ligand as $[\text{CH}_3\text{PCy}_3]\text{Cl}$ following proton and chloride abstraction. Observation of nearly 80% **Ru-6** during RCM by **GI** in the presence of pyridine confirms the relevance of this behaviour to metathesis, and implicates the resting-state methyldiene **GIm** as the vulnerable species, rather than the metallacyclobutane intermediate. Any donor capable of displacing PCy_3 and stabilizing a five-coordinate methyldiene adduct is predicted to trigger the same deactivation sequence, steric factors permitting.

Author Contributions: The manuscript was written by JAML and DEF; WLM aided in establishing the literature context. Complex **Ru-1** was synthesized and characterized by JAML. Select control reactions, and the experiment confirming formation of **Ru-1** during RCM, were performed by WLM. X-ray crystallographic analysis was carried out by RM.

4.2. The Role of Amine Contaminants in Impeding Metathesis by the Second-Generation Grubbs Catalyst

4.2.1. Introduction

The deleterious impact of primary and secondary amines in Ru-catalyzed olefin metathesis is widely accepted.¹⁸ Substrates bearing such functionalities are normally protected to circumvent anticipated problems,¹⁹ while traces of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), morpholine, and other amine impurities have been shown to impair RCM yields in optimization campaigns in pharmaceutical R&D.^{5,6} In an important study by the Moore group (**Scheme 4.1**), the first-generation Grubbs catalyst was shown to rapidly decompose in neat H₂N^{*n*}Bu at RT, while the second-generation catalyst **S-GII** was converted into an isolable bis-amine adduct with marginal RCM activity (RCM = ring-closing metathesis).²⁰ Other catalysts containing secondary or tertiary amines are reported to function with lower RCM efficiency than the parent systems; it is unclear whether poisoning by released amine may contribute.²¹⁻²⁶



Scheme 4.1. Reported reaction of Grubbs catalysts with *n*-butylamine.

Against this, it should be noted that pyridine adducts of **GII**²⁷ (but not **GIIIm**)[†] are superb initiators for ring-opening metathesis polymerization (ROMP).³⁰ Further, Compain has pointed out that substrates bearing bulky amines are often well tolerated in RCM and CM.¹⁸ Here we sought greater insight by examining amines that have been specifically highlighted as detrimental to metathesis, in reports from academia and industry (see **N1-N4**, **Figure 4.1**). We assessed their impact on key species present in the life cycle of the second-generation

[†] Ru-methylidene complexes are decomposed by pyridine (py), as originally reported by Werner and co-workers. Thus, adding pyridine to RuHCl(CO)(P^{*i*}Pr₂Ph)₂(=CH₂) effected transformation into RuHCl(CO)(P^{*i*}Pr₂Ph)₂(py). See Ref. (28). Similarly, Hong and Grubbs reported that addition of excess py to **GII=CH₂** resulted in formation of RuCl₂(H₂IMes)(py)₃ (29% isolated yield) and [MePCy₃]Cl (not quantified). See Ref. (29).

Grubbs catalyst: that is, the benzylidene precatalyst **S-GII**, its methyldene resting state **S-GII^m**, and the metallacyclobutane intermediates **MCB-S-GII**. Key questions were the relative contribution of each to catalyst deactivation during metathesis, and the influence of amine bulk and basicity.

4.2.2. Results and Discussion

Treating **S-GII** with 10 equiv *n*-butylamine **N1** in C₆D₆ at RT resulted in rapid formation of an amine adduct assigned as **Ru-1(N1)** on the basis of the Moore report (Scheme 4.2).²⁰ While **Ru-1(N1)** dominated the ¹H NMR spectrum (90% at 5 min), the singlet for **S-GII** persisted over time, indicating an equilibrium mixture. Both signals diminished on standing, with 50% loss vs. internal standard by 3.5 h. Of keen interest is the fate of the benzylidene moiety. We identify PhCH₂NH^{*n*}Bu **1** as the major organic product (60% at full decomposition) by comparison with an authentic sample. The pathway is discussed below.

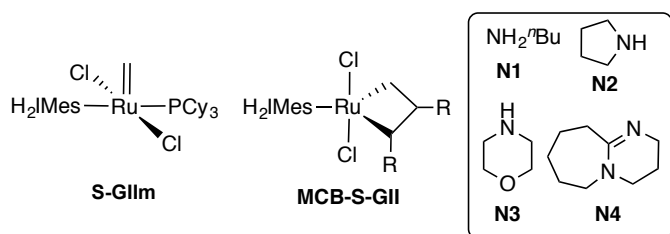
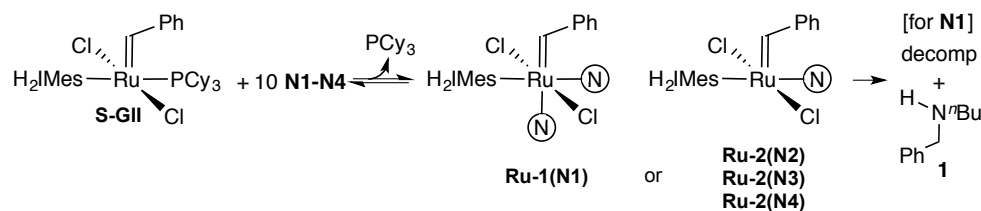


Figure 4.1. Catalyst species derived from **S-GII**, and amines studied.



Scheme 4.2. Equilibrium reactions of **GII** with amines **N1-N4** (C₆D₆, RT): see Figure 4.2a.

The corresponding reactions of **S-GII** with the bulkier amines pyrrolidine (**N2**), morpholine (**N3**) and DBU (**N4**) proceeded more slowly (hours) to yield products that proved stable in solution at RT. The equilibrium yields at 24 h are controlled by a balance of amine basicity[†] and bulk: thus, 94% for pyrrolidine adduct **Ru-2(N2)**, 60% for morpholine adduct **Ru-2(N3)**, and 75% for DBU adduct **Ru-2(N4)**. We were able to isolate these complexes by

[†] Reported *pK_a* values for the conjugate acids in acetonitrile: *n*-butylamine **a**: 18.3; pyrrolidine **b**: 19.6; morpholine **c**: 16.6; DBU **d**, 24.1; cf. 12.6 for pyridine. See Ref. (31).

carrying out the reaction in hexanes, from which they precipitate as a green powder in ca. 70–80% yield. A mono-amine structure is indicated by NMR and combustion analysis in each case, indicating that the increased bulk of these amines relative to $\text{H}_2\text{N}^n\text{Bu}$ inhibits binding of two amine ligands. The DBU ligand is presumed to bind via the $\text{sp}^2\text{-N}$ on the basis of prior reports. Despite the widespread perception of DBU as a non-nucleophilic base, a number of late-metal DBU complexes have been reported.^{32–35}

To assay the stability of these species, we heated the equilibrium mixtures (containing **S-GII**, **Ru-2**, and excess amine) at 60 °C for 24 h. As shown in **Figure 4.2a**, ca. 95% of the total alkylidene integration remained at 24 h for each of **N2–N4**. No benzylamine by-product corresponding to **1** was observed. Given this sensitivity to amine bulk, as well as the stability of **Ru-2**, we propose that decomposition of **Ru-1a** proceeds via nucleophilic attack by the primary amine **N1** on the benzylidene carbon, rather than the elimination pathways seen for alkoxide and aryloxide derivatives.^{†‡} Precedents exist for nucleophilic attack of phosphines at the $[\text{Ru}]=\text{CHPh}$ moiety.^{41,42}

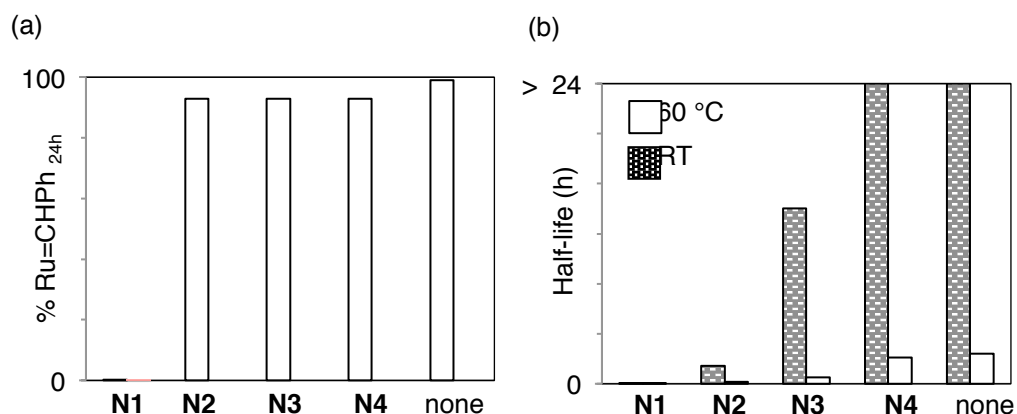
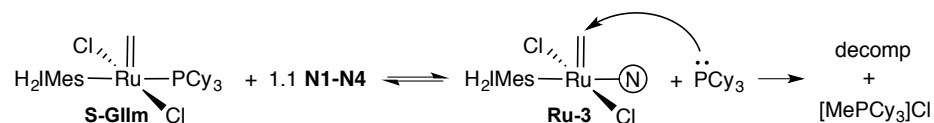


Figure 4.2. Stability of **S-GII**, vs. instability of **S-GIIIm**, to amines **N1–N4**. (a) **S-GII** + 10 amine, 60 °C; total alkylidene integration at 24 h (see **Scheme 4.2**). (b) **S-GIIIm** + 1.1 amine at RT and 60 °C (see **Scheme 4.3**); first half-life, unless >24 h.

[†] These and prior findings highlight the susceptibility of the $[\text{Ru}]=\text{CHR}$ unit to nucleophilic attack. In related work focusing on decomposition of a phenyl-functionalized NHC, Blechert and co-workers proposed that the benzylidene carbon itself can function as a nucleophile. This pathway was observed only in the presence of atmospheric oxygen. See Ref. (36).

[‡] Such pathways could include α -abstraction from bound **N1**, followed by reductive elimination of **1**, or alternatively, β -elimination from bound **N1**, hydride migration to benzylidene, and reductive elimination of **1**. For related pathways involving **GI** or **GII** and aryloxide or alkoxide ligands, see the following. α -Abstraction from aryloxides: See Ref. (37) and (38). β -Elimination from alkoxides (either preformed or generated in situ from primary alcohols): See Ref. (39) and (40).

Recently developed, high-yield routes to methyldiene **S-GIIIm**⁴³ enable us to directly examine the sensitivity of this species to amines (**Scheme 4.3**; **Figure 4.2b**). Again, rates of degradation were gauged from decreases in the intensity of the methyldiene signals for **S-GIIIm** and its amine adducts vs. internal standard. Decomposition was much faster than for the parent benzylidene **S-GII**, even using a *single* equivalent of amine at room temperature. We attribute the greater susceptibility of the methyldiene complexes to their diminutive steric shielding, and the higher electrophilicity associated with the absence of carbon substituents. The inverse dependence on amine size was maintained. Thus, 50% **S-GIIIm** was lost within 12 min for H₂NⁿBu **N1** 1.5 h for pyrrolidine **N2**, 14 h for morpholine **N3**, and >24 h for DBU **N4**. Even at 60 °C, DBU was relatively innocuous, despite its high³¹ basicity: the first half-life of 127 min was only slightly less than **S-GIIIm** alone (144 min at 60 °C). This highlights a steric impediment to decomposition for **N4** not seen for **N1–N3**. We infer that nucleophilic attack by PCy₃ occurs predominantly on five-coordinate **Ru-3(N4)**, rather than the four-coordinate, amine-free active species. Reactions at 60 °C show the same trend: these experiments are important in establishing baseline values from which we can assess the contribution of **MCB** species to degradation by **N1–N4** during RCM (see below).



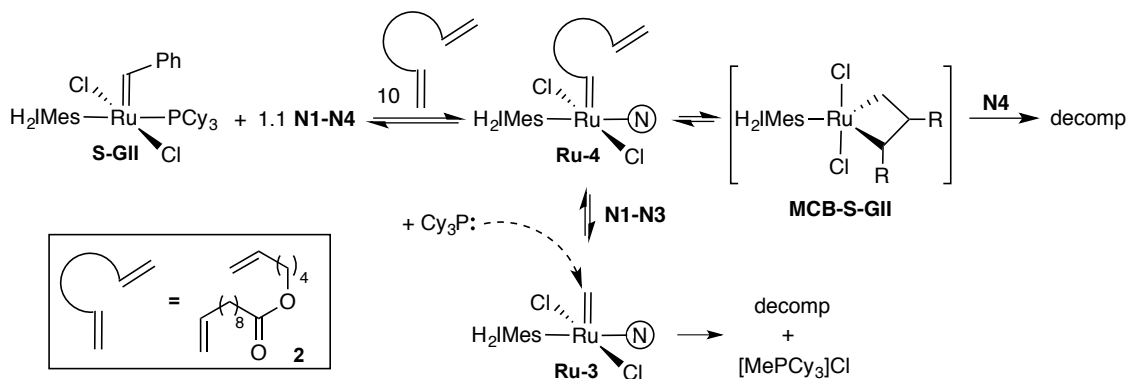
Scheme 4.3. Reaction of **S-GIIIm** with amines **N1–N4** (C₆D₆); see **Figure 4.2b**.

For all amines, decomposition of **S-GIIIm** yielded the phosphonium chloride [MePCy₃]Cl **P1** as the sole ³¹P-containing product at RT, as judged by NMR analysis (see SI). This salt, a marker for nucleophilic attack of PCy₃ on the methyldiene carbon, was originally reported by Hong and Grubbs after heating **S-GIIIm** at 55 °C²⁹ (the thermal treatment being essential to overcome the low lability of the phosphine ligand in this species). It was also observed as a by-product on treating **S-GIIIm** with pyridine. In the present study – as indeed in the pyridine experiments – the free phosphine is liberated by ligand exchange with amine. The striking rapidity of this decomposition pathway for amines **N1/N2** is consistent with the greater steric accessibility of the Ru=CH₂ carbon in **Ru-3**.[†] We cannot exclude the possibility of some competing attack of amine at the [Ru]=CH₂ site, as the methylamine signals would occupy a

[†] Faster exchange with these smaller amines (and hence faster generation of free PCy₃) may also contribute.

crowded region in the ^1H NMR spectra, but the large proportion of $[\text{MePCy}_3]\text{Cl}$ **P1** indicates that attack by phosphine dominates. This surprising preference is under further study.

Lastly, we assessed the amine-sensitivity of the Ru species (including, most importantly, **MCB** intermediates)[‡] generated under conditions of catalysis. These experiments were carried out by equilibrating solutions of **S-GII** and the amine adducts **Ru-2** at 60 °C, then adding α,ω -diene **2** (Scheme 4.4). Macrocyclization of **2** is sufficiently challenging to conscript a significant proportion of the catalyst charge before diene is completely consumed. NMR spectra were acquired to >95% decomposition of the starting catalyst charge (Figure 4.3). In all cases, catalyst decomposition is much faster than in the control RCM experiment with no added amine (see dotted line).



Scheme 4.4. Amine-induced decomposition during RCM of **2**: dominant pathways for attack of various amines on methyldiene vs. **MCB** intermediates.

For **N1–N3**, the $[\text{MePCy}_3]\text{Cl}$ signal accounts for the majority of the final ^{31}P NMR integration (**N1/N3**: 95%; **N2**: 75%), indicating that decomposition occurs chiefly via the methyldiene pathway seen above: that is, attack of free PCy_3 on the $[\text{Ru}]=\text{CH}_2$ moiety. The experiments with **N1/N2** showed *slower* catalyst decomposition during RCM than with isolated **S-GII** or **S-GIIIm**, owing to the capacity of these good donor amines to trap the four-coordinate active intermediates (as, e.g., **Ru-4**). Longer lifetime thus comes at the cost of catalyst productivity. For **N3**, decomposition was slightly faster for the catalytic system, probably because amine binding aids in initiation, but the weaker donor ability of morpholine limits its capacity to trap out the active species. The catalyst thus spends a

[‡] NMR signals for the **MCB** intermediates are not observable in the presence of PCy_3 . Such species have only been observed for phosphine-free catalysts at low temperatures. See, for example, Ref. (44) and (45).

greater proportion of time in the **MCB** state, which contributes more to decomposition in consequence.

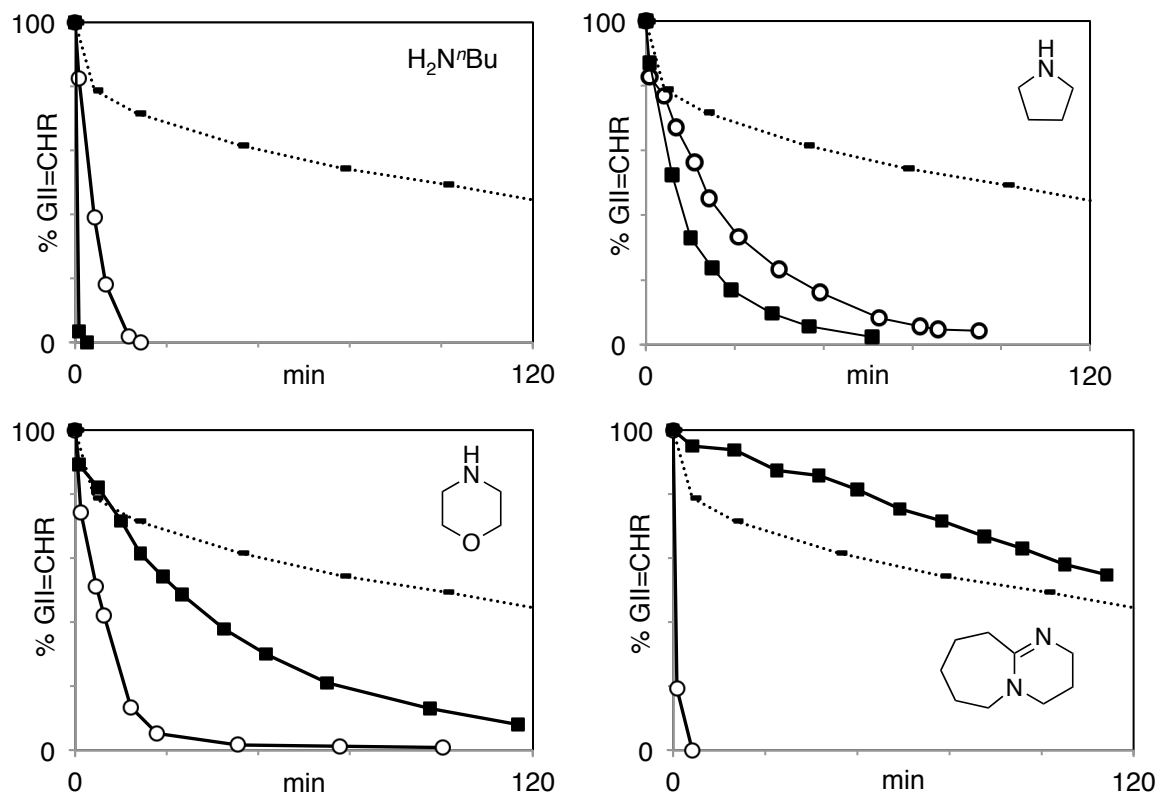


Figure 4.3. Rates of decomposition of catalytic intermediates (open circles), vs. isolated **S-GIIIm** (solid squares), by amines **N1-N4**. Dotted line indicates control RCM experiments with no amines. Conditions: 60 °C, C_6D_6 ; 1.1 equiv **N1-N4**; 200 mM **2** (for RCM experiments).

Very different results are observed for DBU **N4**. Firstly, no $[\text{MePCy}_3]\text{Cl}$ is generated. Instead, the dominant ^{31}P NMR signal is that for free PCy_3 (84%, the balance being due to unidentified products). Secondly, decomposition is essentially immediate, with complete annihilation of all alkylidene signals within 5 min. This is in stark contrast to the timescale of hours or days (respectively) shown above for DBU-induced decomposition of **S-GIIIm** or **S-GII** at 60 °C. Both lines of evidence indicate attack on a species generated predominantly during catalysis. This argues against the involvement of either **S-GIIIm** or its four-coordinate, phosphine-free intermediate, which is accessible at elevated temperatures. A more likely culprit may be the ruthenacyclobutane **MCB**. Given the steric constraints implied by the resistance of **S-GIIIm** to attack by DBU, we suggest that DBU may preferentially attack the

β -CH₂ of the unsubstituted ruthenacyclobutane (the lowest-energy,^{†46} and hence most abundant **MCB**). The extreme rapidity of attack (particularly compared to **N1–N3**) points toward the high Bronsted basicity of DBU as a factor, and a deprotonation event may thus be involved in or before the rate-determining step.

4.2.3. Conclusions

The foregoing sheds new light on the degradation of the second-generation Grubbs catalyst by unprotected amines. Different decomposition pathways are operative for the benzylidene precatalyst, its resting-state methylidene derivative, and the ruthenacyclobutane intermediates. For most amines studied, however (both primary and secondary), we find that the methylidene is the major vector for decomposition during “live” RCM reactions. The exception is highly basic DBU, for which attack on the ruthenacyclobutane intermediate effects complete catalyst destruction within minutes at 60 °C (vs. days or hours for **S-GII** or **S-GIIIm** under the same conditions). This underscores the point that the effects of basicity can be tempered by bulk, and that it is the combined bulk of the amine and [Ru]=CHR moiety that is critical. Thus, the substituted alkylidene in **S-GII** is not decomposed by secondary amines or sp²-N centers (DBU, pyridine), instead undergoing ligand exchange to form nitrogen adducts. Unencumbered primary amines, however, are sufficiently small to attack at the [Ru]=CHPh carbon, inducing loss of the benzylidene functionality as NHR(CH₂Ph).

Decomposition of the resting-state species **S-GIIIm** involves nucleophilic attack on the methylidene carbon. Unexpectedly, attack involves not amine, but free PCy₃, which abstracts the methylidene moiety (inter alia) as [MePCy₃]Cl **P1**. The basis for this preference is the subject of further study. Noteworthy, however, is the fact that the deleterious effect of amine is manifested even with a single equivalent of amine; that it is due to the liberation of PCy₃ via ligand exchange; and that exchange with **S-GIIIm** occurs even at room temperature, despite the low phosphine lability normally characteristic of **GIIIm**. From this perspective, **GII** is seen to be burdened with a latent poison, which is activated toward destruction of its methylidene resting state (the dominant species present during RCM and CM) by any Lewis

[†] NMR signals for the **MCB** intermediates are not observable in the presence of PCy₃. Such species have only been observed for phosphine-free catalysts at low temperatures. See, for example, Ref. (44) and (45).

base that can compete for binding to Ru. Phosphine-free catalysts – still greatly underused in RCM reactions – may thus be inherently more robust in applications where adventitious donors abound. The greater stability of the $[\text{Ru}]=\text{CHR}$ entity ($\text{R} \neq \text{H}$) would also account for the relative robustness of ROMP reactions, which are propagated by alkylidene, rather than methyldiene intermediates.

4.2.4. Experimental Details for Section 4.2

General Procedures

Reactions were carried out in an N_2 -filled glovebox. Dry, oxygen-free solvents were stored under N_2 over Linde 4 Å molecular sieves. Benzene- d_6 (Cambridge Isotopes) was degassed by consecutive freeze/pump/thaw cycles and stored over 4 Å molecular sieves for at least 6 h prior to use. Amines were obtained from Alfa Aesar (*n*-butylamine **N1**, 99%), Sigma-Aldrich (pyrrolidine **N2**, >99%; morpholine **N3**, >99.5%), or Acros (DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene **N4**, 98%). Morpholine (twice-distilled and packaged under N_2) was used without purification; other amines were freeze/pump/thaw-degassed on receipt, and stored under N_2 to prevent contamination by hydrates, oxides, etc., which would reduce amine nucleophilicity. Amine purity was confirmed by NMR analysis. Trimethoxybenzene (TMB, Sigma-Aldrich) and *N*-benzyl-*n*-butylamine **1** (Alfa Aesar, 98%) were used as received. Literature methods were used to prepare **S-GII**,⁴⁷ methyldiene complex **S-GIIIm**⁴³ and diene **2**.⁴⁸

NMR spectra were recorded at probe temperatures of 23 ± 1.5 °C or 60 ± 0.1 °C, and referenced to the residual proton or carbon signals of the deuterated solvent (^1H , ^{13}C NMR), or external 85% H_3PO_4 (^{31}P). Signals are reported in ppm relative to TMS (^1H , ^{13}C) or 85% H_3PO_4 (^{31}P) at 0 ppm. Half-lives were determined by collecting ^1H NMR spectra for 1.5 min at regular intervals. Time zero was either the time of mixing, or (for heated reactions) the time of heating. Each time-point indicated is the time at which the acquisition was started.

Reactions of S-GII with Amines N1–N4. In these experiments, the total benzyldiene integration was measured vs. internal standard after 24 h at RT. Where >50% loss was evident at 24 h (i.e. for reactions of *n*-butylamine **N1**); rate profiles were generated to measure the first half-life. The reaction of **S-GII** with *n*-butylamine was followed to >99%

loss of alkylidene to measure the proportion of *N*-benzyl-*n*-butylamine formed (see below). A representative procedure is provided below.

Representative Procedure for Single Time-Point Reactions. In the glovebox, a J. Young NMR tube was charged with **S-GII** (10.8 mg, 0.0127 mmol), TMB (ca. 1.0 mg), and 0.64 mL C₆D₆, to give a solution 20 mM in Ru. The sample was removed from the glovebox and a ¹H NMR spectrum measured to establish the **S-GII** : TMB ratio at *t*₀. The NMR tube was returned to the glovebox and DBU (19.0 μL, 0.127 mmol, 10 equiv) was added. The sample was shaken vigorously, then removed to a 60 °C oil bath (thermocouple-equipped; ±1.5 °C). For RT experiments, samples were stored at ambient temperature (23 °C ±1.5 °C). At 24 h, ¹H and ³¹P NMR spectra were collected.

Representative Procedure for Half-Life Measurements. In the glovebox, a Rotoflo NMR tube was charged with **S-GII**m (10.1 mg, 0.0131 mmol), trimethoxybenzene (TMB; ca. 1 mg), and 0.65 mL C₆D₆. The sample was transferred to an NMR probe preheated to 60 °C, the starting **S-GII**:TMB ratio was measured, amine **N2** (1.2 μL, 0.0144 mmol, 1.1 equiv) was injected, and the puncture was immediately sealed with tape. The sample was shaken for 1 min and returned to the spectrometer; a stopwatch was started, and spectra were collected until loss of alkylidene signals was complete.

RuCl₂(H₂IMes)(HNC₄H₈)(=CHPh), Ru-2(N2). Pyrrolidine (**N2**: 150 μL, 130 mg, 1.83 mmol) was added to a stirred pink suspension of **S-GII** (150 mg, 0.177 mmol) in 10 mL hexanes. The suspension turned brown within 5 min, and dark green over 18 h. At 18 h, the suspension was filtered off, and the resulting green solid was washed with hexanes (3 x 3 mL). Yield after drying in vacuo: 76 mg (67%). ¹H NMR (C₆D₆, 300.3 MHz): δ 19.67 (s, 1H, [Ru]=CH), 8.33 (d, ³J_{HH} = 7 Hz, 2H, Ph, *o*-CH), 7.31 (t, ³J_{HH} = 7 Hz, 1H, Ph, *p*-CH), 7.10 (t, ³J_{HH} = 7 Hz, 2H, Ph, *m*-CH), 6.98 (s, 2H, Mes *m*-CH), 6.43 (s, 2H, Mes *m*-CH), 3.53-3.41 (m, 2H, NHC CH₂), 3.41-3.21 (m, 3H, **N2** NH; NHC CH₂), 2.81 (s, 6H, Mes *o*-CH₃), 2.49-2.36 (m, 2H, **N2** NCH₂), 2.32 (s, 6H, Mes *o*-CH₃), 2.19 (s, 3H, Mes *p*-CH₃), 2.15-2.03 (m, 2H, **N2** NCH₂), 1.98 (s, 3H, Mes *p*-CH₃), 1.22-1.05 (m, 2H, **N2** NCH₂CH₂), 0.81-0.63 (m, 2H, **N2** NCH₂CH₂). ¹³C{¹H} NMR (C₆D₆, 75.5 MHz): δ 302.1 (s, Ru=CH), 222.9 (s, C_{NHC}), 152.7 (s, Ph, C_i), 140.8 (s, Mes, *o*-C), 138.7 (s, Mes, *p*-C), 137.8 (s, Mes, *p*-C), 137.6 (s, Mes, *o*-C), 137.0 (s, Mes, *i*-C), 135.1 (s, Mes, *i*-C), 130.1 (s, Ph *o*-CH), 129.6 (s, Mes *m*-CH), 129.5 (s, Mes *m*-CH), 128.8 (s, Ph *p*-CH), 128.5 (s, Ph *m*-CH), 51.4 (s, NHC CH₂),

50.3 (s, NHC CH₂), 46.7 (s, **N2** HNCH₂), 24.8 (s, **N2** NCH₂CH₂), 21.0 (br, Mes *o*-CH₃, *p*-CH₃), 18.5 (s, Mes, *o*-CH₃). IR (ATR, cm⁻¹): ν(N-H) 3242. Anal. Calcd. for C₃₂H₄₁N₃Cl₂Ru: C, 60.09; H, 6.46; N, 6.57. Found: C, 59.83; H, 6.22; N, 6.49.

RuCl₂(H₂IMes)(HNC₄H₈O)(=CHPh), Ru-2(N3). Prepared as for **Ru-2(N2)**. Yield: 78%. ¹H NMR (C₆D₆, 500.1 MHz): δ 19.74 (s, 1H, [Ru]=CH), 8.33 (d, ³J_{HH} = 8 Hz, 2H, Ph, *o*-CH), 7.30 (t, ³J_{HH} = 8 Hz, 1H, Ph, *p*-CH), 7.09 (t, ³J_{HH} = 8 Hz, 2H, Ph, *m*-CH), 6.86 (s, 2H, Mes, *m*-CH), 6.41 (s, 2H, Mes, *m*-CH), 3.47-3.39 (m, 2H, NHC CH₂), 3.33-3.24 (m, 2H, NHC CH₂), 3.19 (d, ³J_{HH} = 12 Hz, 2H, OCH₂), 3.14 (t, ³J_{HH} = 12 Hz, 1H, NH), 3.05-2.91 (m, 2H, NCH₂), 2.76 (s, 6H, Mes, *o*-CH₃), 2.58 (td, ³J_{HH} = 12 Hz, ²J_{HH} = 3 Hz, 2H, OCH₂), 2.30 (s, 6H, Mes, *o*-CH₃), 2.06 (s, 3H, Mes, *p*-CH₃), 1.97 (s, 3H, Mes, *p*-CH₃), 1.76 (d, 2H, ³J_{HH} = 12 Hz, NCH₂). ¹³C{¹H} NMR (C₆D₆, 125.8 MHz): δ 304.2 ([Ru]=CH), 221.9 (C_{NHC}), 152.1 (s, Ph, C_i), 140.9 (s, Mes, *o*-C), 138.8 (s, Mes, *p*-C), 137.9 (s, Mes, *p*-C), 137.6 (s, Mes, *o*-C), 136.8 (s, Mes, *i*-C), 134.7 (s, Mes, *i*-C), 130.2 (s, Ph, *o*-CH), 129.6 (s, Mes, *m*-CH), 129.5 (s, Mes, *m*-CH), 129.1 (s, Ph, *p*-CH), 128.7 (s, Ph, *m*-CH), 67.4 (OCH₂), 51.4 (NHC CH₂), 50.2 (NHC CH₂), 45.0 (HNCH₂), 21.0 (s, Mes, *o*-CH₃), 20.9 (br s, Mes, *p*-CH₃), 18.5 (s, Mes, *o*-CH₃). IR (ATR, cm⁻¹): ν(N-H) 3213. Anal. Calc'd. for C₃₂H₄₁N₃OCl₂Ru: C, 58.62; H, 6.30; N, 6.41. Found: C, 58.84; H, 6.37; N, 6.28.

RuCl₂(H₂IMes)(DBU)(=CHPh), Ru-2(N4). Prepared as for **Ru-2(N2)**, at 60 °C. Yield: 76%. ¹H NMR (C₆D₆, 500.1 MHz, 328 K): δ 19.95 (s, 1H, [Ru]=CH), 8.45 (br s, 2H, Ph, *o*-CH), 7.33 (t, ³J_{HH} = 8 Hz, 1H, Ph, *p*-CH), 7.11 (t, ³J_{HH} = 8 Hz, 2H, Ph, *m*-CH), 7.00 (s, 2H, Mes, *m*-CH), 6.48 (s, 2H, Mes, *m*-CH), 3.56 (t, ³J_{HH} = 10 Hz, 2H, NHC CH₂), 3.39 (t, ³J_{HH} = 10 Hz, 2H, NHC CH₂), 2.86 (s, 6H, Mes, *o*-CH₃), 2.80 (br s, 2H, DBU, CH₂), 2.39 (br s, 2H, DBU, CH₂), 2.37 (br s, 2H, DBU, CH₂), 2.36 (br s, 6H, Mes, *o*-CH₃), 2.25 (s, 3H, Mes, *p*-CH₃), 2.03 (s, 3H, Mes, *p*-CH₃), 1.98 (br s, 2H, DBU, CH₂), 1.70-1.00 (br m, 6H, DBU, CH₂), 0.92 (br s, 2H, DBU, CH₂). ¹H-¹³C HMQC NMR (CDCl₃, 75.5 MHz, 296 K): δ 305.1 ([Ru]=CH, major), 297.9 ([Ru]=CH, minor). ¹³C{¹H} NMR (C₆D₆, 125.8 MHz, 328 K): δ 304.6 (br s, [Ru]=CH), 224.2 (br s, C_{NHC}), 164.5 (br s, DBU, C=N) 152.9 (s, Ph, C_i), 141.0 (s, Mes, *o*-C), 138.3 (s, Mes, *o*-C), 138.0 (s, Mes, *p*-C), 137.7 (s, Mes, *i*-C), 137.6 (s, Mes, *p*-C), 136.5 (s, Mes, *i*-C), 130.8 (s, Ph, *o*-CH), 129.9 (s, Mes, *m*-CH), 129.8 (s, Mes, *m*-CH), 128.5 (s, Ph, *p*-CH), 128.1 (s, Ph, *m*-CH), 52.8 (s, DBU, CH₂), 51.8 (s, NHC CH₂), 50.6 (NHC CH₂), 48.0 (s, DBU, CH₂), 36.5 (s, DBU, CH₂), 29.4 (s, DBU, CH₂), 27.9 (s, DBU,

CH₂), 26.1 (br s, DBU, CH₂), 22.9 (s, DBU, CH₂), 21.1 (s, Mes, *p*-CH₃), 21.05 (s, Mes, *p*-CH₃), 20.96 (s, Mes, *o*-CH₃), 18.7 (s, Mes, *o*-CH₃). Anal. Calc'd. for C₃₇H₄₈N₄Cl₂Ru: C, 61.66; H, 6.71; N, 7.77. Found: C, 61.56; H, 6.99; N, 7.79.

4.3. Intercepting a Key Intermediate in Donor-Induced Decomposition

4.3.1. Introduction

Olefin metathesis is now a core tool in organic synthesis.^{49,50} With industrial applications of the molecular metathesis catalysts now emerging, improved understanding of their deactivation pathways^{51,52} is becoming increasingly important.[†] The Grubbs benzylidene precatalysts (**GI** and **S-GII**, **Chart 4.2**) were shown in early work to be significantly more stable than the methyldene derivatives (**GIm** and **S-GIIIm**) that represent the catalyst resting state.^{54,55} High-yield routes to the latter species,^{43,56} including ¹³C-labelled isotopologues (***GI**, ***S-GII**, ***GIm**, and ***S-GIIIm**)⁵⁷ facilitate investigation of decomposition pathways relevant to catalysis.

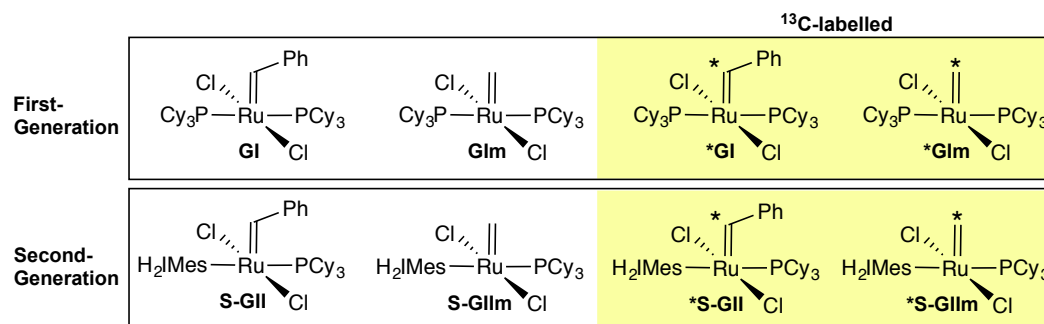
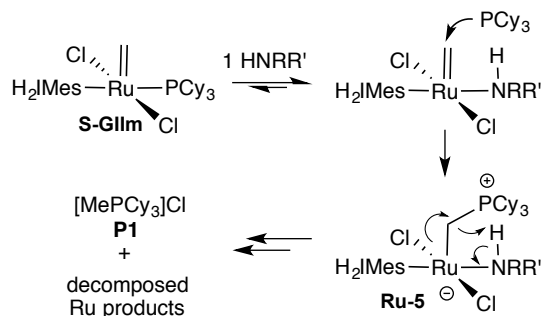


Chart 4.2. Grubbs metathesis catalysts and their resting-state methyldene derivatives.

Reports from pharma highlight NH-amine contaminants, among others,^{1c} as detrimental to RCM.^{5,6} A deeper understanding of amine-mediated deactivation is thus of keen interest.^{7,20,58} Adding a single equivalent of primary or secondary amine to RCM reactions promoted by the second-generation catalyst **S-GII** was recently shown to effect complete loss of the catalyst charge within 90 min at 60 °C.⁵⁸ A plausible mechanism is shown in **Scheme 4.5**. The initial displacement of phosphine has ample precedents in the reactions of **GII** with amines.^{20,58-60} Attack of the liberated PCy₃ on the methyldene ligand is proposed

[†] Much less attention has focused on catalyst reactivation, as pointed out by Schrodi and co-workers in an intriguing approach to the problem for the first-generation Hoveyda catalyst. See Ref. (53).

on the basis of prior work with isolated **GIIIm** discussed below. The ensuing elimination of the alkylphosphine ligand in **Ru-5** as phosphonium salt **P1** is facilitated by the presence of the NH group. Such proton-shuttling pathways are well established in Ru-amine chemistry.^{61,62} In prior examples in which **P1** or related species were observed in the absence of an N-H moiety,^{29,42,63-65} proton abstraction most probably involves C-H activation.



Scheme 4.5. Proposed pathway for decomposition of **S-GIIIm** via zwitterionic **Ru-5**.

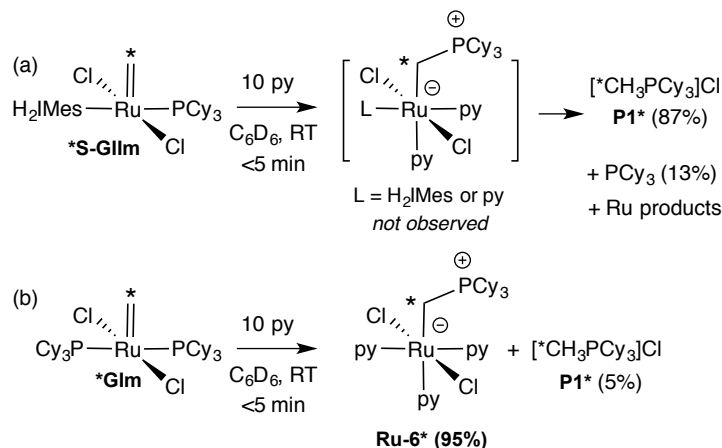
The σ -alkyl moiety in putative intermediate **Ru-5** is modeled on the proposed structure of the key intermediate in decomposition of *isolated* **S-GIIIm**, suggested in a seminal study by Hong and Grubbs.²⁹ Such species have been invoked in other deactivation studies,^{42,63,64,66} while related structures were reported in early work by the Roper⁶⁷ and Hofmann⁴¹ groups. The relevance of the Hong-Grubbs study to deactivation during catalysis is clouded, however, by the much slower rate of decomposition of **S-GIIIm** (days at 55 °C), as well as the observation of multiple products,²⁹ suggesting operation of several competing pathways. Here we describe the successful interception of the first-generation σ -alkyl complex **Ru-6**; we show that formation of **Ru-6** is the primary deactivation event, irrespective of ensuing decomposition pathways, and we demonstrate that this behavior is relevant not merely to methylenide complex **GIm**, but also to RCM reactions promoted by **GI**.

4.3.2. Results and Discussion

With the intention of inhibiting E-H activation pathways that promote elimination of the alkylphosphine ligand, we turned to reactions with pyridine, in place of a secondary amine. From prior work, however, we suspected that use of pyridine would be insufficient to retard proton abstraction from electron-rich **S-GIIIm**. Stirring **S-GIIIm** in 1:5 pyridine-toluene was

reported to yield $\text{RuCl}_2(\text{H}_2\text{IMes})(\text{py})_3$ (29%; isolated), and unspecified amounts of **P1**.^{†29} Indeed, we found that the corresponding in situ reaction of labelled ***S-GIIIm** with 10 equiv py (**Scheme 4.6a**) liberated ca. 90% ***P1** within <5 min at ambient temperature, without observable intermediates.

To retard proton abstraction, we therefore employed the less electron-rich first-generation complex. Addition of pyridine to ^{13}C -labelled ***GIIm** at RT resulted in immediate loss of the methyldiene signal (**Scheme 4.6b**). Only ca. 5% ***P1** was apparent, however. The $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum was instead dominated by a doublet at 55.7 ppm ($^1J_{\text{PC}} = 9.8 \text{ Hz}$),[‡] which accounted for 95% of the ^{13}C -labelled methyldiene moiety. The corresponding $^{13}\text{C}\{^1\text{H}\}$ NMR doublet appeared unusually far upfield (−12.3 ppm; $^1J_{\text{PC}} = 9.8 \text{ Hz}$), implying considerable shielding. Assignment as **Ru-6** was confirmed by X-ray analysis of crystals that deposited from pentane-pyridine, following preparative-scale reaction of **GIIm** (150 mg; 90% crude yield).



Scheme 4.6. Speciation on treating ***GIIm** and ***S-GIIIm** with pyridine (% total $^{31}\text{P}\{^1\text{H}\}$ NMR integration). (a) Decomposition of ***S-GIIIm**. (b) Formation of **Ru-6** via displacement of PCy_3 from ***GIIm**, and attack of liberated PCy_3 at the methyldiene carbon.

The ORTEP plot of **Ru-6** is depicted in **Figure 4.4**. Of note, three pyridine ligands are present, and no Ru-bound PCy_3 remains. In contrast, reaction of the Grubbs catalysts **GI/S-GII** with pyridine shows no evidence for attack on the benzyldiene ligand. Instead, bis-

[†] An early study by Werner and co-workers likewise described complete loss of methyldiene from $\text{RuHCl}(\text{CO})(\text{P}^i\text{Pr}_2\text{Ph})_2(\text{=CH}_2)$ on addition of pyridine, over the time required to warm from -78°C to RT. The fate of the methyldiene ligand was not identified, however. See Ref. (28).

[‡] The magnitude of $^1J_{\text{PC}}$ in tetravalent phosphorus derivatives is highly sensitive to steric factors, an observation frequently attributed to changes in the s-character at phosphorus. See Ref. (68).

pyridine adducts $\text{RuCl}_2(\text{L})(\text{py})_2(=\text{CHPh})$ were reported for both first- and second-generation systems ($\text{L} = \text{PCy}_3$,⁶⁹ H_2IMes ⁵⁹).

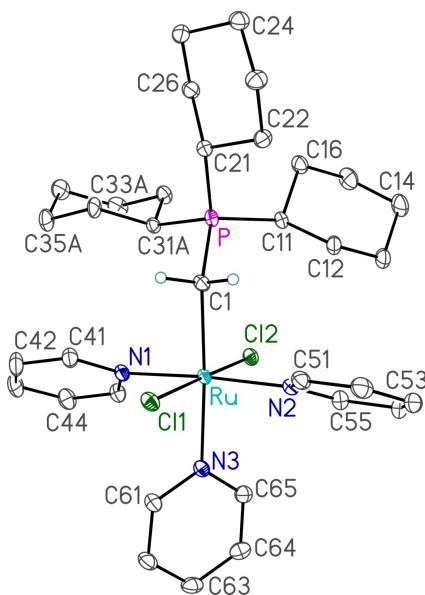
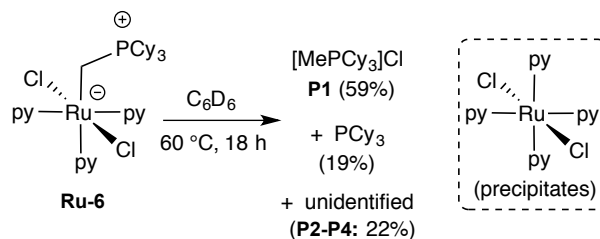


Figure 4.4 Crystal structure of **Ru-6**. Non-hydrogen atoms are represented by Gaussian ellipsoids at the 30% probability level. Hydrogen atoms attached to C1 are shown with arbitrarily small thermal parameters; other hydrogen atoms are omitted.

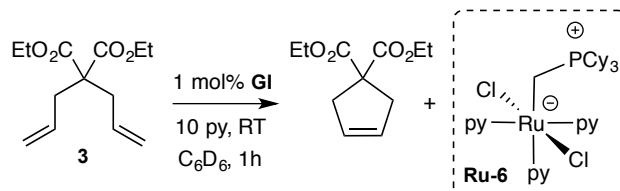
Complete decomposition of isolated **Ru-6** in solution at RT occurred over days in C_6D_6 , or hours in CD_2Cl_2 . At 60 °C in C_6D_6 , no **Ru-6** remained after 18 h. Free PCy_3 was observed by $^{31}\text{P}\{^1\text{H}\}$ NMR analysis, accompanied by significant amounts of **P1** (Scheme 4.7). Crystals of the known[†] complex $\text{RuCl}_2(\text{py})_4$ also deposited. The phosphonium salt **P1** is presumably formed via C-H activation pathways, as noted above. Multiple decomposition reactions are operative, however, as indicated by the observation of three further, unidentified $^{31}\text{P}\{^1\text{H}\}$ NMR signals (**P2–P4**). To determine whether any of these are due to the proposed ylid $\text{Cy}_3\text{P}=\text{CH}_2$,²⁹ we monitored the decomposition of labelled ***Ru-6**. The singlet multiplicity of **P2–P4** was retained, however (see Appendix; Figure A.23). This rules out assignment of any of these compounds as $\text{Cy}_3\text{P}=\text{CH}_2$, and indeed indicates that none retain the ^{13}C -P moiety. Elimination of **P1** via intramolecular proton abstraction may be a valid alternative to the proposed ylid-extrusion pathway.

[†] Preparation of $\text{RuCl}_2(\text{py})_4$ was first reported by Wilkinson and co-workers. See Ref. (70). For the first crystallographic report of this complex, see Ref. (71).



Scheme 4.7. Thermally promoted decomposition of isolated **Ru-6**: products observed by $^{31}\text{P}\{^1\text{H}\}$ NMR analysis (% vs. total integration) or precipitation.

While the data above indicate that the fate of the σ -alkyl moiety is not limited to **P1**,[‡] all of the products observed *originate* in **Ru-6**. Nucleophilic attack of free PCy_3 can thus be identified as the key vector for decomposition of **GIm** in the presence of pyridine. Importantly, **Ru-6** is also observed during metathesis by the first-generation Grubbs catalyst **GI**, where pyridine is present (**Scheme 4.8**). Thus, in RCM of **3**, the proportion of **Ru-6** reached ca. 80% of the theoretical maximum at 1h. We infer that py-induced decomposition during catalysis results from attack on the methylidene resting state **GIm**, rather on than the metallacyclobutane intermediate.[†]

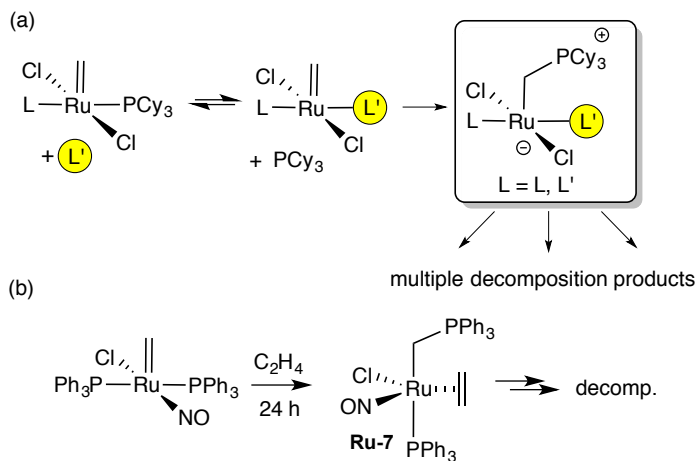


Scheme 4.8. Pyridine-induced decomposition during RCM.

This behavior holds potentially general implications. Of keen interest is the possibility illustrated in **Scheme 4.9a**: that is, that any donor able to displace PCy_3 and impede its re-coordination will promote phosphine attack on the methylidene ligand (steric factors permitting). Notably, ethylene itself may be sufficient to trigger such behavior, as indicated by Roper's report of the ethylene-induced transformation of a methylidene complex into σ -alkyl species **Ru-7** (**Scheme 4.9b**).⁶⁷

[‡] To assess the potential for an equilibrium between the σ -alkyl species **3a** and methylidene **2a** (an inference from the Roper study in Ref. (67)), we added diethyl diallylmalonate (100 equiv) to a solution of isolated **3a** in CD_2Cl_2 . No RCM was evident after 3.5 h at RT, or after 24 h at 60 °C. We conclude that **3a** does not regenerate a metathesis-active species.

[†] Decomposition via attack on methylidene **2b** was similarly observed for **1b**-mediated RCM in the presence of other primary and secondary amines: See Ref. (58). In contrast, the nitrogen base DBU effected decomposition without liberation of **A**. Attack on the ruthenacyclobutane was suggested.



Scheme 4.9. (a) Donor-induced decomposition of the Grubbs catalysts. (b) Ethylene-induced attack of PPh_3 on methyldiene.

4.3.3. Conclusions

The foregoing describes an important deactivation pathway for the Grubbs catalysts, which we term “donor-induced decomposition”. Addition of pyridine to the first-generation methyldiene complex **GIm** enabled interception of σ -alkyl species **Ru-6**. This complex is generated by pyridine-induced displacement of the PCy_3 ligands, and subsequent attack of liberated PCy_3 at the methyldiene carbon. Complex **Ru-6** is the dominant species observed for both isolated **GIm** (the catalytic resting state for **GI**) and for RCM reactions promoted by **GI**. Rapid formation of **Ru-6** is followed by its slower decomposition into multiple products. The σ -alkyl complex is thus the crucial vector for catalyst degradation. Phosphonium salt **P1** is one notable product formed on ensuing decomposition of **Ru-6**. For the first-generation system studied here, however, just 60% of the isolated σ -alkyl species **Ru-6** terminated in the phosphonium salt. While valuable as a qualitative marker for attack of PCy_3 on methyldiene, the *proportion* of **P1** should therefore be regarded as a minimum estimate of the contribution from this pathway. These results highlight the Janus face of the PCy_3 ligand in the Grubbs catalysts, in its dual role as stabilizing ligand, and destructive agent.

4.3.4. Experimental Details for Section 4.3

General procedures

Reactions were carried out using standard glovebox techniques at room temperature (RT; 25 ± 2 °C), unless otherwise indicated. All solvents except CD_2Cl_2 were stored under N_2 in the glovebox over 4Å molecular sieves: pyridine (sigma-Aldrich; anhydrous; stored in an amber

bottle); pentane (Fisher, distilled over sodium benzophenone); C₆D₆ (Cambridge Isotopes; degassed by five successive freeze/pump/thaw cycles). CD₂Cl₂ (Cambridge Isotopes) was purchased in sealed ampoules and used as delivered.

NMR spectra were recorded at 23 ± 2 °C, and referenced to the residual proton or carbon signals of the deuterated solvent (¹H, ¹³C), or external 85% H₃PO₄ (³¹P). Signals are reported relative to TMS (¹H and ¹³C) or 85% H₃PO₄ (³¹P) at 0 ppm. Speciation by ³¹P{¹H} NMR analysis is given as % of total integration: for in situ evaluation of ***GIm** (see next), this is normalized to 200% to account for the presence of two PCy₃ groups per Ru.

NMR-Scale Reaction of RuCl₂(PCy₃)₂(=CH¹³CH₂) (*GIm**) with Pyridine: Observation of RuCl₂(σ-¹³CH₂PCy₃)(py)₃, ***Ru-6**.** In the glovebox, a J-Young NMR tube was charged with ***GIm** (11 mg, 0.014 mmol) and 0.7 mL C₆D₆. On adding pyridine (11.4 μL, 0.140 mmol, 10 equiv), the colour changed from brown to deep red, and the solution became turbid. ³¹P{¹H} NMR (C₆D₆, 202.5 MHz): δ 55.7 (d, ¹J_{PC} = 9.8 Hz, 96%, ***Ru-6**), 46.1 (s, 2%, unknown **P3**), 34.2 (d, ¹J_{PC} = 47.6 Hz, 4%, [¹³CH₃PCy₃]Cl; ***P1**), 28.5 (15%, unknown **P2**), 10.5 (s, 83%, PCy₃). No doublet for starting ***GIm** was observed (43.5 ppm; ²J_{PC} = 8.4 Hz). ¹³C{¹H} NMR (C₆D₆, 125.8 MHz; key Ru-CH₂ signal only): -12.3 ppm (d, ¹J_{PC} = 9.8 Hz, Ru-CH₂PCy₃). A ¹H-¹³C HMQC correlation experiment (C₆D₆, 500.1 MHz) indicated a cross-peak between this diagnostic doublet and the methylene protons of the σ-alkyl group at 1.94 ppm.

After 12 h at RT, 85% ***Ru-6** remained; the signals for ***P1** and unknown **P2/P3** increased accordingly, but no new signals were observed. On heating at 60 °C for 18 h: ³¹P{¹H} NMR (C₆D₆, 121.5 MHz): δ 46.1 (s, 8%, **P3**), 36.4 (s, 2%, unknown **P4**), 34.2 (d, ¹J_{PC} = 47.6 Hz, 63%, ***P1**), 28.5 (29%, **P2**), 10.5 (s, 98%, PCy₃). No ***Ru-6** was present. The singlet multiplicity of the signals for **P2–P4** indicates the absence of a P-¹³C moiety.

Preparative-Scale Synthesis of RuCl₂(σ-CH₂PCy₃)(py)₃, **Ru-6.** In the glovebox, pink **GIm** (150 mg, 0.203 mmol) was dissolved in 410 μL pyridine in a scintillation vial. The solution immediately turned turbid dark red. After 5 min stirring, pentane (20 mL) was added to precipitate a red solid, which was filtered off and washed with pentane (5 x 1 mL). Yield 130 mg (91%). NMR analysis was carried out in C₆D₆ (in which **Ru-6** is sparingly soluble). ³¹P{¹H} NMR (C₆D₆, 121.5 MHz): δ 55.7 (s, **Ru-6**, 90%), 32.1 (s, **P1**, 5%), 28.5 (s, **P2**, 5%). Crude **Ru-6** (117 mg) was crystallized from CH₂Cl₂-pentane at -35 °C, and washed with cold pentane (2 x 1 mL). Yield 52 mg (44%); the low yield is due to competing

decomposition. Anal. Calcd for $C_{34}H_{50}Cl_2N_3PRu$: C, 58.03; H, 7.16; N, 5.97. Found: C, 57.86; H, 6.96; N, 5.75.

Note. In the NMR assignments below, py^A designates pyridine ligands cis to CH_2PCy_3 ; py^B designates the pyridine ligand trans to CH_2PCy_3 . 1H NMR (300.1 MHz, CD_2Cl_2): δ 9.31 (br s, 4H, py^A *o*-CH), 8.89 (d, $^3J_{HH} = 6.3$ Hz, 2H, py^B *o*-CH), 7.52-7.41 (overlapping t, 3H, py^A and py^B *p*-CH), 7.02 (t, $^3J_{HH} = 6.3$ Hz, 2H, py^B *m*-CH), 6.96 (t, $^3J_{HC} = 6.3$ Hz, 4H, py^A *m*-CH), 3.29-0.30 (m, 55H, comprising CH_2PCy_3 of **Ru-6** (35H) and products of decomposition in solution, including **P1**). $^{13}C\{^1H\}$ NMR characterization was hampered by low solubility in C_6D_6 . Solubility was higher in CD_2Cl_2 , but decomposition over 18 h at RT impeded analysis. Even in the solid state under N_2 at $-35^\circ C$, analytically pure **Ru-6** underwent partial decomposition over 10 weeks. $^{31}P\{^1H\}$ NMR (C_6D_6 , 121.5 MHz): δ 55.7 (s, 3, 90%), 52.4 (s, unassigned, 10%). X-ray quality crystals of **Ru-6** deposited from a cold ($-35^\circ C$) solution of 5:1 pentane-pyridine over 12 h.

Thermolysis of Isolated Ru-6. In the glovebox, a J. Young NMR tube was charged with crude **3a** (12 mg, 0.017 mmol) and 0.75 mL C_6D_6 . A $^{31}P\{^1H\}$ NMR spectrum indicated 10% decomposition (5% **P1** and **P2**, respectively). The sample was heated at $60^\circ C$ in a thermocouple-controlled oil bath. $^{31}P\{^1H\}$ NMR spectra were collected over 18 h, at which time no further **Ru-6** remained. $^{31}P\{^1H\}$ NMR (C_6D_6 , 121.5 MHz): δ 46.1 (2%, **P3**), 34.2 (59%, **P1**), 28.6 (20%, **P2**), 10.5 (19%, PCy_3). X-Ray quality orange crystals deposited during thermolysis, and identified as previously characterized trans- $RuCl_2py_4$.

Formation of Ru-6 During RCM. In the glovebox, a 20 mL scintillation vial was charged with **GI** (165 μ L of a 12.1 mM stock solution of **1a** in C_6D_6 ; 0.002 mmol), diluted with C_6D_6 (1.8 mL), and diethyl diallylmalonate **3** (48.4 μ L, 0.200 mM, 100 equiv) was added. A stock solution of pyridine in C_6D_6 (10 μ L of a 2.00 M stock solution; 10 equiv vs. **GI**) was immediately added. The solution was allowed to stir for 1 h open to the glovebox atmosphere, to permit loss of ethylene. Integration values (% of total integration) are normalized to 200% to account for the two PCy_3 groups in **1a**: see above. $^{31}P\{^1H\}$ NMR (C_6D_6 , 121.5 MHz): δ 59.2 (s, unidentified, 16%), 55.7 (s, **Ru-6**, 79%), 46.0 (s, **P3**, 8%), 28.6 (s, **P2**, 29%), 10.5 (s, 70%, PCy_3).

4.4. Scope of the Donor-Induced Decomposition Pathway

4.4.1. Introduction

The previous section described σ -alkyl formation as the key deactivating event in decomposition of **GIm** by pyridine, and predicted that this behaviour should be found for any donor capable of displacing the PCy₃ ligand. Here evidence is presented to show that this pathway is indeed operative for primary and secondary amines, despite the ease with which such donors were expected to promote elimination of the σ -alkyl ligand (Section 4.3.1). The greater susceptibility of **GIm** toward amines, relative to the second-generation methyldiene complexes, is also demonstrated, and a rationale for this difference is advanced.

4.4.2. Results and Discussion

Decomposition of the first-generation complex **GIm** by equimolar amine was explored in a series of NMR-tube experiments. The decrease in the intensity of the alkylidene signals relative to internal standard was monitored following addition of amines **N1-N4** at room temperature. No new alkylidene signals were seen for the putative amine adducts **Ru-8** (**Figure 4.5**) suggesting either that the initial equilibrium lies in favour of **GIm**, or that the adducts, once formed, rapidly convert to their σ -alkyl derivatives **Ru-9**.

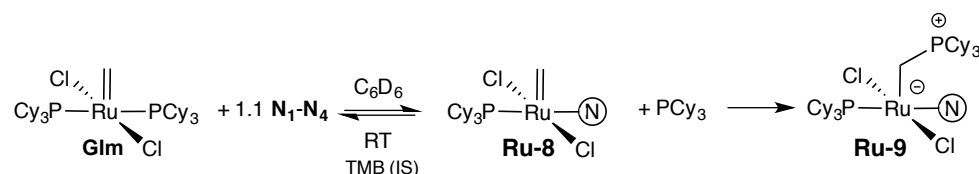


Figure 4.5. Anticipated reactions following addition of amines on **GIm**. Not shown is the putative six-coordinate H₂NⁿBu adducts.

In either case, **GIm** is rapidly decomposed by all amines even at room temperature (**Figure 4.6**). In striking contrast with the control experiment in the absence of amine, which revealed a half-life of 67 h for **GIm** at ambient temperature in C₆D₆, addition of *n*-butylamine **N1** caused 50% loss of all alkylidene signals within <2 min, vs. 5 min for pyrrolidine **N2**, and ca. 70 min for morpholine **N3** and DBU **N4**. The slower decomposition for the latter two amines is probably due to the restricting effects of lower basicity (for **N3**) and greater bulk (for **N4**). The corresponding reactions in the second-generation system showed a similar trend, but proceeded more slowly, as discussed in Section 4.2.2 (values are

reproduced in **Figure 4.6** for convenience). Numerical values for the half-lives shown are summarized in **Table 4.1**.

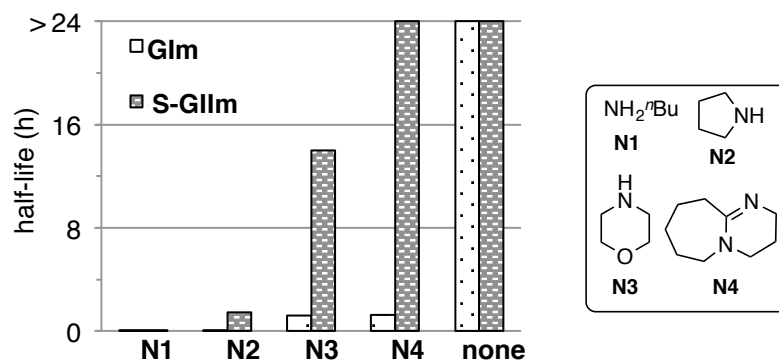


Figure 4.6. Relative susceptibility of **GIm** and **GIm** to decomposition by **N1-N4** at room temperature.

Table 4.1 Summary of half-lives in amine-induced decomposition of **GIm** and **S-GIm**.^a

Catalyst	Amine	Half-life	Error ($\pm$) ^b
GIm	N1 : <i>n</i> -butylamine	<2 min	0.5 min
	N2 : pyrrolidine	5 min	0.5 min
	N3 : morpholine	72 min	1 min
	N4 : DBU	76 min	1 min
	none	67 h	3 h
GIm	N1 : <i>n</i> -butylamine	<3	1 min
	N2 : pyrrolidine	87 min	1 min
	N3 : morpholine	14 h	0.2 h
	N4 : DBU	>1440	-
	none	>1440 min	-

^a Reactions at 20 mM Ru in C₆D₆ using 1.1 equiv amine. ^b Half-lives are average of two independent trials.

³¹P{¹H} NMR spectra for the **GIm** system following addition of **N1-N4** are shown in **Figure 4.7**. Notable is the small proportion of [MePCy₃]Cl **P1**, in contrast with the behaviour seen for **S-GIm** (Section 4.2). Instead, a new pair of doublets ($J_{pp} = 2.3$ Hz) is seen for each amine, the total proportion of which tracks with decreased amine bulk (70% for *n*-butylamine **N1**, essentially zero for **N4** DBU). These signals are provisionally assigned to the σ -alkyl species **Ru-9**. While efforts to fully characterize these species are now under way (work by W. McClennan of this research group), several details support the proposed assignment. (a) The near-zero value of the three-bond coupling constant is consistent with the singlet multiplicity reported by Piers for the related complex [RuCl₂(PCy₃)(=CHPCy₃)] [B(C₆F₅)₄].⁷² (b) The chemical shift for the upfield doublet, at 55.6–56.6 ppm, compares well with the value of 55.7 ppm for σ -alkyl complex **Ru-6**. An

unexpected feature is the unusually downfield location of the second doublet, at 89.5-84.9 ppm, despite the formal negative charge at the metal center.

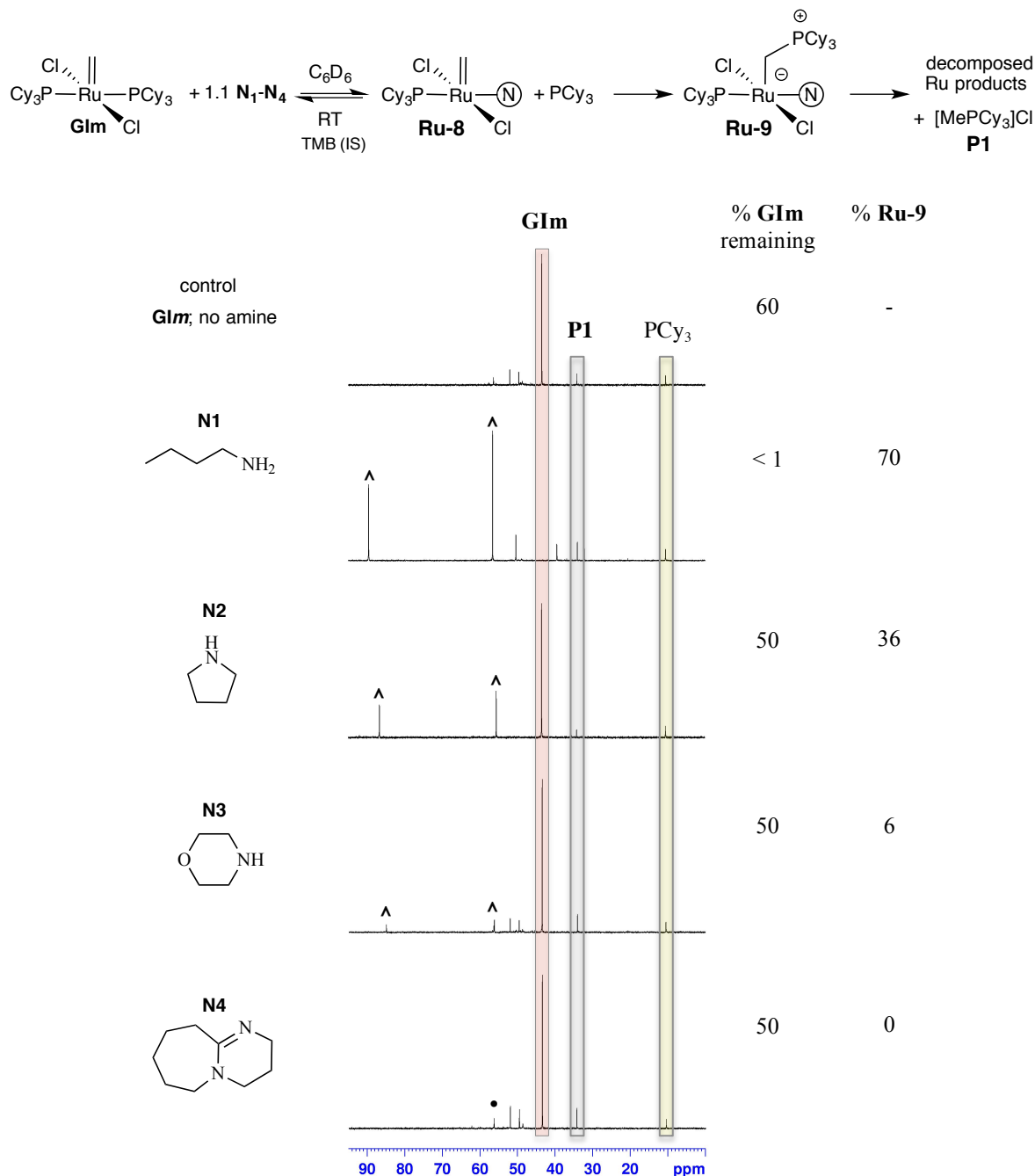


Figure 4.7. $^{31}P\{^1H\}$ NMR spectra (121.5 MHz, C_6D_6) for decomposition of **GIm** by **N1-N4**. Caret (^) indicates **Ru-9**; bullet (•) indicates potential unidentified σ -alkyl; % vs. total $^{31}P\{^1H\}$ integration.

An intriguing question in this chemistry is the basis for the faster transformation of **GIm** by amine, relative to **S-GIm**. Given the well-established dissociative pathways for

metathesis via the Grubbs catalysts, we anticipated that decomposition of **GIm** was mediated by four-coordinate intermediate, $\text{RuCl}_2(\text{PCy}_3)(=\text{CH}_2)$. We find, however, that thermolytic decomposition of isolated **GIm**, in the absence of any additives, is *accelerated* by added PCy_3 **Figure 4.8a**.[†] This implicates the five-coordinate complex **GIm** in decomposition. We conclude that the methyldiene ligand in the first-generation system is much more accessible than that in the NHC derivative. This inference is borne out by the space-filling models in **Figure 4.8**. The greater accessibility of **GIm** presumably contributes to the faster reaction of the first-generation system with amines.

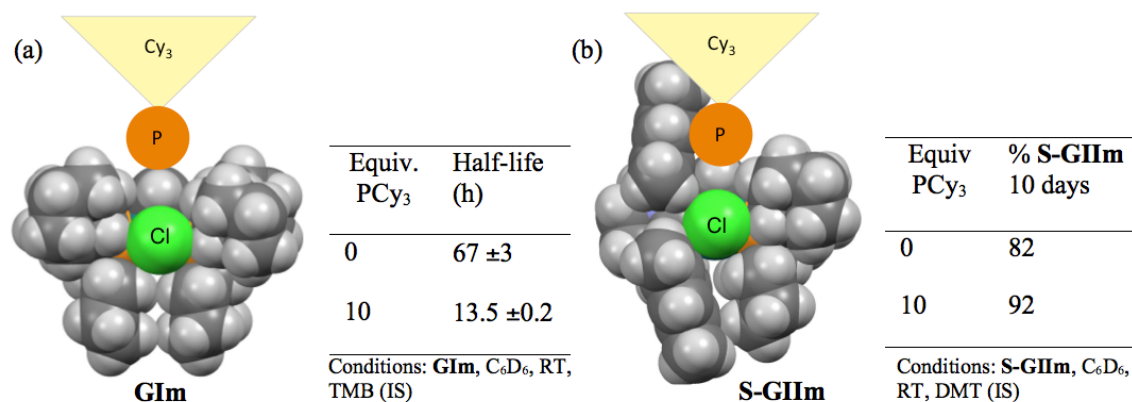


Figure 4.8. Steric accessibility of methyldiene species in (a) **GIm** and (b) **S-GIm**. Assessed at room temperature to limit the contribution of the more vulnerable four coordinate methyldiene species.

4.4.3. Conclusions

The findings in this chapter demonstrate that the first-generation methyldiene **GIm** is much more sensitive to decomposition by added amine than its **S-GIm** analogue. In contrast to the second-generation system, decomposition is rapid even with relatively weak or bulky bases (e.g. morpholine or DBU, respectively). A key, previously unrecognized factor contributing to the sensitivity of **GIm** relative to **S-GIm** is the fact that the methyldiene ligand of **GIm** is sterically accessible, even in the five-coordinate complex. This may suggest that “specialty” second-generation catalysts in which the size of the NHC ligands is reduced (a key goal to accommodate bulky substrates) will be more susceptible to donor-induced deactivation.

[†] These data conflict with a prior report in which the rate of decomposition of **GIm** was found to be unaffected by added PCy_3 .(54).

More generally, this work demonstrates that both the first- and second-generation Grubbs catalysts are burdened with a latent poison. The PCy₃ ligand not only reduces productivity by syphoning the active four-coordinate methyldiene out of the catalytic cycle, but also attacks the methyldiene moiety deactivating the catalyst. These data highlight the need to incorporate ancillary ligands that do not attack the methyldiene intermediate as a key design criteria for the preparation of more robust, functional-group tolerant catalysts.

4.4.4. Experimental Details for Section 4.4 General Procedures

Reactions were carried out in an N₂-filled glovebox. Benzene-d₆ (Cambridge Isotopes) was degassed by consecutive freeze/pump/thaw cycles and stored over 4 Å molecular sieves for at least 6 h prior to use. Amines were obtained from Alfa Aesar (*n*-butylamine **N1**, 99%), Sigma-Aldrich (pyrrolidine **N2**, >99%; morpholine **N3**, >99.5%), or Acros (DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene **N4**, 98%). Morpholine (twice-distilled and packaged under N₂) was used without purification; other amines were freeze/pump/thaw-degassed on receipt, and stored under N₂ to prevent contamination by hydrates, oxides, etc., which would reduce amine nucleophilicity. Amine purity was confirmed by NMR analysis. Trimethoxybenzene (TMB, Sigma-Aldrich) were used as received. Literature methods were used to prepare methyldiene complexes **GIm** and **S-GIm**.⁴³

NMR spectra were recorded at probe temperatures of 23 ±1.5 °C and referenced to the residual proton or carbon signals of the deuterated solvent (¹H, ¹³C NMR), or external 85% H₃PO₄ (³¹P). Signals are reported in ppm relative to TMS (¹H, ¹³C) or 85% H₃PO₄ (³¹P) at 0 ppm. Half-lives were determined by collecting ¹H NMR spectra for 1.5 min at regular intervals. Time zero was either the time of mixing, or (for heated reactions) the time of heating. Each time-point indicated is the time at which the acquisition was started.

Representative Procedure for Half-Life Measurements. In the glovebox, a Rotoflo NMR tube was charged with **GIm** (11.0 mg, 0.0147 mmol), trimethoxybenzene (TMB; ca. 1 mg), and 0.735 mL C₆D₆. The sample was transferred to an NMR probe, the starting **GIm**:TMB ratio was measured, amine **N1** (1.6 µL, 0.0162 mmol, 1.1 equiv) was injected, and the puncture was immediately sealed with tape. The sample was shaken for 1 min and returned to the spectrometer; a stopwatch was started, and spectra were collected until loss of alkylidene signals was complete.

4.5. Subsequent Advances

Further advances in this chemistry have been made by William McClennan of this research group, and will be reported in due course. Outstanding questions and opportunities awaiting study will be discussed in Chapter 6 (Conclusion and Future Work).

4.6. References

- (1) Armstrong, S. K. *J. Chem. Soc., Perkin Trans.* **1998**, 371–388.
- (2) Van de Weghe, P.; Bissere, P.; Blanchard, N.; Eustache, J. *J. Organomet. Chem.* **2006**, 5078–5108.
- (3) Lozano-Vila, A. M.; Monsaert, S.; Bajek, A.; Verpoort, F. *Chem. Rev.* **2010**, *110*, 4865–4909.
- (4) van Lierop, B. J.; Lummiss, J. A. M.; Fogg, D. E., Ring-Closing Metathesis. In *Olefin Metathesis-Theory and Practice*, Grela, K., Ed. Wiley: Hoboken, NJ, 2014; pp 85–152.
- (5) Yee, N. K.; Farina, V.; Houpi, I. N.; Haddad, N.; Frutos, R. P.; Gallou, F.; Wang, X.-J.; Wei, X.; Simpson, R. D.; Feng, X.; Fuchs, V.; Xu, Y.; Tan, J.; Zhang, L.; Xu, J.; Smith-Keenan, L. L.; Vitous, J.; Ridges, M. D.; Spinelli, E. M.; Johnson, M.; Donsbach, K.; Nicola, T.; Brenner, M.; Winter, E.; Kreye, P.; Samstag, W. *J. Org. Chem.* **2006**, *71*, 7133–7145.
- (6) Wang, H.; Goodman, S. N.; Dai, Q.; Stockdale, G. W.; Clark, W. M. *Org. Process Res. Dev.* **2008**, *12*, 226–234.
- (7) Compain, P. *Adv. Synth. Catal.* **2007**, *349*, 1829–1846.
- (8) Rutjes, F. P. J. T., Natural Products Containing Medium-Sized Nitrogen Heterocycles Synthesized by RCM. In *Metathesis in Natural Product Synthesis: Strategies, Substrates and Catalysts*, Cossy, J.; Arseniyadis, S.; Meyer, C., Eds. Wiley-VCH: Weinheim, 2010; pp 45–86.
- (9) Prunet, J. *Eur. J. Org. Chem.* **2011**, 3634–3647.
- (10) Evans, P.; Grigg, R.; Monteith, M. *Tetrahedron Lett.* **1999**, *40*, 5247–5250.
- (11) Yang, Q.; Xiao, W.-J.; Yu, Z. *Org. Lett.* **2005**, *7*, 871–874.
- (12) Kyle, A. F.; Jakubec, P.; Cockfield, D. M.; Cleator, E.; Skidmore, J.; Dixon, D. J. *Chem. Commun.* **2011**, *47*, 10037–10039.
- (13) Yu, M.; Wang, C.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *479*, 88–93.
- (14) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856–9857.
- (15) Fürstner, A.; Leitner, A. *Angew. Chem. Int. Ed.* **2003**, *42*, 308.
- (16) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204–2207.
- (17) Fürstner, A.; Grabowski, J.; Lehmann, C. W. *J. Org. Chem.* **1999**, *64*, 8275–8280.
- (18) For a leading review on this topic, see Ref 7. For additional examples cited in review articles, see: b) R. H. Grubbs, *Handbook of Metathesis*, Wiley-VCH, Weinheim, **2003**. Vol. 1, p. 120; Vol. 2, pp. 48–50, Vol. 3, pp. 319–320; c) A. Deiters, S. F. Martin, *Chem. Rev.* **2004**, *104*, 2199–2238. For an early report noting the importance of protecting groups in RCM of amine-containing substrates, see Ref 14.
- (19) Woodward, C. P.; Spiccia, N. D.; Jackson, W. R.; Robinson, A. J. *Chem. Commun.* **2011**, *47*, 779–781.

- (20) Wilson, G. O.; Porter, K. A.; Weissman, H.; White, S. R.; Sottos, N. R.; Moore, J. S. *Adv. Synth. Catal.* **2009**, *351*, 1817–1825.
- (21) Hahn, F. E.; Paas, M.; Froehlich, R. *J. Organomet. Chem.* **2005**, *690*, 5816–5821.
- (22) P'Pool, S. J.; Schanz, H.-J. *J. Am. Chem. Soc.* **2007**, *129*, 14200–14212.
- (23) Occhipinti, G.; Bjorsvik, H.-R.; Toernroos, K. W.; Jensen, V. R. *Organometallics* **2007**, *26*, 5803–5814.
- (24) Samec, J. S. M.; Grubbs, R. H. *Chem. Commun.* **2007**, 2826–2828.
- (25) Tzur, E.; Szadkowska, A.; Ben-Asuly, A.; Makal, A.; Goldberg, I.; Wozniak, K.; Grela, K.; Lemcoff, N. G. *Chem.--Eur. J.* **2010**, *16*, 8726–8737.
- (26) Jong, H.; Patrick, B. O.; Fryzuk, M. D. *Organometallics* **2011**, *30*, 2333–2341.
- (27) Love, J. A.; Morgan, J. P.; Trnka, T. M.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2002**, *41*, 4035–4037.
- (28) Werner, H.; Stuer, W.; Weberndorfer, B.; Wolf, J. *Eur. J. Inorg. Chem.* **1999**, 1707–1713.
- (29) Hong, S. H.; Wenzel, A. G.; Salguero, T. T.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2007**, *129*, 7961–7968.
- (30) Fogg, D. E.; Foucault, H. M., Ring-Opening Metathesis Polymerization. In *Comprehensive Organometallic Chemistry III*, Crabtree, R. H.; Mingos, D. M. P., Eds. Elsevier: Oxford, 2007; Vol. 11, pp 623–652.
- (31) Cox, B. G., *Acids and Bases: Solvent Effects on Acid-Base Strength*. Oxford University Press: Croydon, 2013.
- (32) Hoberg, H.; Peres, Y.; Krüger, C.; Tsay, Y.-H. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 771–773; *Angew. Chem.* **1987**, *99*, 799–800.
- (33) Florke, U.; Ortmann, U.; Haupt, H.-J. *Acta Cryst.* **1992**, *C48*, 1663–1665.
- (34) Joshi, A. M.; Thorburn, I. S.; Rettig, S. J.; James, B. R. *Inorg. Chim. Acta* **1992**, *198-200*, 283–296.
- (35) Regragui, R.; Dixneuf, P. *J. Organomet. Chem.* **1988**, *344*, C11–C14.
- (36) Vehlow, K.; Gessler, S.; Blechert, S. *Angew. Chem. Int. Ed.* **2007**, *46*, 8082–8085.
- (37) Coalter, J. N.; Bollinger, J. C.; Eisenstein, O.; Caulton, K. G. *New J. Chem.* **2000**, *24*, 925–927.
- (38) Conrad, J. C.; Amoroso, D.; Czechura, P.; Yap, G. P. A.; Fogg, D. E. *Organometallics* **2003**, *22*, 3634–3636.
- (39) Dinger, M. B.; Mol, J. C. *Organometallics* **2003**, *22*, 1089–1095.
- (40) Beach, N. J.; Lummiss, J. A. M.; Bates, J. M.; Fogg, D. E. *Organometallics* **2012**, *31*, 2349–2356.
- (41) Hansen, S. M.; Rominger, F.; Metz, M.; Hofmann, P. *Chem. Eur. J.* **1999**, *5*, 557–566.
- (42) Galan, B. R.; Pitak, M.; Keister, J. B.; Diver, S. T. *Organometallics* **2008**, *27*, 3630–3632.
- (43) Lummiss, J. A. M.; Beach, N. J.; Smith, J. C.; Fogg, D. E. *Catal. Sci. Technol.* **2012**, *2*, 1630–1632.
- (44) van der Eide, E. F.; Piers, W. E. *Nature Chem.* **2010**, *2*, 571–576.
- (45) Wenzel, A. G.; Blake, G.; Vander Velde, D. G.; Grubbs, R. H. *J. Am. Chem. Soc.* **2011**, *133*, 6429–6439.
- (46) Gregg, T. M.; Keister, J. B.; Diver, S. T. *J. Am. Chem. Soc.* **2013**, *135*, 16777–16780..
- (47) van Lierop, B. J.; Reckling, A. M.; Lummiss, J. A. M.; Fogg, D. E. *ChemCatChem* **2012**, *4*, 2020–2025.

- (48) Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792–803.
- (49) A recent book provides a comprehensive update on olefin metathesis. See: (a) Grela, K., *Olefin Metathesis—Theory and Practice*. Wiley: Hoboken, 2014. For a recent review highlighting the synthesis of biologically active molecules using RCM, see: (b) Fürstner, A. *Science* **2013**, *341*, 1229713, and Ref. 50. For a recent comprehensive review of RCM, including emerging applications in pharma, see: Ref. 4. See also: (c) Fandrick, K. R.; Savoie, J.; Jinhua, N. Y.; Song, J. J.; Senanayake, C. H., Challenges and Opportunities for Scaling the Ring-Closing Metathesis Reaction in the Pharmaceutical Industry. In *Olefin Metathesis – Theory and Practice*, pp. 349–366. For a review of asymmetric catalysts for stereocontrolled olefin metathesis, see: (d) Kress, S.; Blechert, S. *Chem. Soc. Rev.* **2012**, *41*, 4389–4408, (e) Hoveyda, A. H.; Malcolmson, S. J.; Meek, S. J.; Zhugralin, A. R. *Angew. Chem. Int. Ed.* **2010**, *49*, 34–44.
- (50) Cossy, J.; Arseniyadis, S.; Meyer, C., *Metathesis in Natural Product Synthesis: Strategies, Substrates and Catalysts*. Wiley-VCH: Weinheim, 2010.
- (51) Chadwick, J. C.; Duchateau, R.; Freixa, Z.; van Leeuwen, P. W. N. M., Alkene Metathesis. In *Homogeneous Catalysts: Activity – Stability – Deactivation*, Wiley-VCH: Weinheim, 2011; pp 347–396.
- (52) Manzini, S.; Poater, A.; Nelson, D. J.; Cavallo, L.; Slawin, A. M. Z.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2014**, *53*, 8995–8999.
- (53) Tabari, D. S.; Tolentino, D. R.; Schrodi, Y. *Organometallics* **2013**, *32*, 5–8.
- (54) Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 7202–7207.
- (55) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543–6554.
- (56) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100–110.
- (57) Lummiss, J. A. M.; Botti, A. G. G.; Fogg, D. E. *Catal. Sci. Technol.* **2014**, *4*, 4210–4218.
- (58) Lummiss, J. A. M.; Ireland, B. J.; Sommers, J. M.; Fogg, D. E. *ChemCatChem* **2014**, *6*, 459–463.
- (59) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *Organometallics* **2001**, *20*, 5314–5318.
- (60) Bolton, S. L.; Williams, J. E.; Sponsler, M. B. *Organometallics* **2007**, *26*, 2485–2487.
- (61) O, W. W. N.; Morris, R. H. *ACS Catal.* **2013**, *3*, 32–40, and references therein.
- (62) Gunanathan, C.; Milstein, D. *Acc. Chem. Res.* **2011**, *44*, 588–602.
- (63) Leitao, E. M.; Piers, W. E.; Parvez, M. *Can. J. Chem.* **2013**, *91*, 935–942.
- (64) Leitao, E. M.; Dubberley, S. R.; Piers, W. E.; Wu, Q.; McDonald, R. *Chem. Eur. J.* **2008**, *14*, 11565–11572.
- (65) van Rensburg, W. J.; Steynberg, P. J.; Meyer, W. H.; Kirk, M. M.; Forman, G. S. *J. Am. Chem. Soc.* **2004**, *126*, 14332–14333.
- (66) Zhao, Z.-X.; Wang, H.-Y.; Guo, Y.-L. *Rapid Commun. Mass Spectrom.* **2011**, *25*, 3401–3410.
- (67) Burrell, A. K.; Clark, G. R.; Rickard, C. E. F.; Roper, W. R.; Wright, A. H. *J. Chem. Soc., Dalton Trans.* **1991**, 609–614.
- (68) Kuhl, O., *Phosphorus-31 NMR Spectroscopy: A Concise Introduction for the Synthetic Organic and Organometallic Chemist*. Springer-Verlag Heidelberg, 2008.
- (69) Getty, K.; Delgado-Jaime, M. U.; Kennepohl, P. *Inorg. Chim. Acta* **2008**, *361*, 1059–1065.
- (70) Wilkinson, G.; Gilbert, J. D.; Rose, D. *J. Chem. Soc. A* **1970**, 2765–2769.

- (71) Wong, W.-T.; Lau, T.-C. *Acta Crystallogr., Sect. C Cryst. Struct. Commun.* **1994**, C50, 1406–1407.
- (72) Romero, P. E.; Piers, W. E.; McDonald, R. *Angew. Chem. Int. Ed.* **2004**, 43, 6161–6165.

Chapter 5. Sustainable Metathesis: Augmenting the Complexity of Bio-Renewable Feedstocks via Olefin Metathesis

5.1. Context, Objectives, and Overview of Content

In recent years, ethenolysis has received significant attention for its ability to convert renewable resources, such as those derived from seed oils, into simple building blocks.^{1-10 11-13} This is typically achieved by saponification of crude seed or vegetable oils, which cleaves the triglycerides into their fatty acid methyl esters (FAMES) and glycerol, followed by cross-metathesis with ethylene (**Figure 5.1**). A mixture of terminal olefin products is thus obtained.

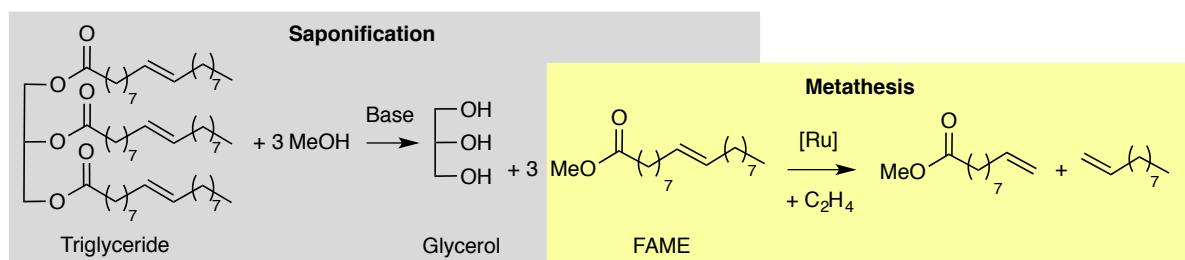


Figure 5.1. Cleaving internal olefin into two simpler terminal olefins via ethenolysis. Representative example depicting the fatty acid methyl ester (FAME) as methyl oleate.

The present work differed in using cross-metathesis to augment, rather than reduce, the complexity of renewable feedstocks. In an exemplary reaction, the essential oil anethole was converted in a single step to octylmethoxycinnamate,[†] the active ingredient in most commercially available sunscreen formulations. The target cross-metathesis reaction presents a number of potential difficulties, arising from the combination of steric and electronic deactivation. Thus, the electron-poor nature of the acrylate olefin hampers binding to the four-coordinate ruthenium intermediate, and (for the catalyst class selected for use: see below) this retards reaction.¹⁴ Moreover, the phenylpropenoids studied (anethole, isosafrole, and isoeugenol) are internal, predominantly trans-substituted olefins, the steric demand of which further slows the rate of cross-metathesis. Competing decomposition is thus expected.

[†] Octylmethoxycinnamate is more commonly referred to by the trivial name octinoxate, or by its trade names, Eusolex 2292 and Uvinul MC80.

Over the last two decades, hundreds of metathesis catalysts have been reported.^{15,16} Published applications, however, are dominated by two commercially available ruthenium complexes: the second-generation Grubbs and Hoveyda catalysts, **S-GII**¹⁷ and **S-HII**,¹⁸ respectively.¹⁵ While **S-GII** is historically the catalyst of first choice for organic chemists,¹⁹ the work presented in Chapters 3 and 4 suggests that **S-HII** may offer advantages in terms of lifetime and productivity. Acrylate cross-metathesis (CM) appears to be particularly sensitive to the catalyst used, and dramatically higher productivity was reported for **S-HII** by the Maier and Rennes groups.²⁰⁻²⁴ The work in the present Chapter therefore utilized **S-HII**.

In using this chelating styrenyl ether catalyst, it is important to recognize that its initiation mechanism differs from that for the phosphine-bound Grubbs catalysts discussed in the prior Chapters. While **S-GII** initiates via a dissociative mechanism,²⁵ the less encumbered styrenyl ether catalyst **S-HII** was recently shown to initiate via an interchange-associative mechanism, at least for sterically accessible olefins.²⁶⁻³⁰ From a practical standpoint, this is important because it means that reaction rates with **S-HII** can be increased by use of high olefin concentrations. Less clear-cut are apparent differences in behaviour at low concentration: specifically, better performance for **S-GII** in several cases involving relatively high dilutions (substrate concentrations of 20 mM or less).³¹⁻³⁴

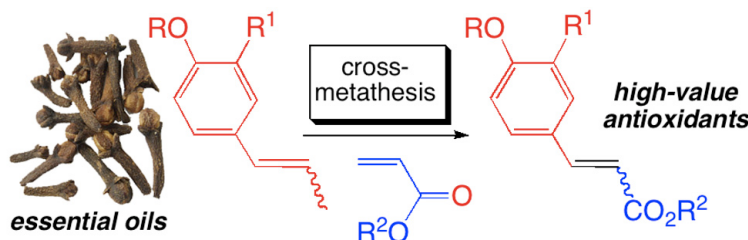
Yields for acrylate CM with **S-GII** as catalyst are generally poor, although the Sasol group showed that phenol additives improve performance to some extent.³⁵ Phenol was suggested to increase the electrophilicity of the metal via an H-bonding interaction between the phenolic proton and the chloride ligand, thus reducing the electron density at ruthenium. This in turn was proposed to favour olefin binding and to stabilize the MCB intermediate, albeit at the cost of initiation rates. Sequestration of free PCy₃ by phenol (as (PhOH)_nPCy₃) was also suggested.³⁶ The need for super-stoichiometric phenol (500 equiv relative to catalyst) is a major practical limitation, however. While the excess phenol can be recovered, the added cost associated with recycling of the phenol and purifying the cinnamate render phenol additives an impractical solution for industrial-scale application.

The primary focus of this chapter is therefore on the opportunities presented by **HII** in the metathesis of phenylpropenoids with acrylates. This work complements the mechanistically-focused studies of the previous Chapters in focusing on a new, potent application of olefin metathesis in sustainable chemistry.

5.1.1. Table of Contents Entries (published work only)

Chemical Plants: High-Value Molecules from Essential Oils. Justin A.M. Lummiss, Kelley C. Oliveira,^a Alexandre M.T. Prankevicus, Alexandra G. Santos,^a Eduardo N. dos Santos,^{a*} Deryn E. Fogg.* *J. Am. Chem. Soc.* **2012**; 134, 18889–18891.

^a*Departamento de Química-ICEx, Universidade Federal de Minas Gerais, 31270-901 Belo Horizonte, Brazil*



Abstract: As society faces a future of dwindling petrochemical supplies at increasing costs, much attention has focused on methods to degrade biomass into renewable commodity-chemical building blocks. Reported here is a powerful complementary approach that instead amplifies the complexity of molecular structures present in plant materials. Essential-oil phenylpropenoids are transformed via acrylate cross-metathesis into potent antioxidants that are widely used in perfumery and cosmetics, and in treating disorders associated with oxidative damage.

Author Contributions: The content of this manuscript was written by JAML and DEF. The initial catalytic conditions were based on preliminary unpublished results provided by KCO and AGS. The experiments ultimately presented in the manuscript are the work of JAML; AMTP (a second-year undergraduate student working with JAML) isolated and characterized all cross-metathesis products. The paradigm shift from reducing natural complexity by ethenolysis to building on natural complexity using cross-metathesis was conceived by DEF and ENdS.

5.2. Synthesis of High-Value Molecules from Essential Oils

5.2.1. Introduction

Olefin metathesis, as a technology that enables direct modification of the internal C=C bonds of unsaturated fats and oils, has enormous potential in the transition from petrochemicals to renewable feedstocks.^{5,37-39} The dominant focus is on degrading seed oils

into α -olefin,^{5,38-40} ester,^{24,41} or nitrile^{24,42} building blocks for commodity manufacturing (**Figure 5.2a**). Terpenes can be treated similarly, yielding products that span the commodity and fine-chemicals sectors (**Figure 5.2b**).^{21,43} Essential oils, in comparison, offer potential access to high-value, low-tonnage products. Abundant in these volatile oils are phenylpropenoids: functionalized phenol derivatives that are challenging to synthesize, which represent important fine-chemical building blocks. Here we describe the use of olefin metathesis to elaborate essential-oil phenylpropenoids into powerful antioxidants that represent key products and platforms for the personal care market (**Figure 5.2c**). This represents a paradigm shift in biomass utilization from degradation to enhancement: that is, adding to the complexity of structures assembled by Nature, rather than breaking these entities down into simple building blocks that must then be reassembled.

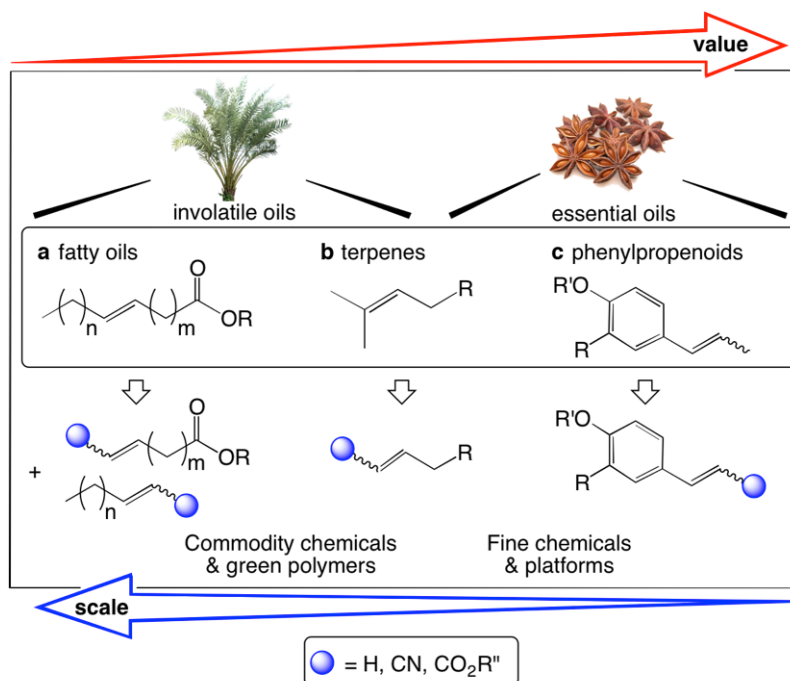


Figure 5.2. Existing (a, b) and proposed (c) approaches to "renewables metathesis".

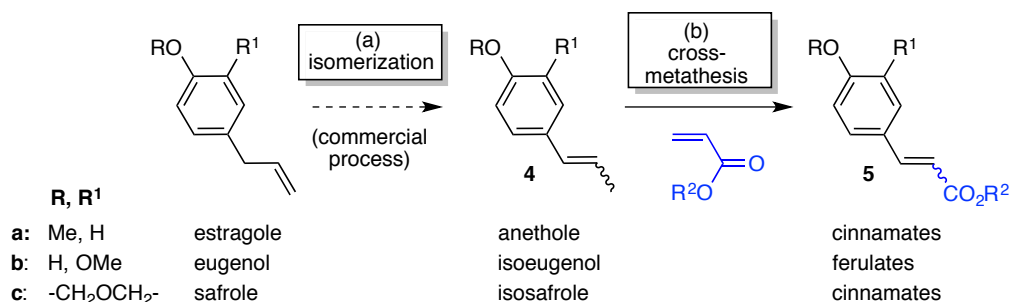
Phenylpropenoids such as safrole, eugenol, and estragole are major constituents of essential oils. Existing commercial processes (**Scheme 5.1a**) transform these allylbenzenes into their conjugated isomers isosafrole, isoeugenol, and anethole; the latter two are also abundant in some essential oils.⁴⁴ These compounds have long been regarded as renewable

synthons.^{45,46†} Anethole **4a** is produced on largest scale (750,000 t/y), from star anise, anise, and fennel, as well as turpentine oils from wood processing; additional amounts are generated by isomerization of estragole.^{44,47} Production of eugenol and safrole is lower, approaching 2,000 t/y each from commercial and clandestine sources,⁴⁸ but all three represent low-tonnage, high-value renewables. Notable derivatives range from fragrance components to piperonyl butoxide (an essential synergist for natural pyrethrum insecticides), and the recreational drug 3,4-methylenedioxymethamphetamine, MDMA.⁴⁸

Olefin metathesis creates new opportunities to amplify the scope and value of these building blocks, via elaboration into (e.g.) conjugated esters (**5**, **Scheme 5.1b**).[‡] Such entities are important in the billion-dollar perfumery and cosmetics industries. UVB-absorbing cinnamates potentially accessible from anethole, for example, are now widely used as the active ingredients in sunscreens and cosmetics.^{45,53} More generally, the potent antioxidant properties of these compounds has focused attention on their potentially protective role in disorders associated with oxidative damage, including arthritis and other inflammatory diseases, coronary thrombosis, neurodegeneration, and some cancers.⁵⁴⁻⁵⁸

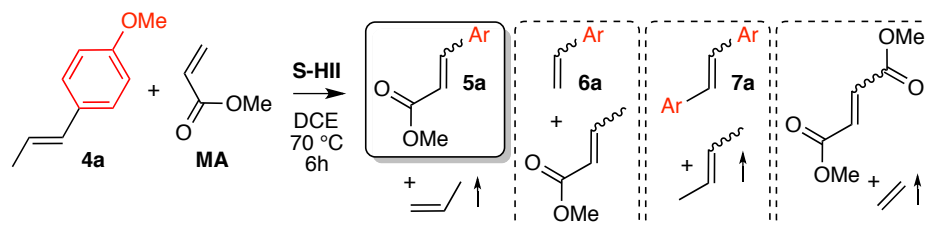
[†] Safrole is obtained chiefly from sassafras oil, produced by the destructive felling of slow-growing trees (e.g. *Cinnamomum Camphora*), particularly in south-east Asia. Proposed as a more sustainable source is "pimenta-longa" (*Piper hispidinervium*), a pioneer shrub in degraded Amazonian forest land, and a high-value alternative crop for the tropical rainforest. Its essential oil (90–94% safrole) is extracted from the leaves and thin branches; see Ref. (46).

[‡] Non-conjugated products result from cross-metathesis of the terminal olefin in eugenol (and *O*-protected eugenol derivatives) with electron-deficient olefins. Of particular relevance to the present work is a recent, systematic study that describes problems with competing isomerization. Isomerization-metathesis reactions proceed via isoeugenol, resulting in formation of **5** as a byproduct. Isomerization was inhibited by adding 1,4-benzoquinone. See Ref. (49). Other instances of eugenol or estragole cross-metathesis have appeared: See Ref. (50), (51), (52).



Scheme 5.1. Strategy for elaboration of phenylpropenoids (for specific acrylates explored, see **Table 5.2**).

The classical Perkin condensation route to cinnamic acid itself requires 8-12 h at $>180\text{ }^{\circ}\text{C}$, and yields reach only ca. 80%.⁵⁹ Conventional routes to *functionalized* cinnamates rely on multistep, stoichiometric processes.⁶⁰ Catalytic cross-coupling of halogenated aromatics offers improvements, but remains wasteful.⁶¹ Cross-metathesis (CM) of β -methylstyrene phenylpropenoids offers a potentially succinct, powerful alternative with several compelling features. First, Nature has already addressed the challenge of conjugating a C=C bond with the functionalized phenol. Second, CM of the near-terminal olefin in **4** eliminates the unwanted olefinic substituent as volatile propylene (**Scheme 5.2**). This sidesteps the purification issues inherent in metathesis of "deep-internal" unsymmetrical olefins (**Figure 5.2**); i.e. formation of two product streams requiring separation. Third, the electron-deficiency of the acrylate olefin inhibits self-metathesis,¹⁴ enabling use of acrylate in excess to minimize homocoupling of **4**. In sum, these features offer a powerful opportunity for clean capture and elaboration of the valuable phenylpropenoid moiety.



Scheme 5.2. Cross metathesis of anethole with methyl acrylate.

5.2.2. Results and Discussion

While self-metathesis⁶² and CM⁴⁹⁻⁵² of anethole have been reported, the intended cross-metathesis reaction poses a greater challenge to reactivity, owing to the electronic

deactivation of the acrylate combined with the steric deactivation of the predominantly trans-configured double bond in the precursors **4**. Impressive efficiencies have been achieved in CM of internal olefins with acrylates using the Hoveyda catalyst **S-III**,^{5,41,63} however, and we thus sought to build on these advances. In probe experiments, we employed anethole with a fourfold excess of methyl acrylate (MA) at high catalyst loadings (2 mol %); elevated temperatures were also required (**Scheme 5.2**) Efficient volatilization of propylene and ethylene byproducts is essential to promote selectivity for the desired CM reaction. Near-quantitative yields of **5a** were attained within 6 h by stirring in open vessels in the glovebox: (**Table 5.1**, entry 1.[†] Yields of **5a** decline as the headspace is reduced, as shown most dramatically in entry 2). On decreasing the catalyst loading to 0.1 mol % **S-III** (**Table 5.1**, entry 3), yields of **5a** drop to 78% at 6 h. They increase by only 2% after 12 h, consistent with catalyst deactivation. Dropwise infusion of **S-III**, a protocol that has proven effective in other contexts,^{41,64} gave essentially identical results (**Table 5.1**, entry 4). At a catalyst loading of 0.5 mol %, however, yields of **5a** were restored to 97% (**Table 5.1**, entry 5), and this was used as a baseline for further improvement.

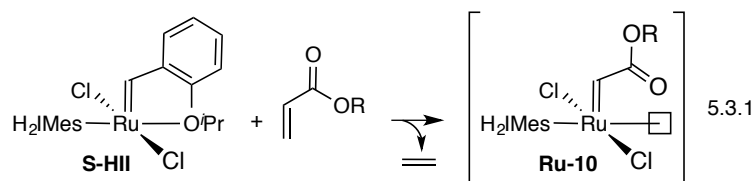
Table 5.1. Maximizing cross-metathesis selectivity for cinnamate **5a**.^a

Entry	mol % S-III	Equiv MA	% Conv	% Yield			% <i>E</i> (for 5a)
				5a	6a	7a	
1	2	4	100	99	0	0	97
2 ^b	2	4	100	72	15	6	99
3	0.1	4	99	78	2	18	>99
4 ^c	0.1	4	99	82	2	15	>99
5	0.5	4	100	97	0	3	99
6	0.5	2	100	90	2	7	99
7	0.5	10	100	93	0	5	98
8	0.5	20	97	89	1	6	99
9	0.5	6	100	99	0	1	99

^aConversions based on anethole **4a**; yields are relative to the sum of anisole derivatives. ^b10% headspace; unidentified byproducts present. ^cCatalyst added over 4 h (syringe pump).

[†] Reactions were carried out in open Schlenk vessels in the glovebox, for ease of monitoring. Use of a Schlenk manifold gave less satisfactory reproducibility, owing to the introduction of air during sampling.

In the experiments above, we employed excess acrylate to minimize self-metathesis of **4a** (i.e. formation of stilbenoid **7a**). A disadvantage of high acrylate concentrations, however, is faster catalyst deactivation. Efficient CM of acrylates is promoted by reaction of the catalyst with the olefinic coupling partner. Direct reaction with acrylate would give unstable ester-alkylidene **Ru-10** (Eqn 5.3.1), and hence accelerate decomposition.[†]



Additional experiments were therefore carried out to establish optimal acrylate loadings. At 2 equivalents MA (**Table 5.1**, entry 6), **4a** is fully consumed, but yields of **5a** drop to 90%, owing to buildup of the sterically deactivated stilbenoid **7a**. At 10 equiv (**Table 5.1**, entry 7), yields of **5a** are likewise poor, in this case reflecting increased catalyst decomposition. (Indeed, at 20 equiv MA, this effect is sufficient to inhibit complete conversion of anethole; **Table 5.1**, entry 8). Use of 6 equiv MA, however, represents a "sweet spot" at which formation of **5a** is essentially quantitative: no evidence is seen of the vinylnisole intermediate **6a**, and the proportion of stilbenoid **7a** drops to 1% (**Table 5.1**, entry 9; see also entry 1).

The corresponding reactions of isoeugenol and isosafrole yield **5b** (99%) and **5c** (97%; **Table 5.2**, entries 2, 3). Indicative of the potentially broad scope of this methodology, comparable or higher yields were achieved with ethyl acrylate (**Table 5.2**, entries 4-6) and, of particular note, 2-ethylhexylacrylate (**Table 5.2**, entries 7-9). Reaction of the latter with anethole generates the important sunscreen agent octylmethoxycinnamate in 99% yield (**Table 5.2**, entry 7). Reactions on 1 g scale proceeded over 15-22 h to give the desired compounds in 81-98% isolated yield. The lower values reflect the similar polarity of the targets, vs. the maleate / fumarate products of acrylate coupling.

[†] In prior work, small amounts of a related, PCy₃-stabilized ester-alkylidene (observed by NMR analysis) were found to rapidly decompose in solution. See Ref. (65).

Table 5.2. Expanding the scope of arylpropenoid cross-metathesis.^a

Entry	Acrylate	Phenyl-propenoid	% Conv	% Yield ^b	% <i>E</i>
1	methyl	4a	100	99 (83)	99
2		4b	100	99 (90)	98
3		4c	100	97 (85)	99
4	ethyl	4a	100	99 (85)	>99.5
5		4b	100	100 (95)	99.5
6		4c	100	98 (90)	99
7	2-ethylhexyl	4a	100	99 (89)	99.5
8		4b	100	>99 (98)	>99.5
9		4c	100	98 (81)	99.5

^aConditions as in Scheme 2 (6 equiv acrylate). Conversions based on **4**, yields on **5**. ^bIsolated yields given in brackets.

5.2.3. Conclusions

To date, the overwhelming focus in biomass utilization has been on degrading renewable resources into the basic chemical building blocks central to chemical manufacturing. Olefin metathesis creates new opportunities in two respects: it enables net augmentation, rather than degradation of biomass, and it enables capture of complex structures relevant to fine chemicals markets. These concepts are illustrated above by the succinct synthesis of high-value *E*-cinnamate and *E*-ferulate esters from the renewable phenylpropenoids anethole, isoeugenol, and isosafrole. The general approach, in which metathesis is used to capture and elaborate synthetically demanding structural motifs assembled by Nature, represents a powerful, potentially versatile platform for sustainable synthesis. From a broader perspective, these methodologies offer potential for economic expansion via the sustainable cultivation and elaboration of high-return source species in the tropical countries that represent the major producers of essential oils.

5.2.4. Experimental Details for Section 5.1

General Procedures

Reactions were carried out in an N₂-filled glove-box or under Ar on a Schlenk line. Dry, oxygen-free dichloroethane was obtained by pre-drying over CaSO₄ for 12 h, then refluxing over P₂O₅ for 6 h prior to distillation. The dry solvent was then stored in the glovebox in an

amber bottle over 5 Å molecular sieves. Acrylates (Sigma-Aldrich; 99% (methyl, ethyl); 98% (ethylhexyl)) were used without removing the phenolic stabilizers, given evidence that closely related phenols are not detrimental in acrylate metathesis.³⁵ The purity of the arylpropene substrates was confirmed by gas chromatography (GC) analysis prior to use; isosafrole (Pflatz & Bauer, 98%; *E:Z* 4:1) was purified by passing through neutral alumina prior to use to remove a yellow contaminant. Acrylates and phenylpropenes were degassed by five freeze-pump-thaw degassing cycles, and stored protected from light under N₂ in the glovebox freezer (-35 °C). *trans*-Anethole (99%), isoeugenol (98%; *E:Z* 9:1), catalyst **S-III**, and anhydrous decane (internal standard for gas chromatography) were purchased from Sigma-Aldrich. NMR solvents (CDCl₃, Sigma-Aldrich; CD₃OD, Cambridge Isotopes) were used as received. Samples for gas chromatography were diluted in CH₂Cl₂ (ACS reagent grade).

NMR spectra were recorded on a Bruker Avance 300 or 500 MHz spectrometer at 298 K, and referenced to the residual proton or carbon signals of the deuterated solvent (¹H, ¹³C{¹H} NMR). Signals are reported in ppm, relative to TMS (¹H, ¹³C) at 0 ppm. GC quantification was performed on an Agilent 7890A Series GC equipped with a flame ionization detector (FID), an Agilent 7683B Series autosampler and an Agilent HP-5 polysiloxane column (30 m length, 320 µm diameter), using an inlet split ratio of 10:1, an inlet temperature of 250 °C, and helium (UHP grade) as the carrier gas to maintain column pressure at 11.512 psi. The FID response was maintained between 50-2000 pA, using analyte concentrations of ca. 5 mM. Retention times for acrylates, phenylpropene **4a-c**, ester **5a**,⁶⁶ styrenyl byproduct **6a**,⁶⁷ and stilbenoid **7a**⁶⁸ were confirmed by comparison with authenticated samples (NMR spectra confirmed by comparison to literature values). Calibration curves (peak areas vs. concentration) were constructed in the relevant concentration regime, to account for the dependence on detector response for substrates, products and decane (internal standard in catalytic runs). Yields in catalytic runs were determined from the integrated peak areas, referenced against decane, and compared to the substrate: decane integration ratio at time zero (*t*₀). Conversions of isoeugenol **4b** and isosafrole **4c** were assessed by GC-FID, but quantification of the products for these reactions by GC-FID was hampered by poor peak shapes for stilbenoids **7b** and **7c**, which also "bleed" over subsequent runs. Yields of the methyl esters of ferulate **5b**, cinnamate **5c**, and all ethyl and 2-ethylhexyl esters (**5a'-c'**, **5a''-**

c'') were quantified by NMR analysis, by mutual integration of well-isolated signals: 1H for **5b-c**, **5a'-c'**, **5a''-c''** and **5a-c**; 2H for **7c**; 6H for **7a-b**. NMR assignments for compounds **5b**,⁶⁹ **5c**,⁷⁰ **5a'**,⁷¹ **5b'**,⁷² **5c'**,⁷³ **5a''**,⁷⁴ **6a**,⁶⁷ **6b**,⁷⁵ **6c**,⁷⁶ **7a**,⁶⁸ **7b**,⁷⁷ and **7c**⁷⁸ were confirmed by comparison to reported values. Characterization data for compounds **5b''** and **5c''** are given below.

Details of Cross-Metathesis Procedures. Stock solutions of substrate were prepared by diluting the appropriate amount of substrate (anethole: 296.3 mg; isoeugenol: 328.4 mg; isosafrole: 324.3 mg; all 2.000 mmol) and decane (284.5 mg, 2.000 mmol) with dichloroethane to 330 mM. An aliquot was removed from the stock solution for GC analysis to establish the integration of substrate relative to decane at time zero (t_0). Stock solutions of catalyst **S-III** were prepared by dissolving 12.6 mg (0.0200 mmol) of **S-III** in 1.0 mL of dichloroethane to generate a 20 mM solution of **S-III**. All stock solutions were prepared immediately prior to use.

In a representative catalytic probe reaction, 1.5 mL of the substrate stock solution (0.50 mmol) was added to a 50 mL Schlenk tube equipped with a magnetic stir bar. Methyl acrylate (270 μ L, 3.0 mmol, 6 equiv) was added. The solution was diluted with dichloroethane to 2.5 mL, giving a final substrate concentration of 0.20 mM. (In the experiment with 20 equiv methyl acrylate, the final volume was 3.4 mL, corresponding to an anethole concentration of 0.15 mM). The appropriate volume of catalyst stock solution was added (0.5 mol % Ru: 125 μ L). Reactions were then heated at 70 °C (sand-bath) in an N₂-filled glovebox for 6 h. A colour change from green to brown-yellow occurred within 5 min. The initial reactions between anethole and methyl acrylate (see **Table 5.1**) were left open to a freshly purged glovebox atmosphere for the duration of the reaction, with periodic purging (every 2 h) to maintain quality of atmosphere. From gram-scale reactions, it was observed that gas evolution is rapid over the first 30 minutes, but minimal thereafter, and no difference was evident between reactions carried out in 50 mL Schlenk tubes that were sealed, vs. open to the glovebox atmosphere. Subsequent reactions (Table 2) were therefore left open for the first 30 minutes, and then sealed to minimize the odor associated with the acrylates. After 6 h, samples were analyzed: at this point the reactions remained brown-yellow, homogeneous solutions.

Gram-Scale Synthesis of Cinnamate and Ferulate Esters, 5a-c, 5a'-c', 5a''-c''.

Preparative-scale CM experiments were carried out on a Schlenk line under Ar. In the glovebox, a 100 ml Schlenk tube was charged with 800 mg of substrate (anethole **4a**: 5.4 mmol; isoeugenol **4b**: 4.8 mmol; isosafrole **4c**: 4.2 mmol), acrylate (6 equiv), and **S-HII** (0.5 mol %) and diluted with dichloroethane to 200 mM. The reaction vessel was then removed to a Schlenk line, and the reaction was heated under a slow flow of argon at 70 °C, using a thermocouple to maintain the oil-bath temperature. Heating was carried out for 15-22 h, with consumption of arylpropene being confirmed by GC analysis prior to workup. The solvent was then removed using a rotary evaporator. Crude products were purified by column chromatography on silica gel 60. Solvent systems: for **5a'** and **5c''**, 1:1 CH₂Cl₂:hexanes; for **5a**, **5c**, and **5c'**, 2:1 CH₂Cl₂:hexanes; for **5b** and **5b'**, 1:3 EtOAc:hexanes, for **5b''**, 1:5 EtOAc:hexanes; for **5a''**, 1:19 EtOAc:hexanes.

(E)-2-Ethylhexylferulate, 5b''. ¹H NMR spectrum (300.1 MHz, CDCl₃): δ 7.60 (d, ²J_{HH} = 15.8 Hz, 1H), 7.08 (dd, ³J_{HH} = 8.1 Hz, ⁴J_{HH} = 2.0 Hz, 1H), 7.04 (d, ⁴J_{HH} = 2.0 Hz, 1H), 6.92 (d, ³J_{HH} = 8.1 Hz, 1H), 6.29 (d, ²J_{HH} = 15.8 Hz, 1H), 5.88 (s, 1H), 4.11 (dd, ³J_{HH} = 6.0 Hz, ⁴J_{HH} = 1.7 Hz, 2H), 3.93 (s, 3H), 1.65 (m, 1H), 1.48-1.24 (overlapping multiplets, 8H), 0.96-0.86 (2 overlapping triplets, 6H). ¹³C{¹H} (75.5 MHz, CDCl₃): δ 167.7, 148.0, 146.9, 144.7, 127.2, 123.2, 115.9, 114.8, 109.4, 67.0, 56.1, 39.0, 30.6, 29.1, 24.0, 23.2, 14.2, 11.2. IR (neat, cm⁻¹) 3384 (s), ν(O-H); 1701 (s), ν(C=O). Anal. Calcd. for C₁₈H₂₆O₄: C, 70.56%; H, 8.55%. Found: C, 70.59%; H, 8.76%.

(E)-2-Ethylhexyl-3,4-(methylenedioxy)cinnamate, 5c''. ¹H NMR spectrum (300.1 MHz, CDCl₃): δ 7.58 (d, ²J_{HH} = 15.9 Hz, 1H), 7.04 (d, ⁴J_{HH} = 1.7 Hz, 1H), 7.00 (dd, ³J_{HH} = 8.0 Hz, ⁴J_{HH} = 1.7 Hz, 1H), 6.81 (d, ³J_{HH} = 8.0 Hz, 1H), 6.27 (d, ²J_{HH} = 15.9 Hz, 1H), 6.00 (s, 2H), 4.10 (dd, ³J_{HH} = 5.9 Hz, ⁴J_{HH} = 1.5 Hz, 2H), 1.64 (m, 1H), 1.49-1.22 (overlapping m, 8H), 0.97-0.84 (overlapping t, 6H). ¹³C{¹H} (75.5 MHz, CDCl₃): δ 167.6, 149.7, 148.5, 144.3, 129.1, 124.5, 116.4, 108.7, 106.6, 101.7, 67.0, 39.0, 30.6, 29.1, 24.0, 23.1, 14.2, 11.2. IR (neat, cm⁻¹) 1704 (s), ν(C=O). Anal. Calcd. for C₁₈H₂₄O₄: C, 71.03%; H, 7.95%. Found: C, 70.78%; H, 8.12%.

5.3. Subsequent Advances

The chemistry of Section 5.2 may be expanded by post-metathesis transesterification. The methyl esters obtained by use of methyl acrylate as a CM partner are well suited for transesterification with larger alcohols under acidic conditions. Removal of the methanol product by distillation would aid in driving the reaction to completion.

The basis for the improved performance of **S-HII** in acrylate CM remains incompletely understood. One plausible contributor is the “release-return” mechanism for **S-HII**.⁷⁹ According to this mechanism, a molecule of *o*-isopropoxystyrene is liberated during the catalyst initiation, but can re-enter the metathesis cycle, recapturing the four-coordinate catalyst once the concentration of the metathesis substrate(s) is depleted. Shuttling from this protected recapture cycle into the productive metathesis cycle has been presumed to contribute to the improved performance of **S-HII** relative to **S-GII** (Figure 5.3).

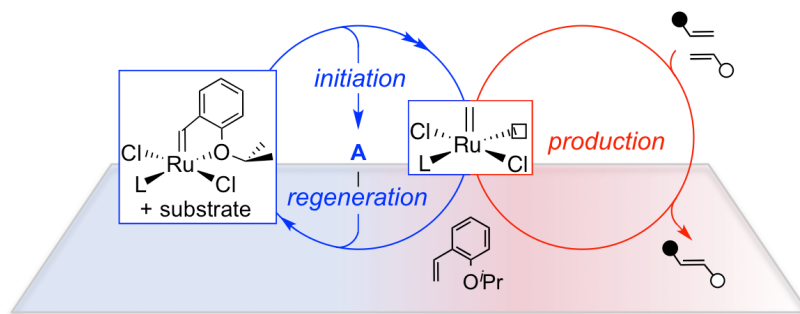


Figure 5.3. Shuttling of **HII** between protected initiation cycle (blue) and productive metathesis cycle (red).

Whether the “release-return” mechanism is actually operative has been the subject of long debate.^{32,80-82} We recently examined this point,^{83†} using ¹³C-labelled crossover experiments. Highly efficient release and recapture of *o*-isopropoxystyrene was demonstrated for **S-HII** during RCM and CM of challenging substrates. (It may be noted that these catalysts had been widely assumed to turn on rather sluggishly: in fact, it proved facile, meaning that **HII** readily enters into the metathesis cycle). Uptake of the styrenyl ether was also rapid, meaning the the resting state for the catalyst is thus **S-HII** itself (which is sterically protected against deactivation), but the catalyst shuttles readily in and out of the active cycle.

[†] This chemistry was described in the M.Sc. thesis of Jennifer M. Bates (84).

Perhaps the most important aspect of this study, however, was the finding that adding additional *o*-isopropoxystyrene to reactions catalyzed by **S-HII** inhibited metathesis, without increasing overall turnover numbers. We conclude that the release-return mechanism, while operative, is not in fact responsible for the improved productivity observed for **HII**. Work by Gwendolyn Bailey of this research group has recently pinpointed poisoning by PCy₃ as the key contributor to the poorer performance of **GII**. Broadly, this implies that the PCy₃ ligand in the Grubbs catalyst acts as a latent poison. It traps the active four-coordinate methyldiene in a five-coordinate resting state that is slow to re-enter the catalytic cycle, and it can also directly attack the vulnerable ruthenium methyldiene (see Chapter 4). While facile cycling of **HII** between the protected pre-catalyst and the vulnerable resting state is important, the real advance of the styrenyl ether ligand is the lower bulk and donicity of the styrenyl ether donor, which permits associative pathways that help promote activation. Also key is the minimal basicity of the ether ligand, which – unlike free PCy₃ – does not participate in nucleophilic attack at the vulnerable methyldiene site.

5.4. References

- (1) Le Ravalec, V.; Dupe, A.; Fischmeister, C.; Bruneau, C. *ChemSusChem* **2010**, *3*, 1291–1297.
- (2) Marinescu, S. C.; Schrock, R. R.; Muller, P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 10840–10841.
- (3) Le Ravalec, V.; Fischmeister, C.; Bruneau, C. *Adv. Synth. Catal.* **2009**, *351*, 1115–1122.
- (4) Mecking, S.; Chikkali *Angew. Chem., Int. Ed.* **2012**, *51*, 5802–5808.
- (5) Biermann, U.; Bornscheuer, U.; Meier, M. A. R.; Metzger, J. O.; Schafer, H. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 3854–3871.
- (6) Wolf, S.; Plenio, H. *Green Chem.* **2011**, *13*, 2008–2012.
- (7) Bidange, J.; Dubois, J.-L.; Couturier, J.-L.; Fischmeister, C.; Bruneau, C. *Eur. J. Lipid Sci. Technol.* **2014**, *116*, 1583–1589.
- (8) Miao, X.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *ChemSusChem* **2008**, *1*, 813–816.
- (9) Thomas, R. M.; Keitz, B. K.; Champagne, T. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2011**, *133*, 7490–7496.
- (10) Park, C. P.; Van Wingerden, M. M.; Han, S.-Y.; Kim, D.-P.; Grubbs, R. H. *Org. Lett.* **2011**, *13*, 2398–2401.
- (11) Schrodi, Y.; Ung, T.; Vargas, A.; Mkrtumyan, G.; Lee, C. W.; Champagne, T. M.; Pederson, R. L.; Hong, S. H. *Clean Soil, Air, Water* **2008**, *36*, 669–673.
- (12) Behr, A.; Krema, S.; Kaemper, A. *RSC Adv.* **2012**, *2*, 12775–12781.
- (13) van der Klis, F.; Le Notre, J.; Blaauw, R.; van Haveren, J.; van Es, D. S. *Eur. J. Lipid Sci. Technol.* **2012**, *114*, 911–918.

- (14) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.
- (15) Grela, K., *Olefin Metathesis-Theory and Practice*. Wiley: Weinheim, 2014.
- (16) Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Rev.* **2010**, *110*, 1746–1787.
- (17) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.
- (18) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.
- (19) van Lierop, B. J.; Lummiss, J. A. M.; Fogg, D. E., Ring-Closing Metathesis. In *Olefin Metathesis-Theory and Practice*, Grela, K., Ed. Wiley: Hoboken, NJ, 2014; pp 85–152.
- (20) Miao, X.; Fischmeister, C.; Dixneuf, P. H.; Bruneau, C.; Dubois, J. L.; Couturier, J. L. *Green Chem.* **2012**, *14*, 2179–2183.
- (21) Bilel, H.; Hamdi, N.; Zagrouba, F.; Fischmeister, C.; Bruneau, C. *Green Chem.* **2011**, *13*, 1448–1452.
- (22) Malacea, R.; Fischmeister, C.; Bruneau, C.; Dubois, J.-L.; Couturier, J.-L.; Dixneuf, P. H. *Green Chem.* **2009**, *11*, 152–155.
- (23) Djigoué, G. B.; Meier, M. A. R. *Applied Catal. A* **2009**, *368*, 158–162.
- (24) Rybak, A.; Meier, M. A. R. *Green Chem.* **2007**, *9*, 1356–1361.
- (25) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543–6554.
- (26) Ashworth, I. W.; Hillier, I. H.; Nelson, D. J.; Percy, J. M.; Vincent, M. A. *ACS Catal.* **2013**, *3*, 1929–1939.
- (27) Ashworth, I. W.; Hillier, I. H.; Nelson, D. J.; Percy, J. M.; Vincent, M. A. *Chem. Comm.* **2011**, *47*, 5428–5430.
- (28) Nelson, D. J.; Carboni, D.; Ashworth, I. W.; Percy, J. M. *J. Org. Chem.* **2011**, *76*, 8386–8393.
- (29) Vorfalt, T.; Wannowius, K. J.; Plenio, H. *Angew. Chem. Int. Ed.* **2010**, *49*, 5533–5536.
- (30) Thiel, V.; Hendann, M.; Wannowius, K.-J.; Plenio, H. *J. Am. Chem. Soc.* **2012**, *134*, 1104–1114.
- (31) Garzon, C.; Attolini, M.; Maffei, M. *Eur. J. Org. Chem.* **2013**, *2013*, 3653–3657.
- (32) Bieniek, M.; Michrowska, A.; Usanov, D. L.; Grela, K. *Chem. Eur. J.* **2008**, *14*, 806–818.
- (33) Michrowska, A.; Bujok, R.; Harutyunyan, S.; Sashuk, V.; Dolgonos, G.; Grela, K. *J. Am. Chem. Soc.* **2004**, *126*, 9318–9325.
- (34) Buschmann, N.; Wakamatsu, H.; Blechert, S. *Synlett* **2004**, 667–670.
- (35) Forman, G. S.; Tooze, R. P. *J. Organomet. Chem.* **2005**, *690*, 5863–5866.
- (36) Forman, G. S.; McConnell, A. E.; Tooze, R. P.; Van Rensburg, W. J.; Meyer, W. H.; Kirk, M. M.; Dwyer, C. L.; Serfontein, D. W. *Organometallics* **2005**, *24*, 4528–4542.
- (37) Sheldon, R. A. *Catal. Today* **2011**, *167*, 3–13.
- (38) Mol, J. C. *Green Chem.* **2002**, *4*, 5–13.
- (39) Corma, A.; Iborra, S.; Vely, A. *Chem. Rev.* **2007**, *107*, 2411–2502.
- (40) Burdett, K. A.; Harris, L. D.; Margl, P.; Maughon, B. R.; Mokhtar-Zadeh, T.; Saucier, P. C.; Wasserman, E. P. *Organometallics* **2004**, *23*, 2027–2047.
- (41) Miao, X.; Malacea, R.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Green Chem.* **2011**, *13*, 2911–2919.
- (42) Miao, X.; Dixneuf, P. H.; Fischmeister, C.; Bruneau, C. *Green Chem.* **2011**, *13*, 2258–2271.
- (43) Borré, E.; Dinh, T. H.; Caijo, F.; Crévisy, C.; Mauduit, M. *Synthesis* **2011**, 2125–2130.

- (44) Fahlbusch, K.-G.; Hammerschmidt, F.-J.; Panten, J.; Pickenhagen, W.; Schatkowski, D., Flavors and Fragrances. In *Ullman's Encyclopedia of Industrial Chemistry (Electronic Release)*, Wiley-VCH: Weinheim, 2012.
- (45) Milne, G. W., *Gardner's Commercially Important Chemicals*. Wiley & Sons: Hoboken, 2005; p 547.
- (46) Maia, J. G. S.; Andrade, E. H. A. *Quim. Nova* **2009**, *32*, 595–622.
- (47) Sharma, S. K.; Srivastava, V. K.; Jasra, R. V. *J. Mol. Catal. A* **2006**, *245*, 200–209.
- (48) Chawla, S., *World Drug Report*. United Nations Office on Drugs and Crime: New York, 2010; p 111.
- (49) Bilel, H.; Hamdi, N.; Zagrouba, F.; Fischmeister, C.; Bruneau, C. *RSC Adv.* **2012**, *2*, 9584–9589.
- (50) Broggi, J.; Urbina-Blanco, C. A.; Clavier, H.; Leitgeb, A.; Slugovc, C.; Slawin, A. M. Z.; Nolan, S. P. *Chem. - Eur. J.* **2010**, *16*, 9215–9225.
- (51) Moiese, J.; Arseniyadis, S.; Cossy, J. *Org. Lett.* **2007**, *9*, 1695–1698.
- (52) Taber, D. F.; Frankowski, K. J. *J. Chem. Educ.* **2006**, *83*, 283–284.
- (53) Paye, M.; O. Barel, A.; Maibach, H. I., *Handbook of Cosmetic Science and Technology*. 2nd Ed. ed.; Taylor and Francis: New York, 2006; p 306.
- (54) Hu, L. H.; Zou, H. B.; Gong, J. X.; Li, H. B.; Yang, L. X.; Cheng, W.; Zhou, C. X.; Bai, H.; Gueritte, F.; Zhao, Y. *J. Nat. Prod.* **2005**, *68*, 342–348.
- (55) Ou, S. Y.; Kwok, K. C. *J. Sci. Food Agric.* **2004**, *84*, 1261–1269.
- (56) Graf, E. *Free Rad. Biol. & Med.* **1992**, *13*, 435–448.
- (57) Calabrese, V.; Guagliano, E.; Sapienza, M.; Panebianco, M.; Calafato, S.; Puleo, E.; Pennisi, G.; Mancuso, C.; Butterfield, D. A.; Stella, A. G. *Neurochem. Res.* **2007**, *32*, 757–773.
- (58) Chen, M. P.; Yang, S. H.; Chou, C. H.; Yang, K. C.; Wu, C. C.; Cheng, Y. H.; Lin, F. H. *Inflamm. Res.* **2010**, *59*, 587–595.
- (59) Eilerman, R. G., Cinnamic Acid, Cinnamic Aldehyde, and Cinnamyl Alcohol. In *Kirk-Othmer Encyclopedia of Chemical Technology (online edition)*, John Wiley & Sons, Inc. 2000.
- (60) Barma, D. K.; Kundu, A.; Bandyopadhyay, A.; Kundu, A.; Sangras, B.; Briot, A.; Mioskowski, C.; Falck, J. R. *Tetrahedron Lett.* **2004**, *45*, 5917–5920.
- (61) de Vries, J. G. *Can. J. Chem.* **2001**, *79*, 1086–1092.
- (62) Sauvage, X.; Borguet, Y.; Noels, A. F.; Delaude, L.; Demonceau, A. *Adv. Synth. Catal.* **2007**, *349*, 255–265.
- (63) Ho, T. T.; Jacobs, T.; Meier, M. A. R. *ChemSusChem* **2009**, *2*, 749–754.
- (64) Monfette, S.; Eyholzer, M.; Roberge, D. M.; Fogg, D. E. *Chem. Eur. J.* **2010**, *16*, 11720–11725.
- (65) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783–3784.
- (66) Senra, J. D.; Malta, L. F. B.; da Costa, M. E. H. M.; Michel, R. C.; Aguiar, L. C. S.; Simas, A. B. C.; Antunes, O. A. C. *Adv. Synth. Catal.* **2009**, *351*, 2411–2422.
- (67) Denmark, S. E.; Butler, C. R. *Org. Lett.* **2006**, *8*, 63–66.
- (68) Khartulyari, A. S.; Kapur, M.; Maier, M. E. *Org. Lett.* **2006**, *8*, 5833–5836.
- (69) Putt, K. S.; Nesterenko, V.; Dothager, R. S.; Hergenrother, P. J. *ChemBioChem* **2006**, *7*, 1916–1922.
- (70) Angle, S. R.; Choi, I.; Tham, F. S. *J. Org. Chem.* **2008**, *73*, 6268–6278.

- (71) Hyotanishi, M.; Isomura, Y.; Yamamoto, H.; Kawasaki, H.; Obora, Y. *Chem. Commun.* **2011**, 47, 5750–5752.
- (72) Vafiadi, C.; Topakas, E.; Wong, K. K. Y.; Suckling, I. D.; Christakopoulos, P. *Tetrahedron: Asymmetry* **2005**, 16, 373–379.
- (73) Sharma, A.; Sharma, N.; Sharda, A.; Kumar, R.; Mohanakrishnan, D.; Saima; Sinha, A. K.; Sahal, D. *Org. Biomol. Chem.* **2011**, 9, 5211–5219.
- (74) Monhaphol, T.; Albinsson, B.; Wanichwecharungruang, P. S. *J. Pharm. Pharmacol.* **2007**, 59, 279–288.
- (75) Lebel, H.; Ladjel, C. *Organometallics* **2008**, 27, 2676–2678.
- (76) Sharma, A.; Kumar, R.; Sharma, N.; Kumar, V.; Sinha, A. K. *Adv. Synth. Catal.* **2008**, 350, 2910–2920.
- (77) Li, L.; Seeram, N. P. *J. Agric. Food Chem.* **2011**, 58, 11673–11679.
- (78) Hua, G.; Li, Y.; Slawin, A. M. Z.; Woollins, J. D. *Dalton Trans.* **2007**, 1477–1480.
- (79) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, 121, 791–799.
- (80) Kingsbury, J. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, 127, 4510–4517.
- (81) Vorfalt, T.; Wannowius, K. J.; Thiel, V.; Plenio, H. *Chem. Eur. J.* **2010**, 16, 12312–12315.
- (82) Núñez-Zarur, F.; Solans-Monfort, X.; Pleixats, R.; Rodríguez-Santiago, L.; Sodupe, M. *Chem. Eur. J.* **2013**, 19, 14553–14565.
- (83) Bates, J. M.; Lummiss, J. A. M.; Bailey, G. A.; Fogg, D. E. *ACS Catal.* **2014**, 4, 2387–2394.
- (84) Bates, J. M. Ruthenium Catalysts for Olefin Metathesis: Understanding the Boomerang Mechanism and Challenges Associated with Stereoselectivity. M.Sc. Dissertation, University of Ottawa, Ottawa, ON, 2014.

Chapter 6. Conclusions and Future Directions

Fundamental research and applied research are often viewed as incompatible in their philosophies and objectives. The work described in this thesis illustrates the interplay that can (and arguably should) exist between these “opposites”. This work was aimed at improving our understanding of the organometallic chemistry of olefin metathesis, and using these insights to clarify the contributions of the various species present to catalyst deactivation, to understand the mechanisms underlying their vulnerability, and to identify potentially potent new directions for catalyst and reaction design.

Addressing these issues promises to realize the potential of metathesis as an enabling tool in sustainable chemical manufacturing. To date, high catalyst costs have limited industrial deployment of this Nobel-Prize winning technology. At the outset of this thesis work, no industrial processes had been developed using the molecular metathesis catalysts recognized with the Nobel Prize in 2005. That significant interest was present, however, was evident from the large number of scouting reports from pharma, chiefly describing bench-scale reactions. Best-known of these is the case of Ciluprevir.¹ Development of a viable synthetic route to this macrocyclic tripeptide was the goal of a decade-long program by Boehringer-Ingelheim. The anticipated market size and pricing for this HCV inhibitor was evidently regarded as sufficient to offset the significant research and development costs, as well as the direct catalyst costs.^{2,3}

While Ciluprevir ultimately failed in clinical trials due to its cardiac toxicity, 2014 has been a banner year for olefin metathesis. Simeprevir, a related HCV protease inhibitor co-developed by Medevir and Janssen Pharma, is the first pharmaceutical product using metathesis. It is also a blockbuster drug that is driving the profits necessary for commercial production. Despite this huge success, it is important to note that the disclosed route to this compound uses a catalyst loading of 2.5 mol%, for a yield of 80%.⁴ This represents a turnover number of just 32. While improvements were undoubtedly made during process optimization, this value should be compared with TONs approaching a thousand ultimately attained for Ciluprevir. The tolerance for such poor catalyst performance in a lead result illustrates both the value of the API target, and the limited synthetic options available. Few markets can tolerate the costs of such performance.

Beyond the world of blockbuster drugs, exciting developments are coming online at Elevance Renewable Sciences, with commissioning of the world's first metathesis bio-refinery. A joint venture with the Asian agrochemicals giant Wilmad, this plant is situated within Wilmad's Indonesia facility. Among the "high-value commodity" targets are surfactants, specialty waxes, lubricants, and personal care products, generated by metathesis of palm oil. Use of metathesis in this context is impressive, given the razor-thin profit margins in the commodity market. Against this, it should be noted that the Elevance products are high-performance compounds only attainable using metathesis technology. While Elevance does not disclose the conditions, yields, or catalysts used in their processes, an important aspect of their operation is undoubtedly Materia's involvement, which shields them from the full costs of catalyst deactivation. Even if Elevance has overcome the challenges of catalyst lifetime, disclosing their solutions to the community is unlikely to form part of their business plan. These developments underscore the potential of metathesis, but also highlight the need for improved understanding of the organometallic chemistry that governs catalyst behaviour. That is the focus of this thesis. In the summary of advances below, new opportunities are also discussed on a chapter-by-chapter basis.

Essential to developing an understanding of the second-generation Grubbs catalyst are reliable, high-yield, high-purity routes to the second-generation methylidene complexes. Such routes, described in Chapter 2, represent the single most important advance in facilitating study of these key species. Incorporation of ^{13}C labels in the methylidene and benzyldiene sites was a further advance that facilitates tracking of the alkylidene/methylidene moiety following deactivation. Additional studies using these labelled compounds illustrate their value in giving insight into the nature of the $\text{Ru}=\text{CHR}$ bond. In an illustrative example, the chemical shift tensors of the methylidene and benzyldiene complexes have been measured by solid-state NMR analysis. These studies have given the first insights into the much slower initiation characteristic of the resting state methylidene species relative to the precatalyst benzyldiene. Additionally, Adrian Botti from this research group is employing the ^{13}C -labelled methylidene complexes in crossover experiments to measure the rate and extent to which the methylidene species re-enters the catalytic cycle. Commitment is an important consideration in determining catalyst performance, but has to date frustrated all attempts at experimental quantification. These

systems represent the first experimentally viable means of assaying this property, a key element of catalyst design.

The unexpected impact of NHC saturation on catalyst lifetime is described in Chapter 3. The IMes ligand has generally been regarded as a poor man's H_2IMes , and has seen relatively little use in metathesis. An unexpected finding was the capacity of these NHC ligands to modulate the electron density at the metal in the Grubbs catalyst system. Higher net charge donation from the unsaturated NHC (a function of its much poorer π -acidity) results in a more electron-rich metal center. Compensating π -backbonding onto the trans- PCy_3 placeholder ligand accounts for the very low phosphine lability in the **GII**-IMes system, which results in longer lifetime, but low initiation efficiency. The impact on total turnover numbers of the dramatic decrease in lifetime for the H_2IMes methyldiene complex, relative to its IMes analogue, is a question currently being examined by Adrian Botti of the Fogg group.

In many ways, however, this finding contains a more fundamental lesson about catalyst design. Stronger charge donation limits turnover efficiency (where the trans-ligand is a π -acid). However, it is also expected to stabilize the Ru(IV) metallacyclobutane, and olefin activation. Taken together, these points lead to the conclusion that the NHC and the trans ancillary ligand must be chosen as a pair in order to optimize catalyst activity. Major opportunities for the IMes systems are anticipated from use of a non- π -acid ancillary ligand, which would accelerate both initiation and, potentially, propagation. This tightly-coupled relationship between permanent and placeholder ligands has not previously been acknowledged.

A theme explored in Chapter 4 is the vulnerability of the methyldiene ligand to nucleophilic attack. An unexpected finding was the tendency of small donors, such as amines, to induce decomposition via a two-step pathway, involving displacement of PCy_3 and attack of the liberated phosphine on the methyldiene carbon. Only when the amine is present in significant excess does it compete for attack at the methyldiene site. The scope of this "donor-induced deactivation" pathway is the subject of ongoing studies by William McClennan of this research group. Two important points are already apparent, however. First, this highlights a fundamental problem built into the Grubbs catalysts: the fact that they bear a ligand that is ultimately the agent of their own demise. Secondly, it suggests that the

nature of the ancillary ligands must be considered much more closely: any ligand that can act as a nucleophile is a potential methyldene poison.

Chapter 5 turns to the Hoveyda catalyst, in which the reduced basicity of the isopropoxystyrene ligand eliminates the direct problem of nucleophilic deactivation. This study highlights the difference between the two dominant metathesis catalysts in use today, the Grubbs and Hoveyda catalysts. These can be viewed as the two archetypal structures that define virtually all known ruthenium metathesis catalysts. In this analysis, the Grubbs catalyst is destined for deactivation by its PCy₃ ancillary ligand, whereas the Hoveyda catalyst carries no such suicide ligand. Moving forward, development of additional weakly nucleophilic stabilizing ligands is likely to be key to improving catalyst lifetime. Additional options worth considering are means for removing the ancillary ligand from the system, following release.

Chapter 5 also presents a new approach to renewable metathesis. The overwhelming focus in the application of metathesis to renewable feedstocks is “metathesis cracking”: that is, degrading unsaturated oils into simple mono-olefin building blocks. By augmenting on natural complexity rather than adding functionality to renewable feedstocks, higher-value fine chemical products are obtainable. This represents an alternative approach to “sustainable metathesis” which, as with the pharma examples, seeks to amortize high catalyst costs by targeting high-value targets. Efficient access to high-value cinnamates from renewable phenylpropenoids by cross metathesis with acrylate represents an important new approach to sustainable synthesis using metathesis.

As a final note, an area of research not addressed in this thesis but worthy of consideration centers on methodologies for recycling spent catalyst. A clever first example was recently published by the Schrodi group, which described methods for recovering and reactivating spent Hoveyda catalyst.⁵ The reported process is long and energy intensive (18 h at 67 °C), but it serves as an important proof of concept. In-situ methods to regenerate lost alkylidene, may ultimately prove a powerful means of increasing total turnover numbers, and of addressing purification costs.

The high-value and high-performance metathesis products highlighted above represent the tip of the iceberg in terms of the potential scope and impact of olefin metathesis. Continued advances in process efficiency will drive the evolution of this field. As financial barriers to

implementation are surmounted, metathesis technologies will reach their potential in sustainable chemical manufacturing. Such cost reductions in pharmaceutical manufacturing are essential to deliver large-scale treatment to emerging economies, at prices these markets can support.

6.1. References

- (1) Nicola, T.; Brenner, M.; Donsbach, K.; Kreye, P. *Org. Process Res. Dev.* **2005**, *9*, 513–515.
- (2) Georgopapadakou, N. *Expert Opin. Investig. Drugs* **2007**, *16*, 1-10.
- (3) Hinrichsen, H.; Benhamou, Y.; Wedemeyer, H.; Reiser, M.; Sentjens Roel, E.; Calleja Jose, L.; Forns, X.; Erhardt, A.; Cronlein, J.; Chaves Ricardo, L.; Yong, C.-L.; Nehmiz, G.; Steinmann Gerhard, G. *Gastroenterology* **2004**, *127*, 1347-1355.
- (4) Rosenquist, Å.; Samuelsson, B.; Johansson, P.-O.; Cummings, M. D.; Lenz, O.; Raboisson, P.; Simmen, K.; Vendeville, S.; Kock, H. d.; Nilsson, M.; Horvath, A.; Kalmeijer, R.; Rosa, G. d. l.; Beumont-Mauviel, M. *J. Med. Chem.* **2014**, *57*, 1673–1693.
- (5) Tabari, D. S.; Tolentino, D. R.; Schrodi, Y. *Organometallics* **2013**, *32*, 5-8.

Appendices

A. NMR Spectra

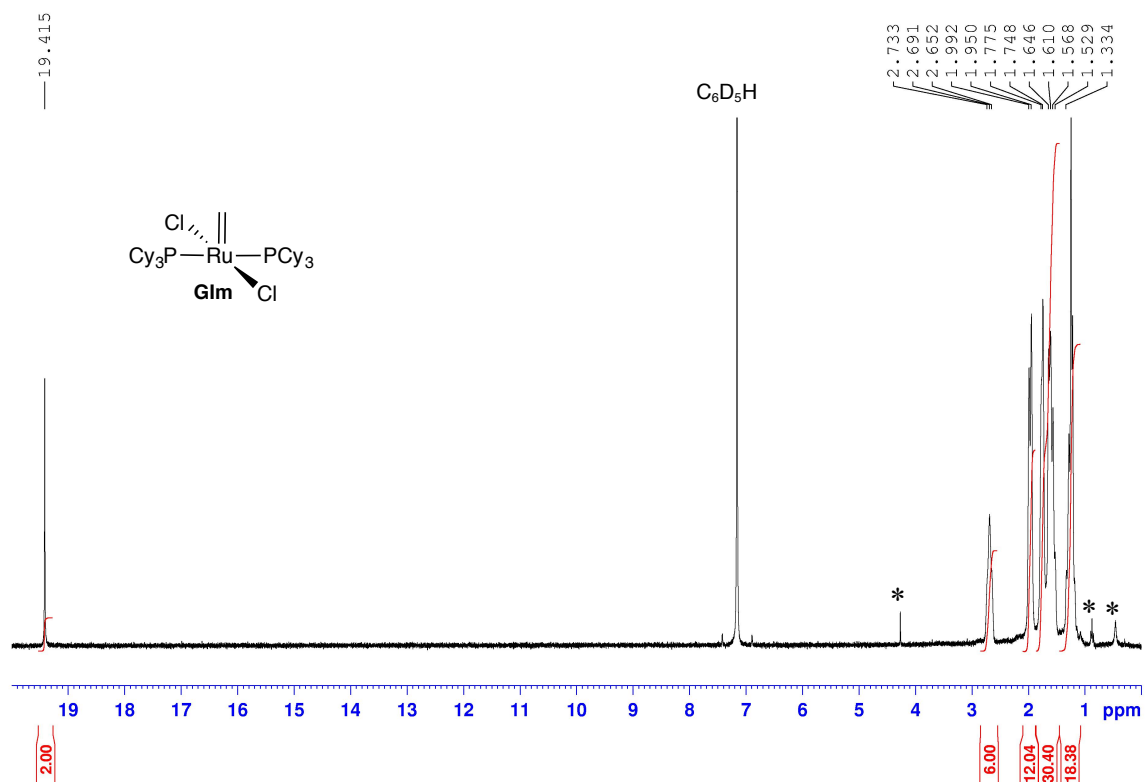


Figure A.1. ^1H NMR spectrum (300.1 MHz, C_6D_6) of **GIm**. Residual solvent is designated by (*).

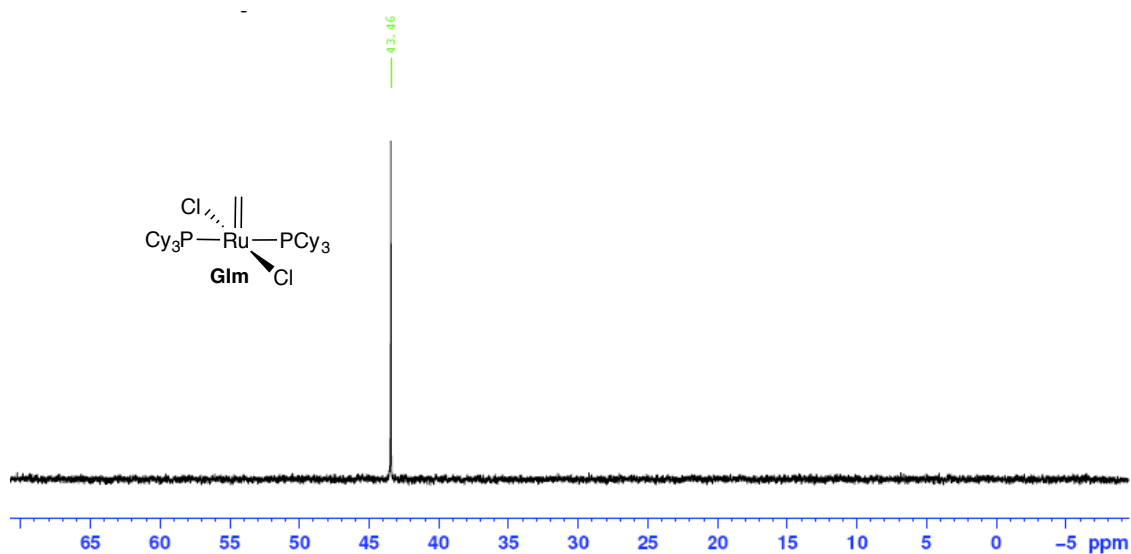


Figure A.2. $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum (121.5 MHz, C_6D_6) of **GIm**.

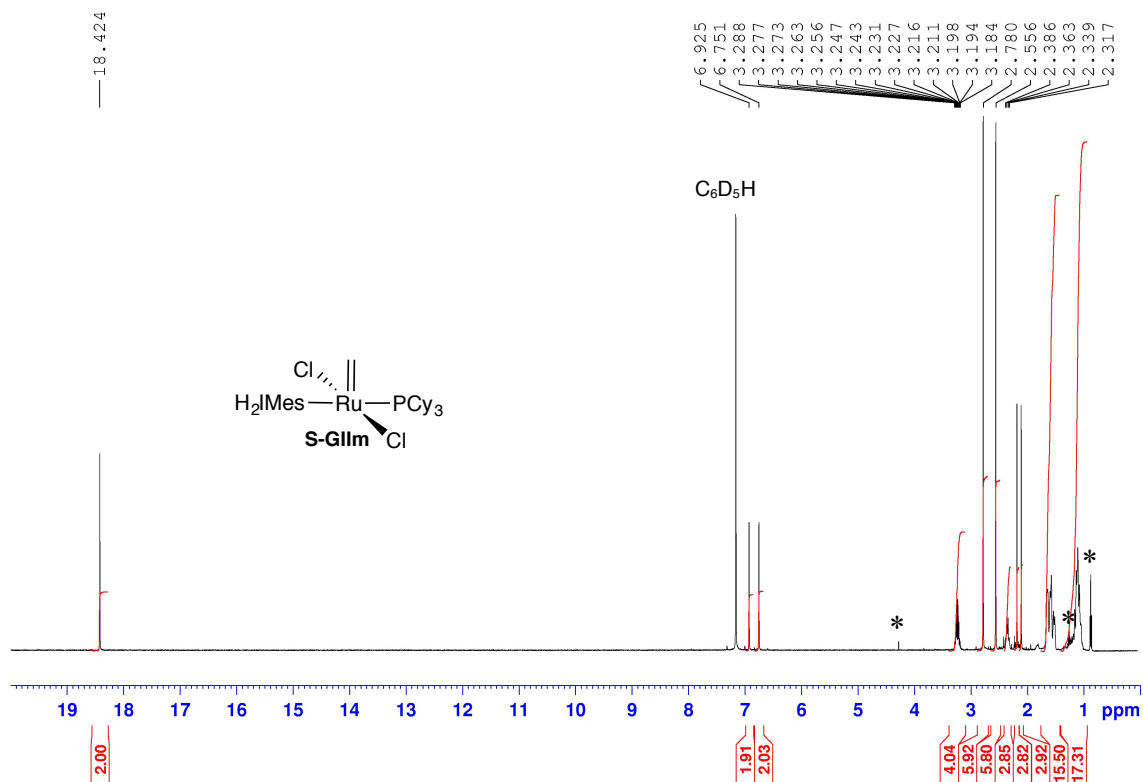


Figure A.3. ¹H NMR spectrum (500.1 MHz, C₆D₆) of **S-GIIIm**. Residual solvent is designated by (*).

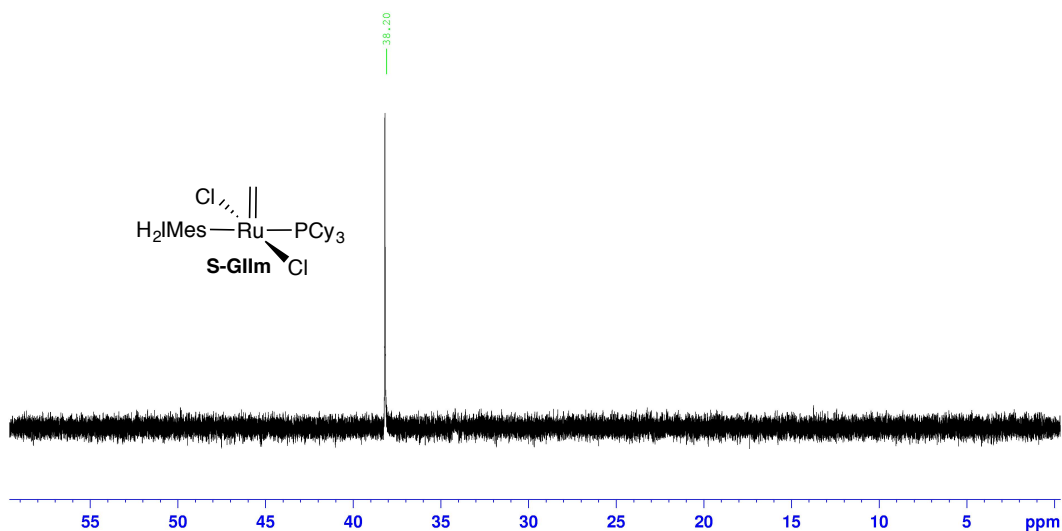


Figure A.4. ³¹P{¹H} NMR spectrum (202.5 MHz, C₆D₆) of **S-GIIIm**.

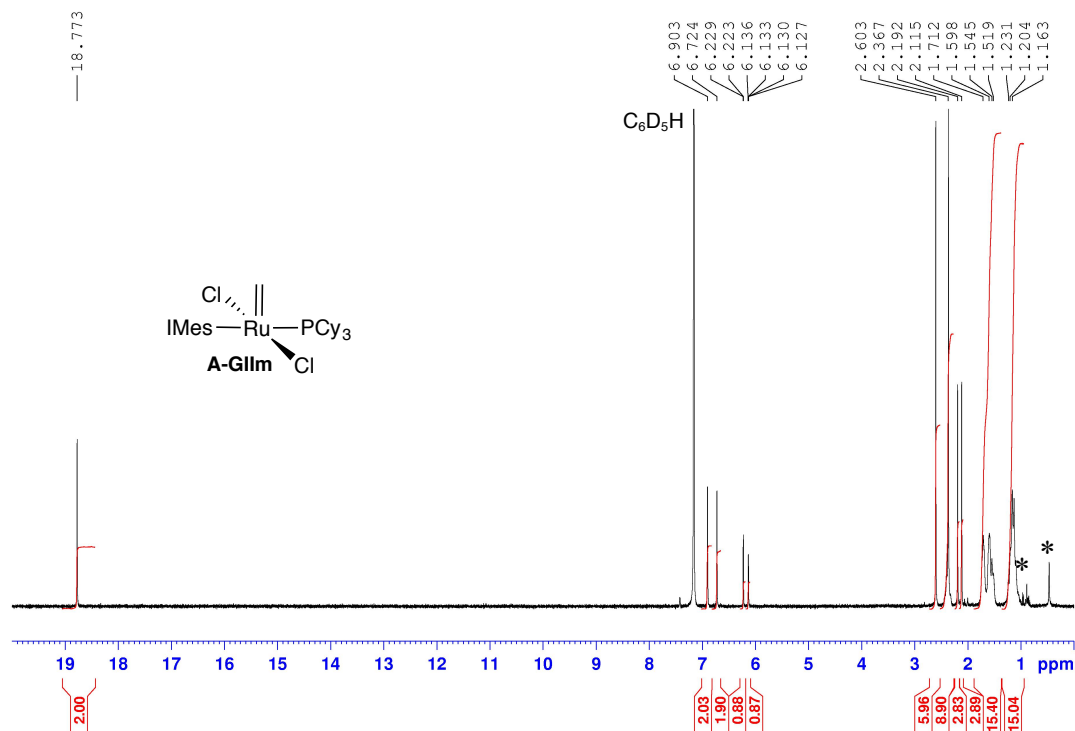


Figure A.5. ^1H NMR spectrum (500.1 MHz, C_6D_6) of **A-GIIIm**. Residual solvent is designated by (*).

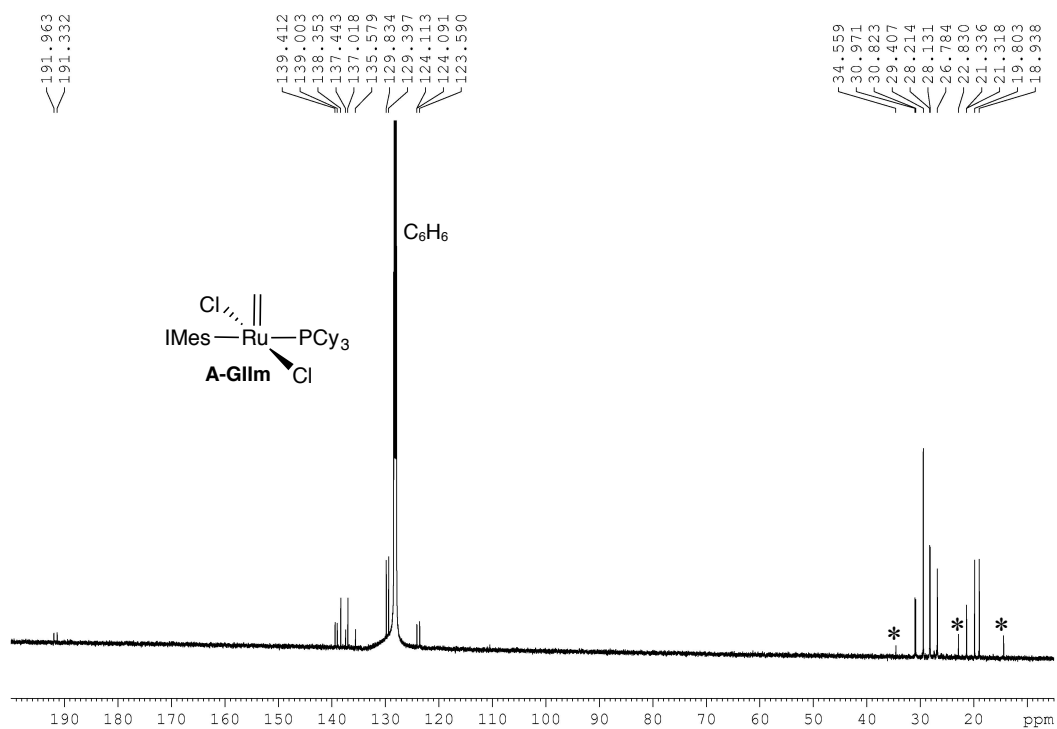


Figure A.6. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum (125.8 MHz, C_6D_6) of **A-GIIIm**. Residual solvent is designated by (*).

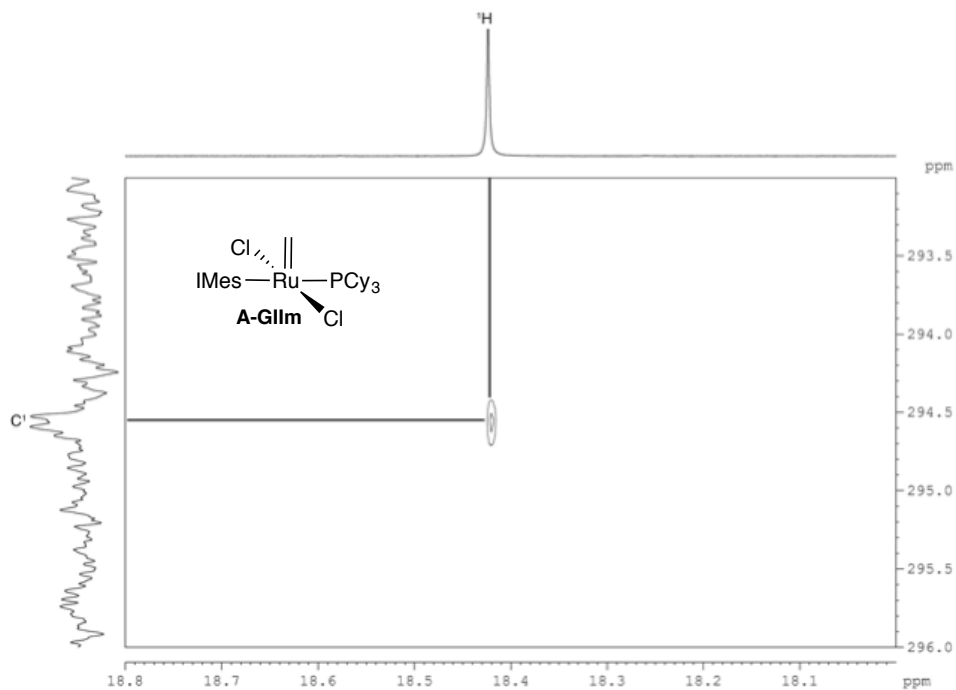


Figure A.7. ^1H - ^{13}C HMBC correlation spectrum of **A-GIIIm** (500.1 MHz, C_6D_6), showing location of $\text{Ru}=\text{CH}_2$ carbon signal.

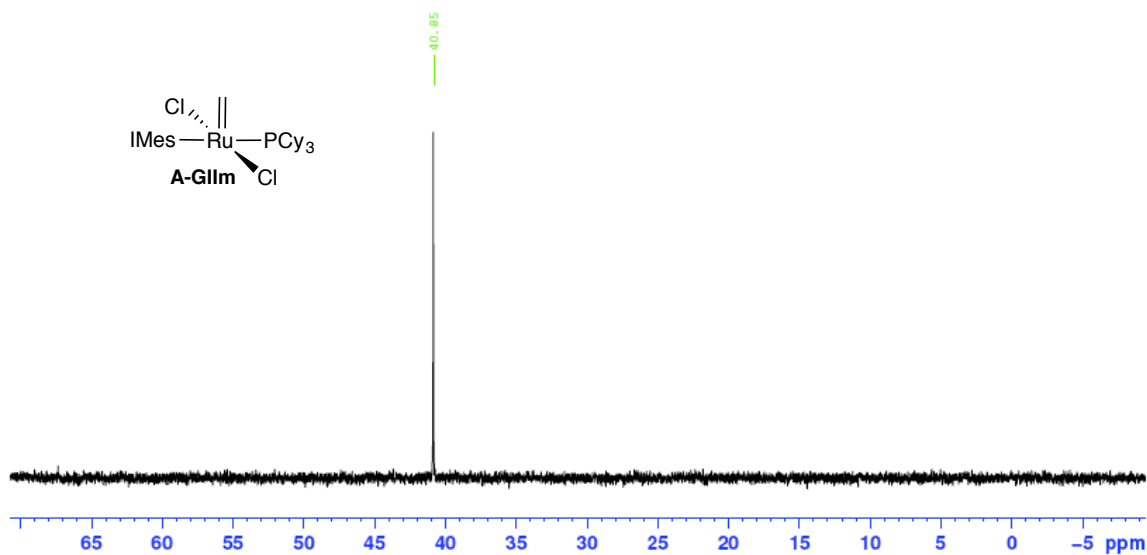


Figure A.8. $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum (202.5 MHz, C_6D_6) of **A-GIIIm**.

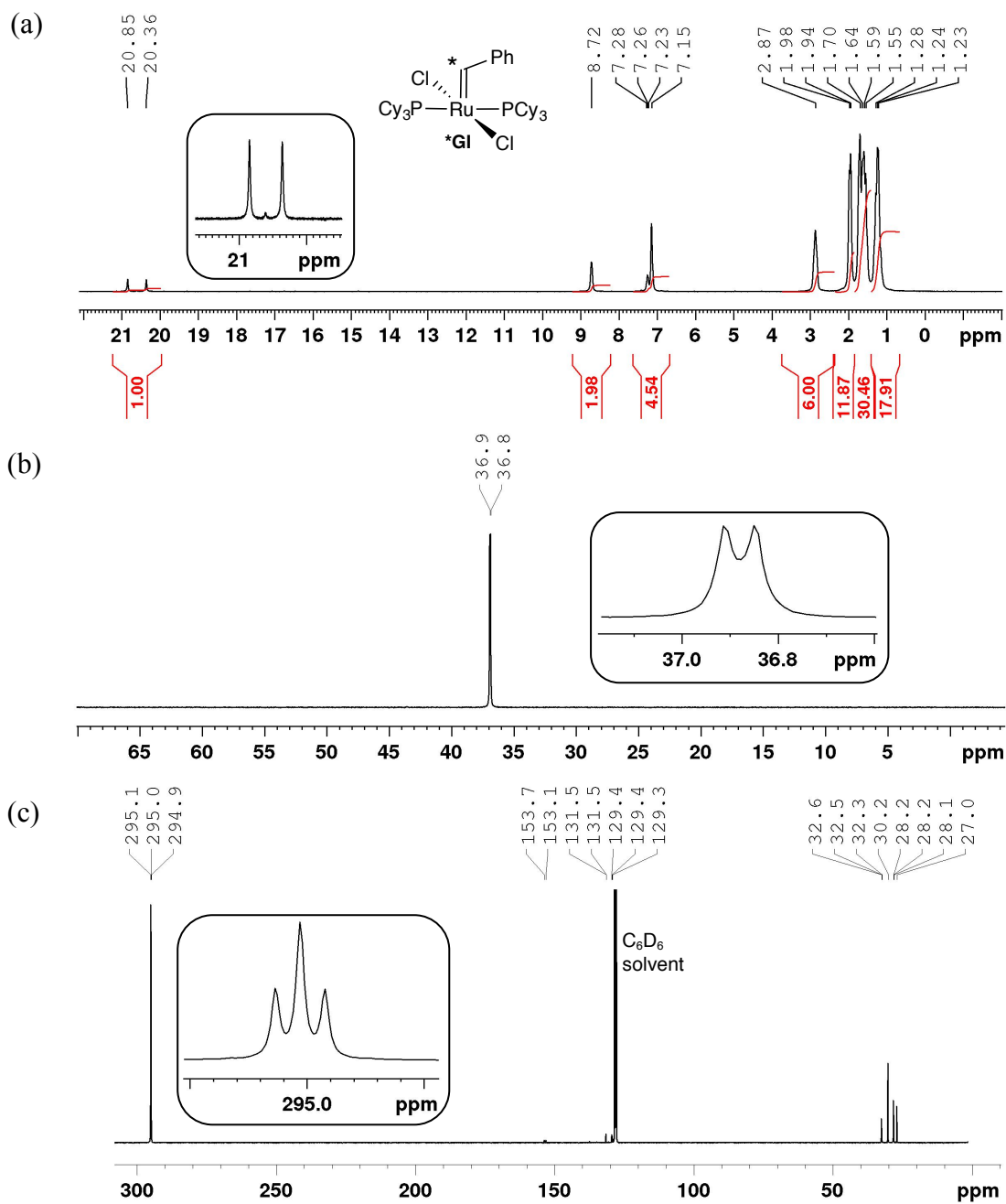


Figure A.9. NMR spectra for $\text{RuCl}_2(\text{PCy}_3)_2(=\text{CHPh})$, *GI : (a) ^1H NMR spectrum (300.1 MHz, C_6D_6). (b) $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum (121.5 MHz, C_6D_6). (c) $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum (75.5 MHz, C_6D_6).

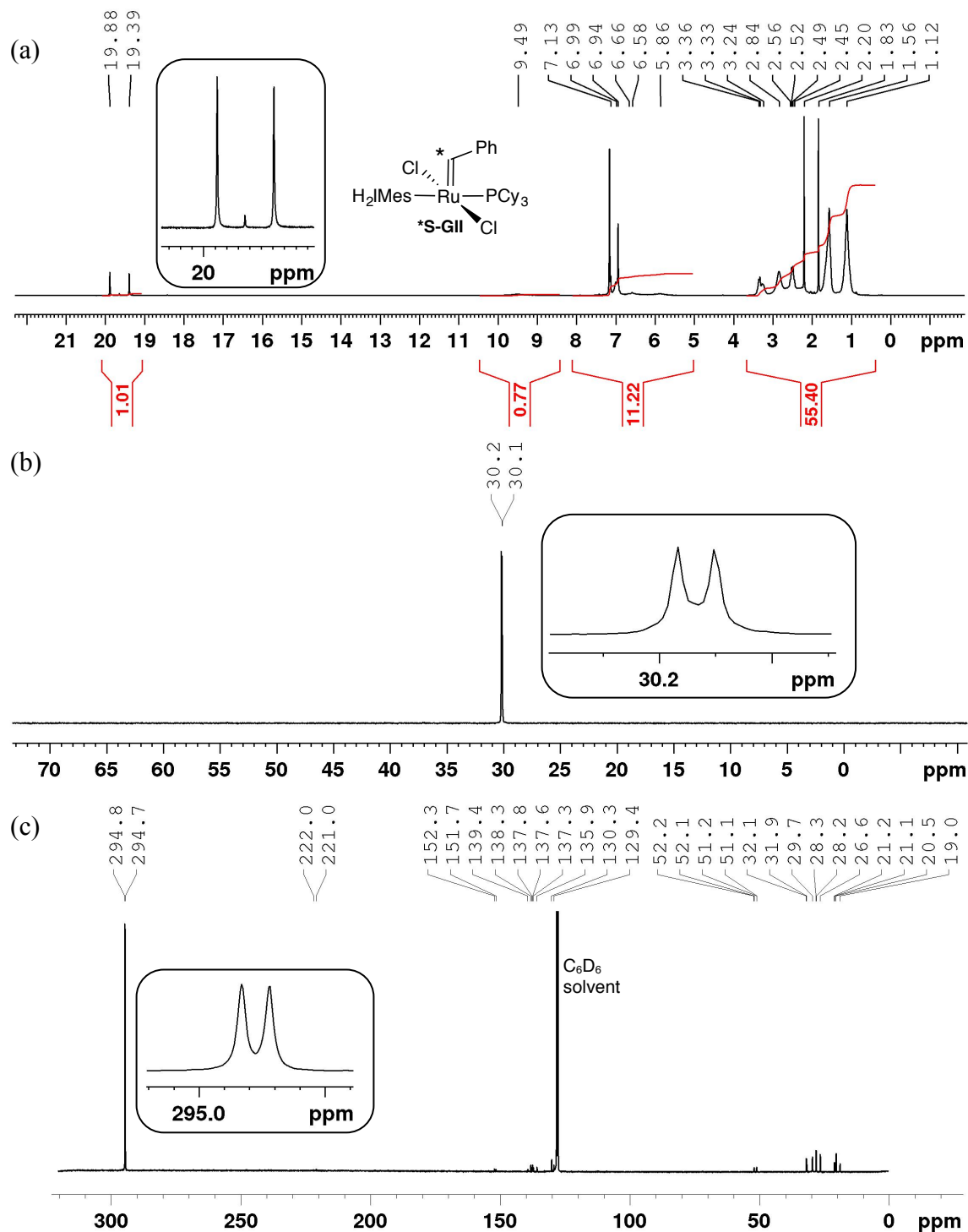


Figure A.10. NMR spectra for $\text{RuCl}_2(\text{PCy}_3)(\text{H}_2\text{IMes})(=^{13}\text{CHPh})$, ***S-GII**: (a) ^1H NMR spectrum (300.1 MHz, C_6D_6). (b) $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum (121.5 MHz, C_6D_6). (c) $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum (75.5 MHz, C_6D_6). The poor resolution of the benzyldiene phenyl signals is due to swiveling of this group.^{1,2}

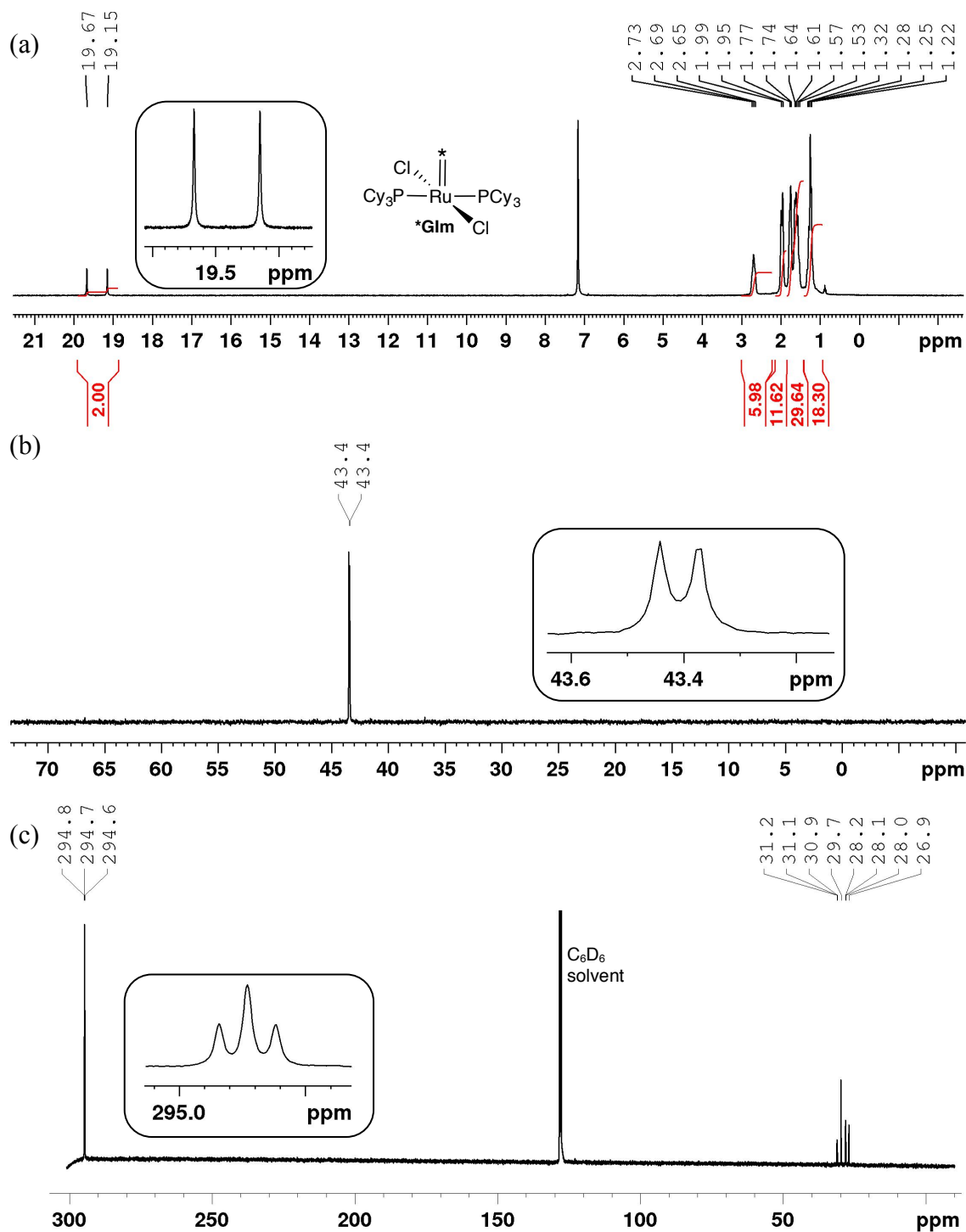


Figure A.11. NMR spectra for $\text{RuCl}_2(\text{PCy}_3)_2(=\text{CH}_2)$, $^*\text{Glm}$: (a) ^1H NMR spectrum (300.1 MHz, C_6D_6). (b) $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum (121.5 MHz, C_6D_6). (c) $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum (75.5 MHz, C_6D_6).

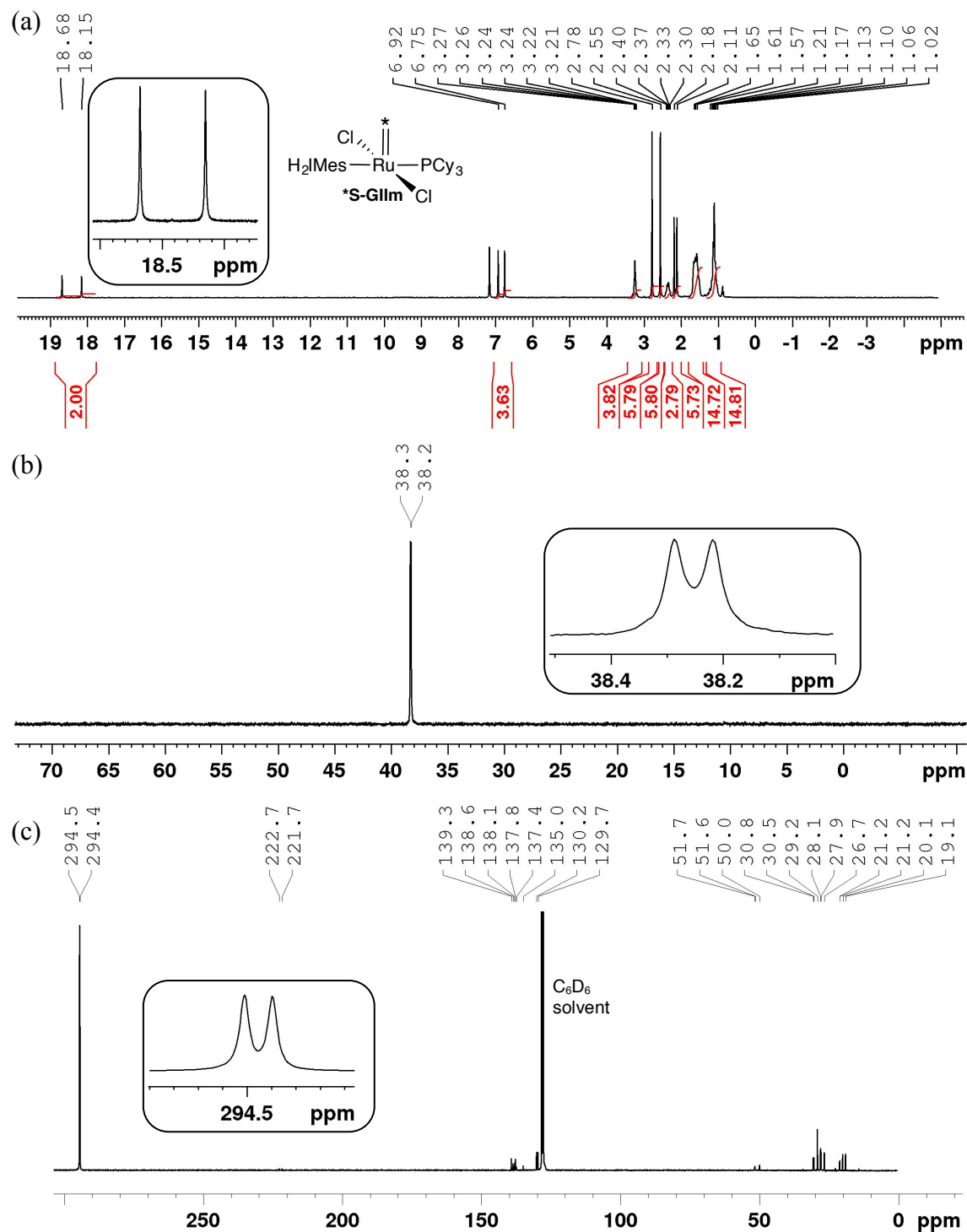


Figure A.12. NMR spectra for $\text{RuCl}_2(\text{PCy}_3)(\text{H}_2\text{IMes})(=^{13}\text{CH}_2)$, ***S-GIIIm**: (a) ^1H NMR spectrum (300.1 MHz, C_6D_6). (b) $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum (121.5 MHz, C_6D_6). (c) $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum (75.5 MHz, C_6D_6).

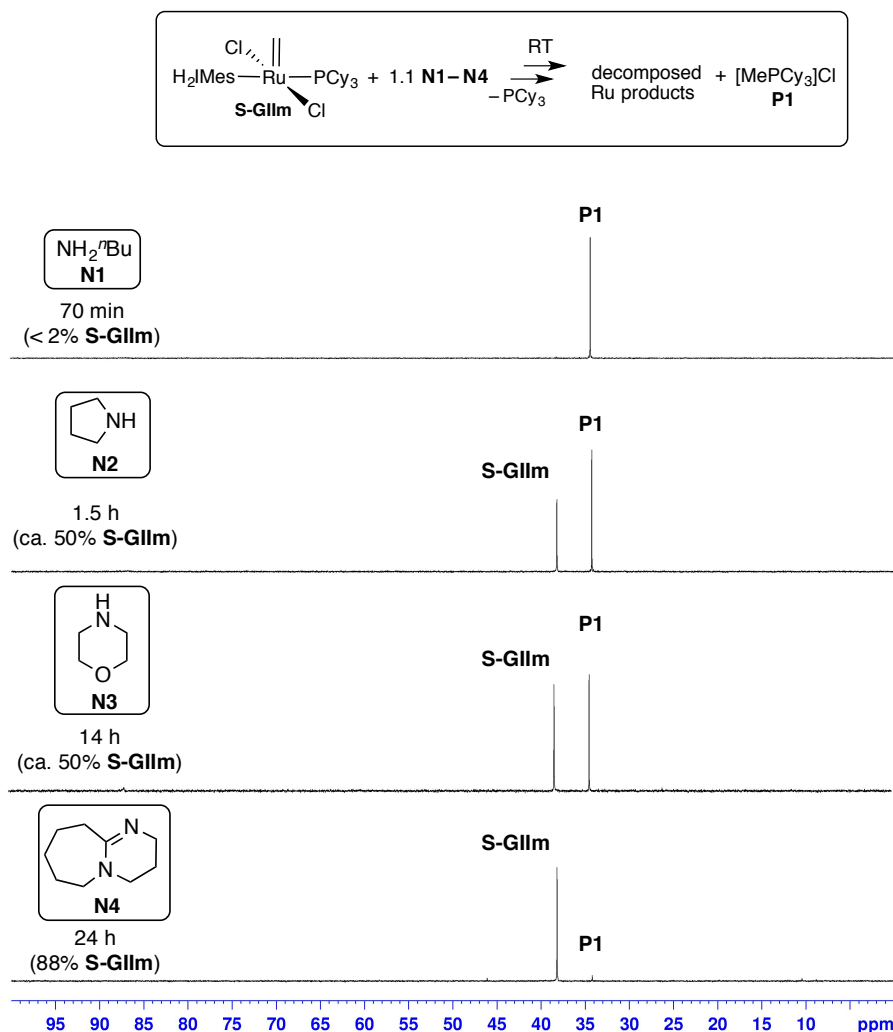


Figure A.13. $^{31}\text{P}\{^1\text{H}\}$ NMR spectra (121.5 MHz, C_6D_6) showing decomposition of **S-GIIIm** by amines **N1–N4** at RT, at the first half-life where accessible. For product distribution, see **Table A.1**.

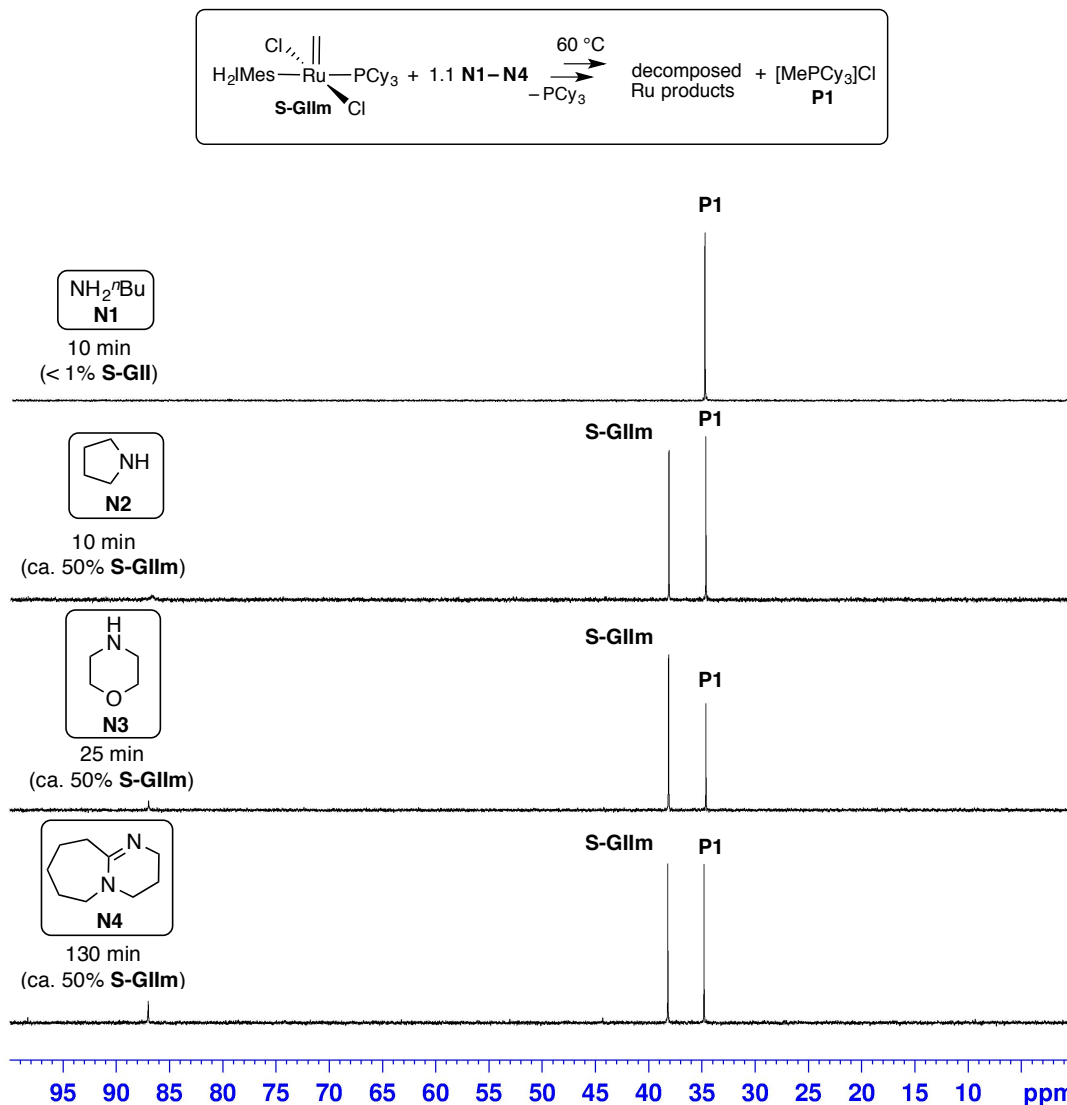


Figure A.14. $^{31}\text{P}\{^1\text{H}\}$ NMR spectra (121.5 MHz, C_6D_6) showing decomposition of **S-GIIIm** by **N1–N4** at 60 °C. **P1** shifted 0.5 ppm upfield at 60 °C. The singlet at 87.0 ppm (unassigned) in the bottom NMR spectrum accounts for 14% of total integration. For product distribution, see **Table A.1**.

Table A.1. Product distribution in decomposition of **S-GIIIm** by amines **N1–N4** (data from **Figures A13, A14**).^a

amine	T (°C)	time	amine adducts δ_p ; amount	# new ³¹ P NMR signals	% decomp	% P1
N1	23	70 min	N/A	1	>99	100
	60	10 min	N/A	1	>99	100
N2	23	90 min	19.01 (s); 1%	1	50	45
	60	10 min	19.03 (s); 2%	2	50	46
N3	23	14 h	19.16 (s); <1%	2	50	37
	60	25 min	19.18 (s); 1%	2	50	34
N4	23	24 h	19.51 (s); 1%	3	16	5
	60	130 min	19.32 (s); 2% 19.25 (br); 12%	3	50	37
none	60	160 min	N/A	1	53	45

^a 20 mM Ru in C₆D₆ at RT (23 °C); 1.1 equiv amine. Decomposition assessed from total alkylidene integration, normalized to TMB as internal standard. Phosphonium salt quantified as % of total ³¹P NMR integration. Values are average of two independent trials ($\pm 3\%$).

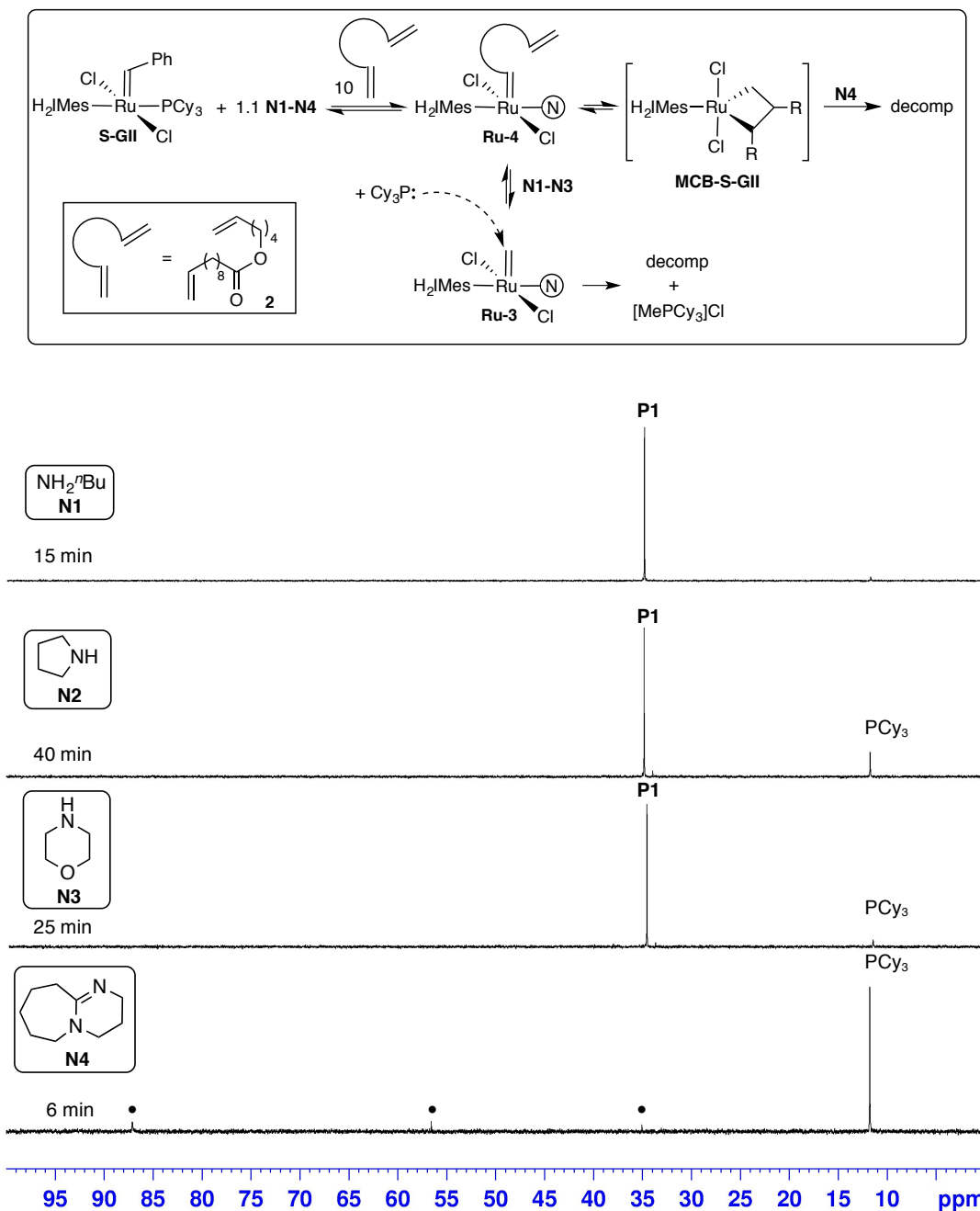


Figure A.15. $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum (121.5 MHz) showing decomposition of **MCB** by **N1–N4** (1.1 equiv) at 60 °C in C_6D_6 , shown at >95% decomposition. The symbol (•) denotes unknown products. For product distribution, see **Table A.2**.

Table A.2. Product distribution in RCM reactions carried out in the presence of amines **N1**–**N4**.^a

Additive	% P1	% PCy ₃	Other
N1	97	3	0
N2	73	24	0
N3	96	4	0
N4	0	84	16
None	63	20	16

^a 20 mM Ru in C₆D₆ at RT (60 °C); 1.1 equiv amine. Phosphonium salt (**P1**) and free PCy₃ are shown as % of total ³¹P NMR integration. Values are average of two independent trials (±3%).

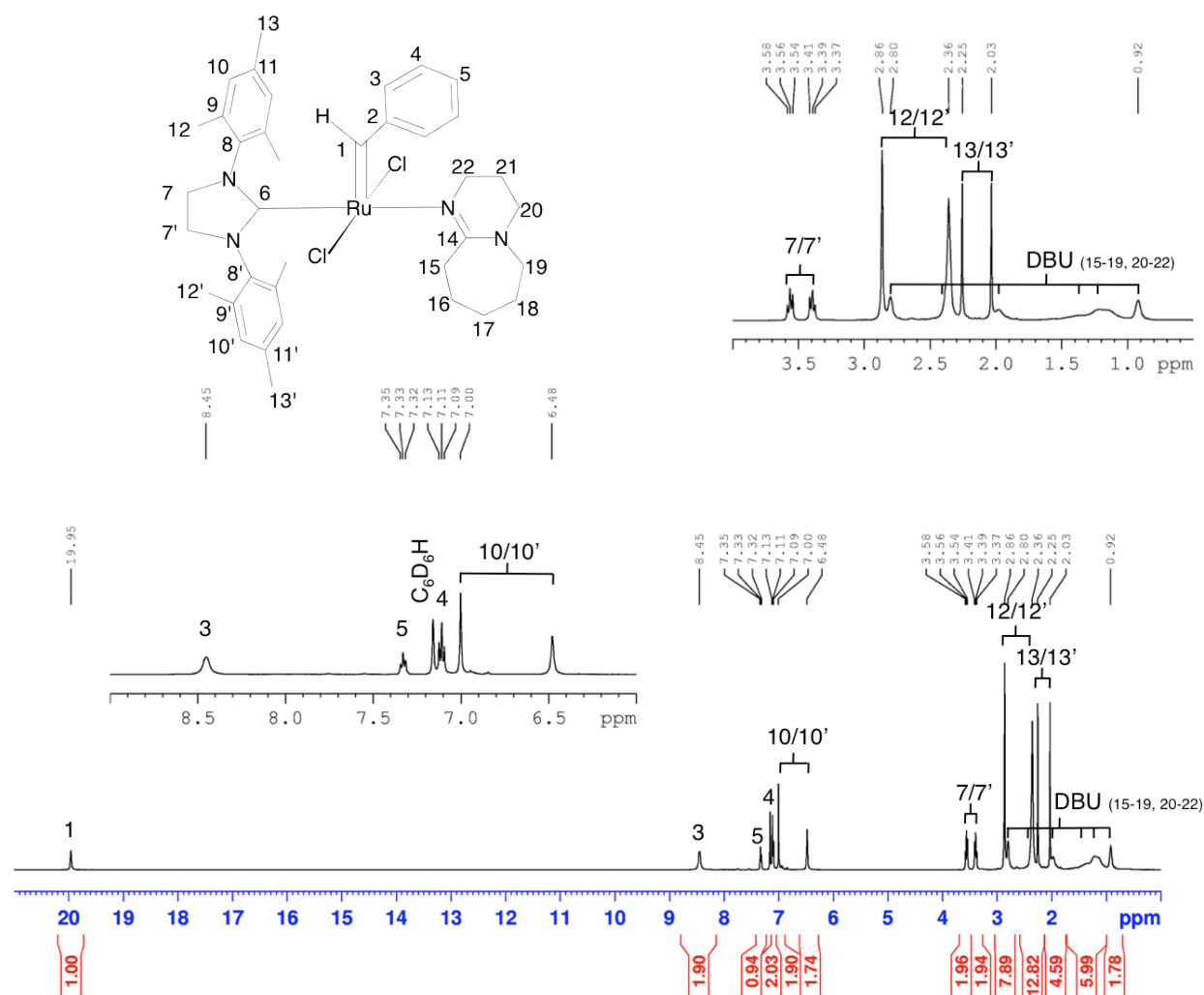


Figure A.16. ¹H NMR spectrum for RuCl₂(H₂IMes)(DBU)(=CHPh) **Ru-2(N4)** (C₆D₆, 500.1 MHz, 328 K).

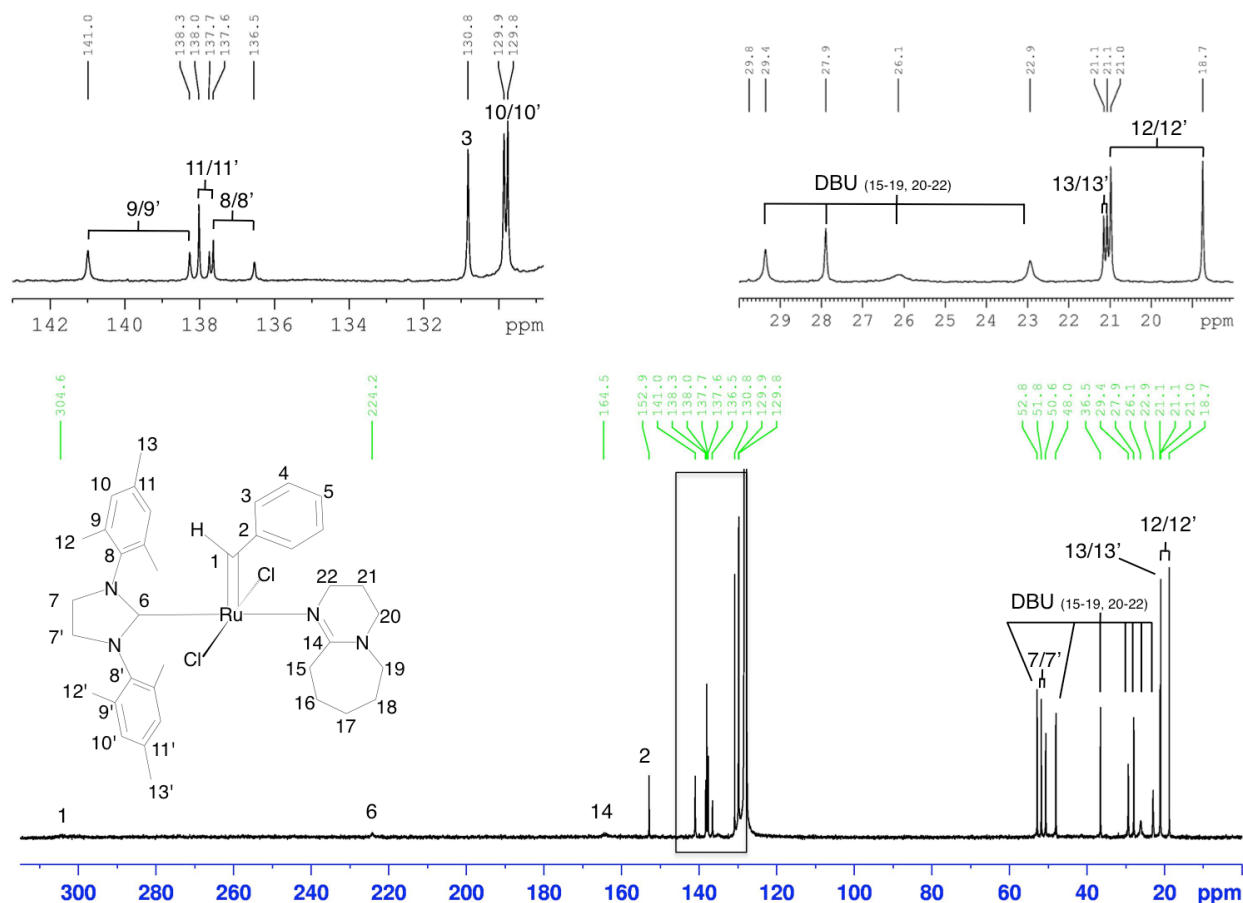


Figure A.17. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of $\text{RuCl}_2(\text{H}_2\text{IMes})(\text{DBU})(=\text{CHPh})$ **Ru-2(N4)** (C_6D_6 , 125.8 MHz, 328 K).

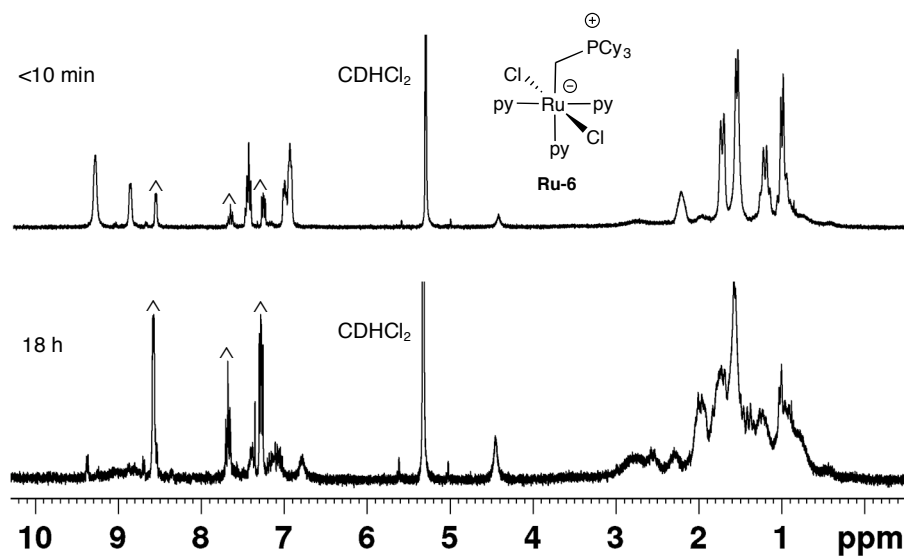


Figure A.18. ^1H NMR spectrum (300.1 MHz, CD_2Cl_2) of $\text{RuCl}_2(\sigma\text{-CH}_2\text{PCy}_3)(\text{py})_3$ **Ru-6** after 10 min or 18 h at 25 °C, with a constant number of scans (64). The label ^ denotes free pyridine.

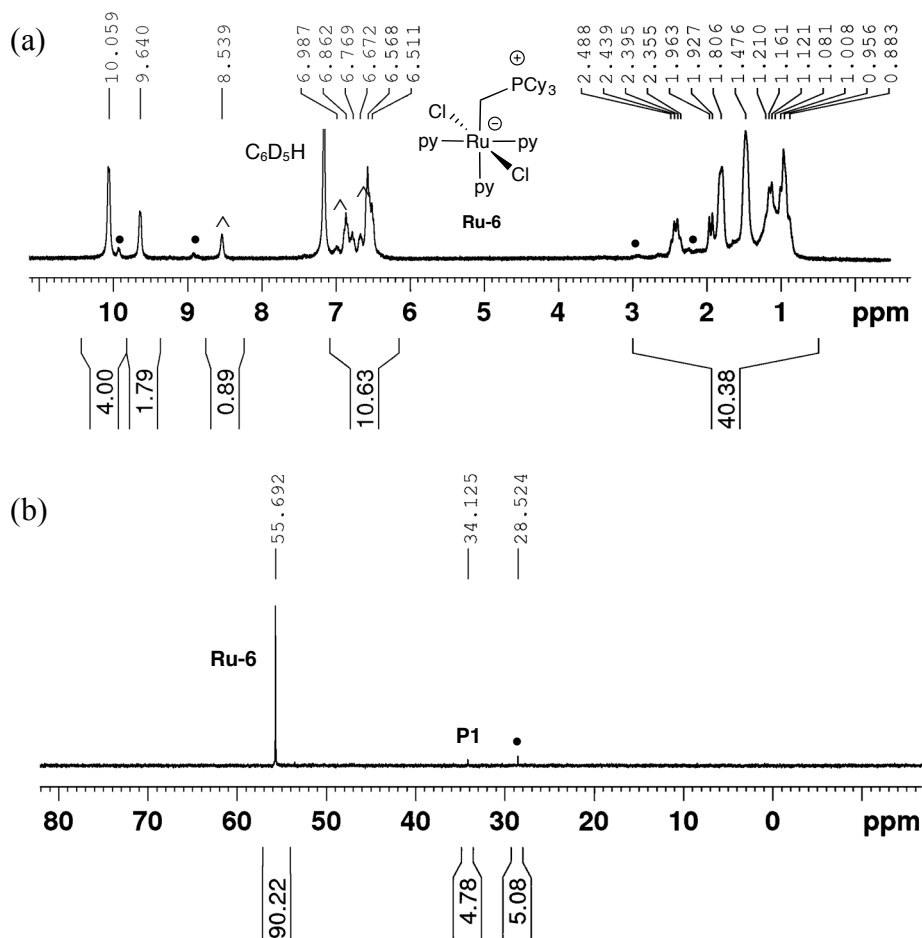


Figure A.19. NMR spectra for **Ru-6** in C_6D_6 (in which **Ru-6** is longer-lived relative to CD_2Cl_2 , but less soluble). (a) ^1H NMR spectrum (300.1 MHz, C_6D_6). (b) $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum (75.5 MHz, C_6D_6). The label ^ denotes free pyridine; signals marked (•) are unassigned.

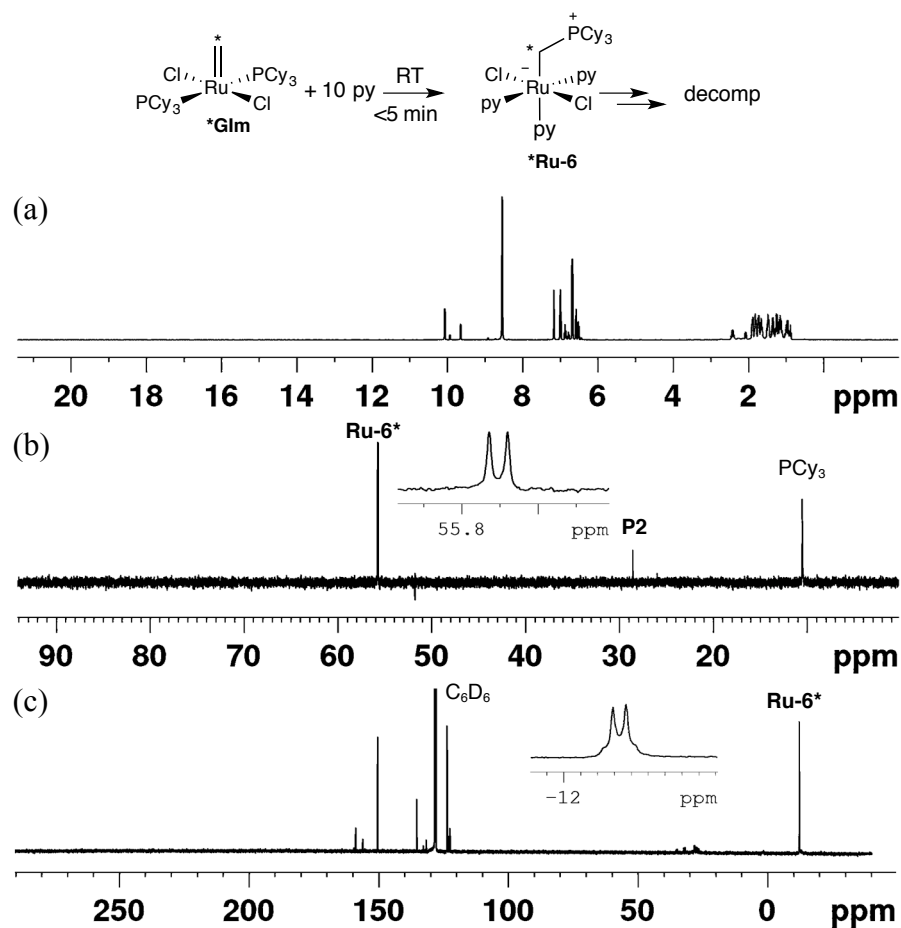


Figure A.20. Reaction of $\text{RuCl}_2(\text{PCy}_3)_2(=^{13}\text{CH}_2)$ ***Glm** with pyridine, under the conditions shown. (a) ^1H NMR spectrum (500.1 MHz, C_6D_6). (b) $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum (202.5 MHz, C_6D_6); signal marked **P2** is unassigned. (c) $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum (125.8 MHz, C_6D_6).

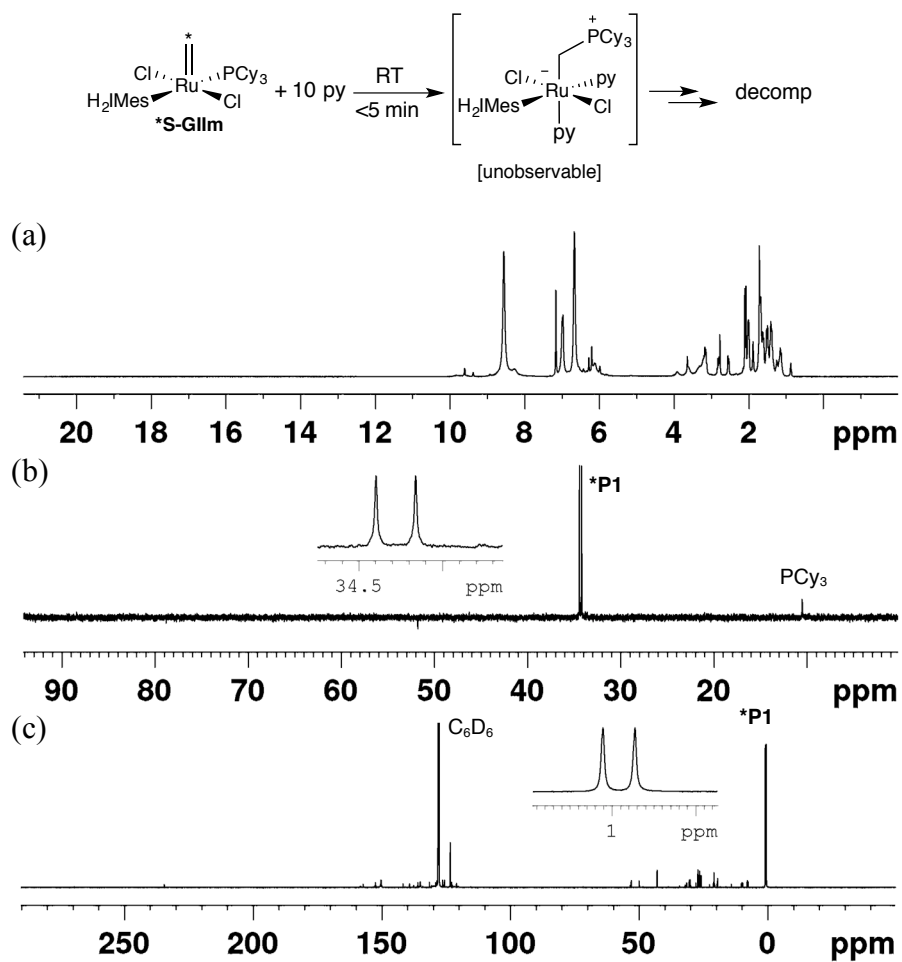


Figure A.21. Reaction of ***S-GIIIm** with pyridine, under the conditions shown. (a) ^1H NMR spectrum (500.1 MHz, C_6D_6). (b) $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum (202.5 MHz, C_6D_6). (c) $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum (125.8 MHz, C_6D_6).

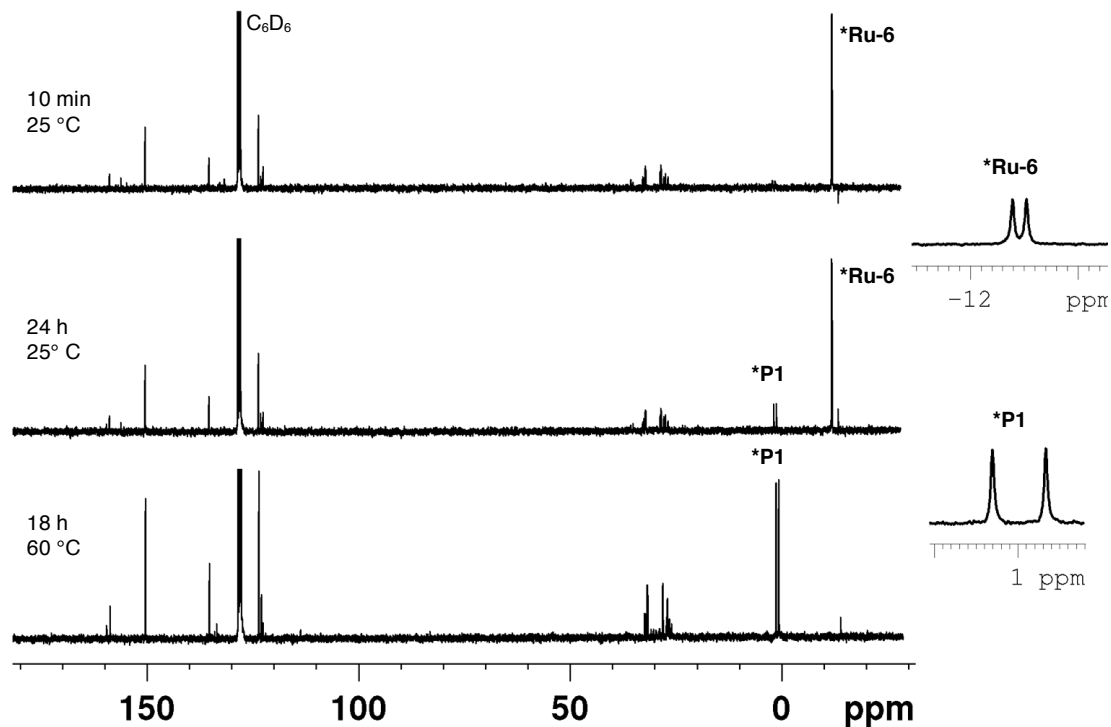


Figure A.22. $^{13}\text{C}\{^1\text{H}\}$ NMR spectra (75.5 MHz, C_6D_6) showing decomposition of in-situ generated ***Ru-6**, and formation of ***P1**.

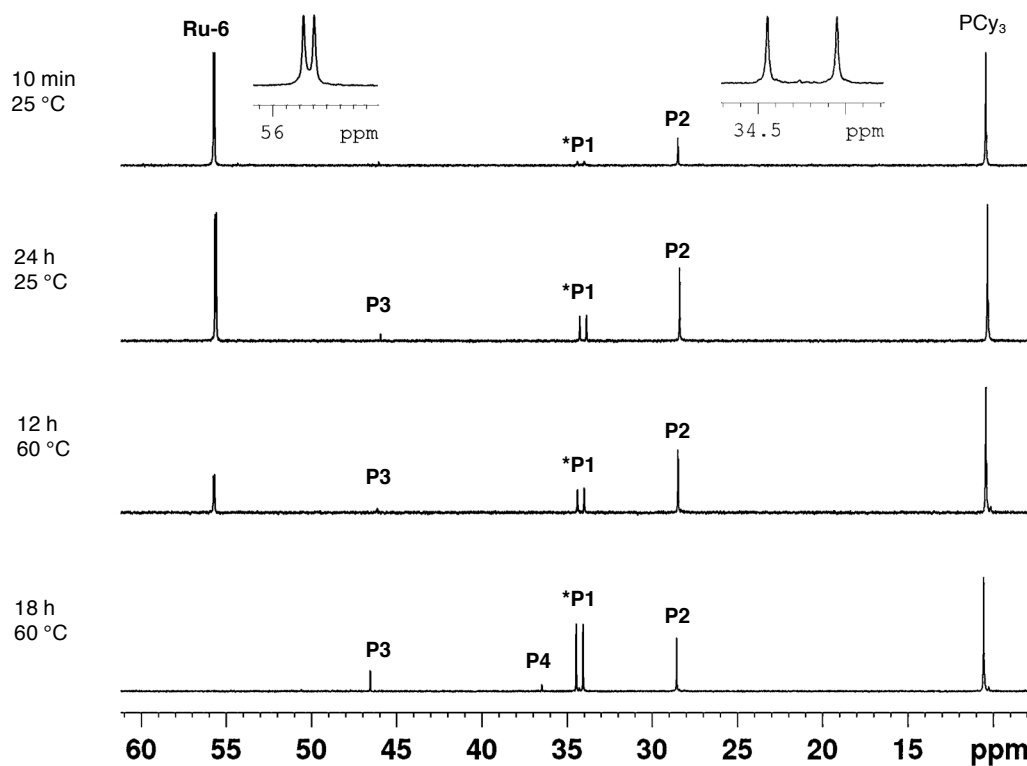


Figure A.23. $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum (75.5 MHz, C_6D_6) corresponding to the experiment of Figure A.22. Signals **P2-P4** are unassigned.

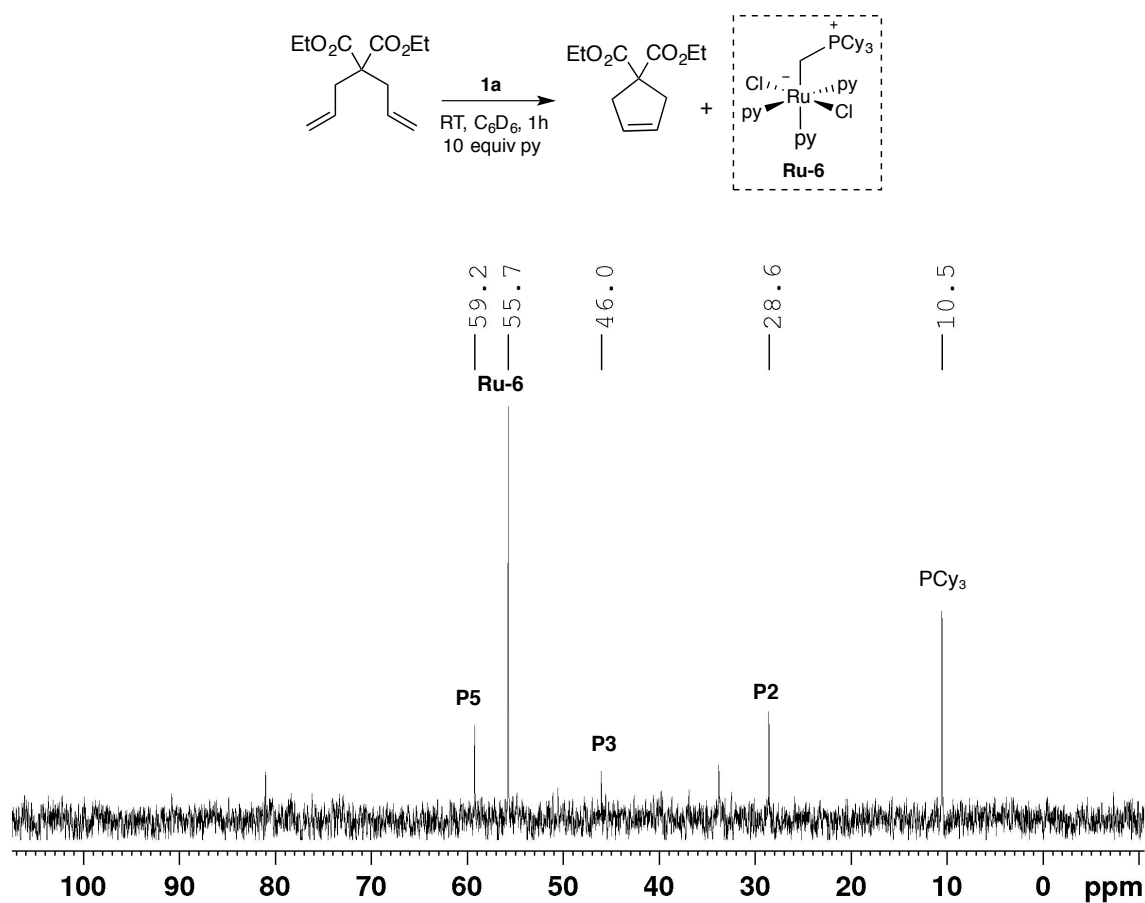


Figure A.24. ³¹P{¹H} NMR spectrum (75.5 MHz, C₆D₆) showing the formation of **Ru-6** during **GI**-promoted RCM in the presence of pyridine. Signals **P2**, **P3**, and **P5** are unassigned.

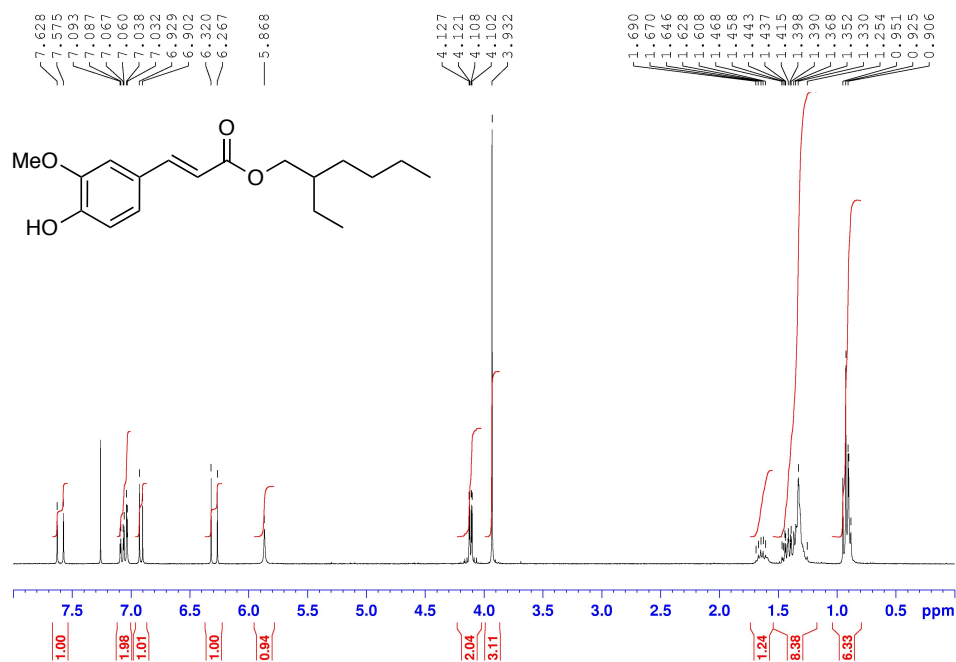


Figure A.25. ¹H NMR spectrum (300.1 MHz, CDCl₃) of (E)-2-ethylhexylferulate 5b''.

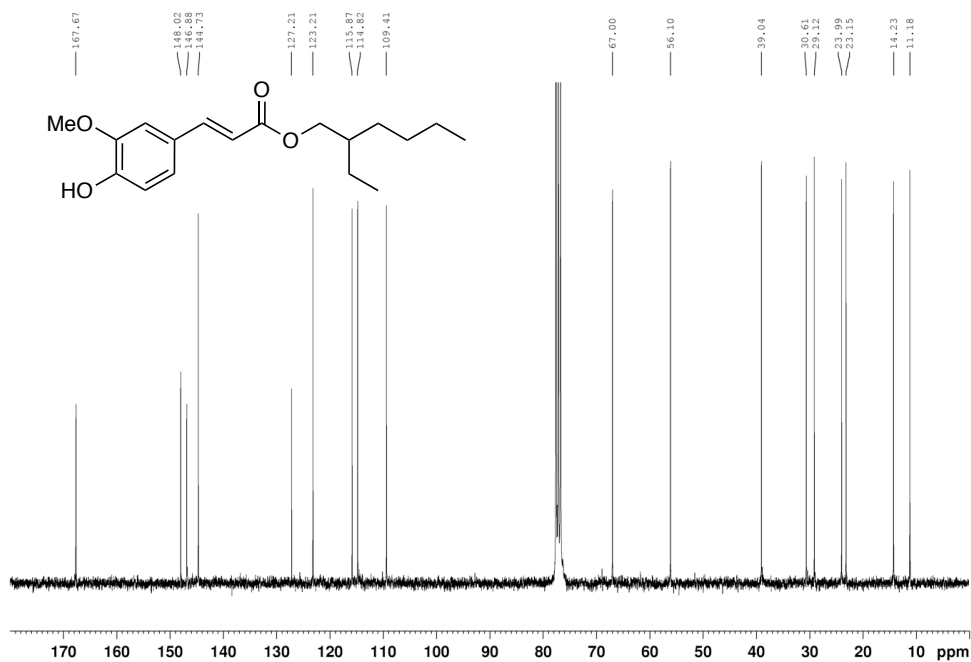


Figure A.26. ¹³C{¹H} NMR spectrum (75.5 MHz, CDCl₃) of 5b''.

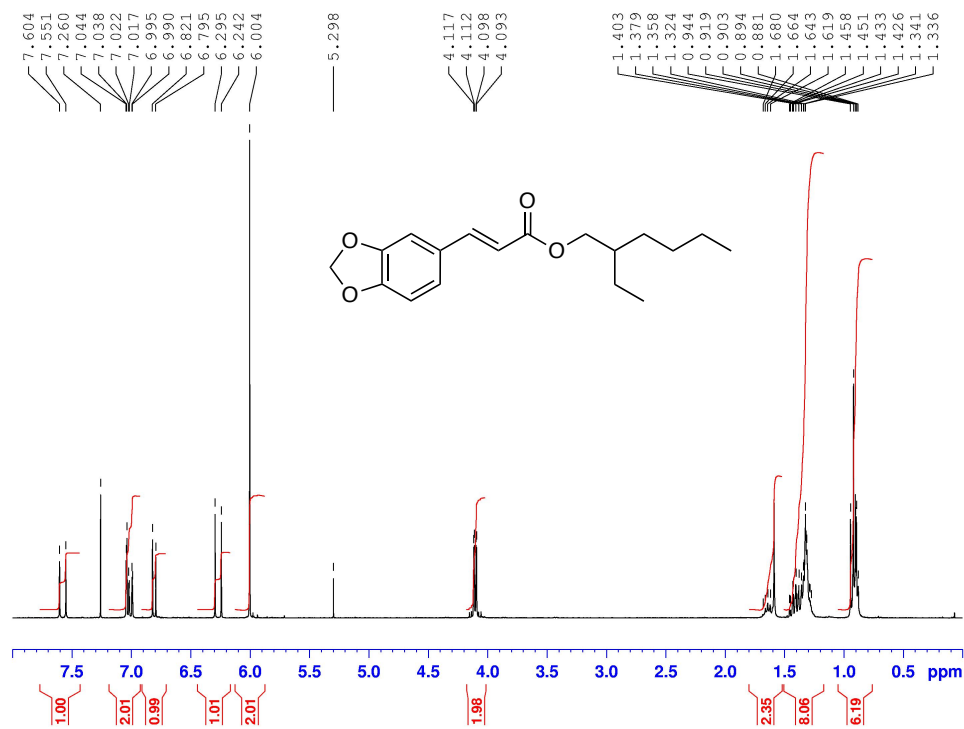


Figure A.27. ¹H NMR spectrum (300.1 MHz, CDCl₃) of (E)-2-ethylhexyl-3,4-(methylenedioxy)cinnamate **5c''**.

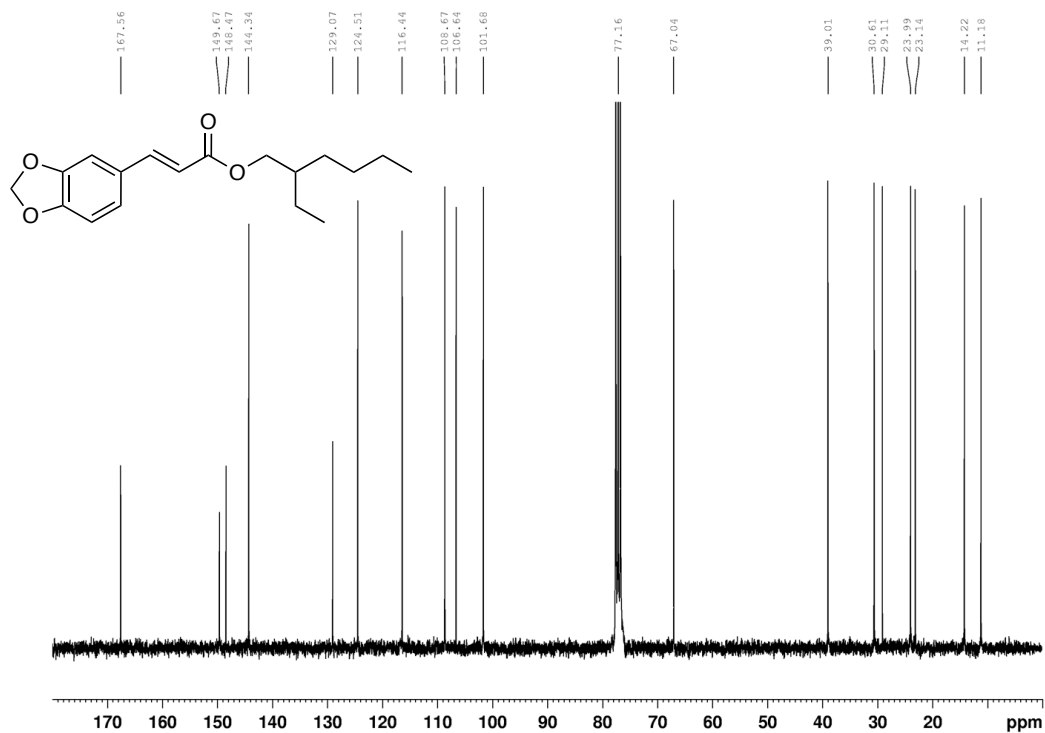


Figure A.28. ¹³C{¹H} NMR spectrum (75.5 MHz, CDCl₃) of **5c''**.

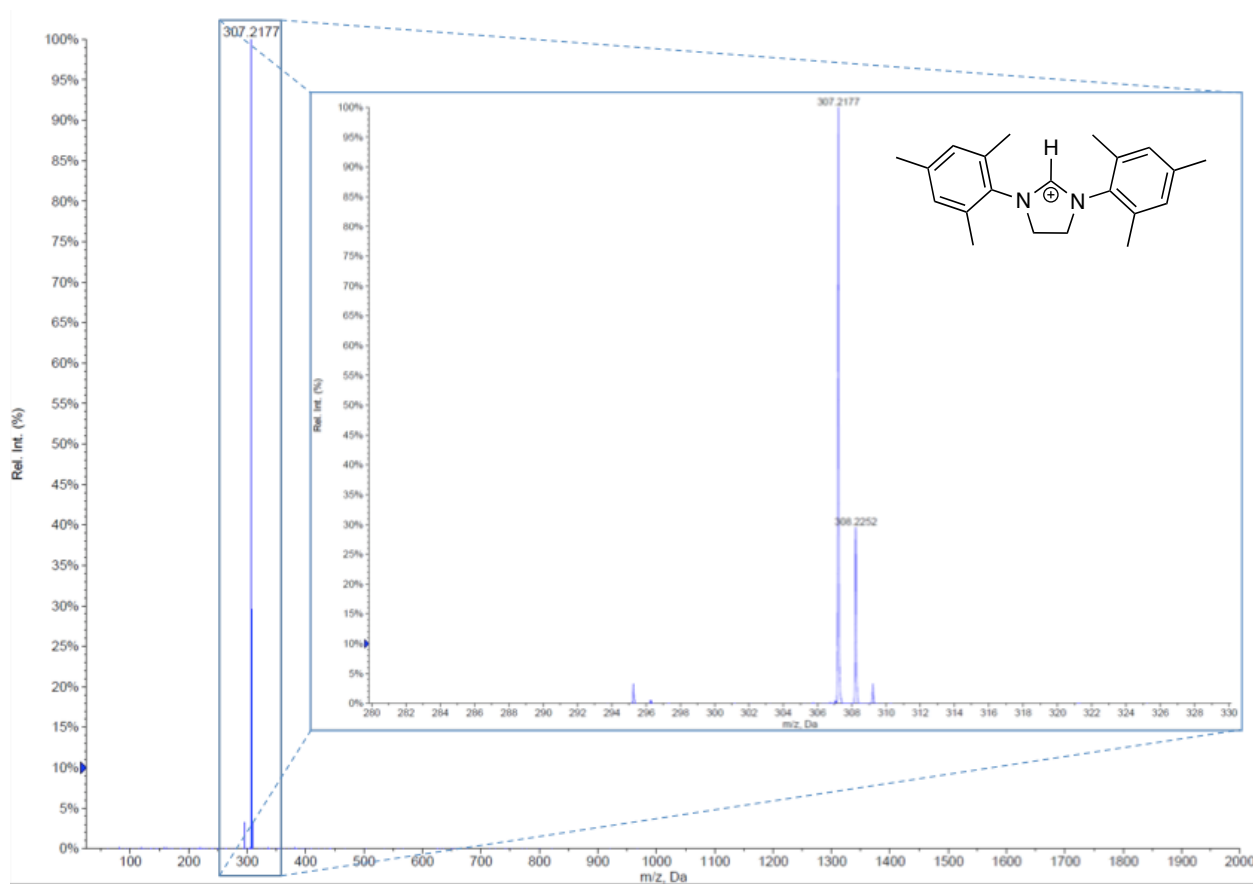
B. Mass Spectra

Figure B.1. ESI mass spectrum of imidazolinium cation present in one batch of free H₂IMes. Sample measured in aqueous MeCN (33% v/v) with 0.1% v/v formic acid.

C. Crystallographic Data

Table C.1. Crystallographic parameters for **A-GIIIm**.

<i>A. Crystal data</i>	
formula	C ₄₀ H ₅₉ Cl ₂ N ₂ PRu
formula weight	770.83
crystal dimensions (mm)	0.16 × 0.14 × 0.02
crystal system	monoclinic
space group	<i>P</i> 2 ₁ / <i>n</i> (an alternate setting of <i>P</i> 2 ₁ / <i>c</i> [No. 14])
unit cell parameters ^a	
<i>a</i> (Å)	12.2117 (3)
<i>b</i> (Å)	18.0562 (6)
<i>c</i> (Å)	18.2926 (6)
β (deg)	103.741 (2)
<i>V</i> (Å ³)	3918.0 (2)
<i>Z</i>	4
ρ_{calcd} (g cm ⁻³)	1.307
μ (mm ⁻¹)	5.088
<i>B. Data collection and refinement</i>	
Diffractometer	Bruker D8/APEX II CCD ^b
radiation (λ [Å])	Cu K α (1.54178) (microfocus source)
temperature (°C)	−100
scan type	ω and ϕ scans (1.0°) (5 s exposures)
data collection 2θ limit (deg)	135.98
total data collected	25622 ($-14 \leq h \leq 14$, $-21 \leq k \leq 21$, $-21 \leq l \leq 21$)
independent reflections	6912 ($R_{\text{int}} = 0.1444$)
number of observed reflections (<i>NO</i>)	4015 [$F_o^2 \geq 2\sigma(F_o^2)$]
structure solution method	Patterson/structure expansion (<i>DIRDIF-2008</i> ^c)
refinement method	full-matrix least-squares on F^2 (<i>SHELXL-97</i> ^d)
absorption correction method	Gaussian integration (face-indexed)
range of transmission factors	0.8876–0.4910
data/restraints/parameters	6912 / 1 ^e / 429
extinction coefficient (<i>x</i>) ^f	0.00016(3)
goodness-of-fit (<i>S</i>) ^d [all data]	0.954
final <i>R</i> indices ^e	
R_1 [$F_o^2 \geq 2\sigma(F_o^2)$]	0.0517
wR_2 [all data]	0.0517
largest difference peak and hole	0.499 and −0.699 e Å ⁻³

^aObtained from least-squares refinement of 3223 reflections with $7.92^\circ < 2\theta < 105.86^\circ$.

^bPrograms for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

^cBeurskens, P. T.; Beurskens, G.; de Gelder, R.; Smits, J. M. M.; Garcia-Granda, S.; Gould, R. O. (2008). The *DIRDIF-2008* program system. Crystallography Laboratory, Radboud University Nijmegen, The Netherlands.

^dSheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112–122.

^eThe C1–H1A and C1–H1B distances were constrained to be equal (within 0.06 Å) during refinement.

^f $F_c^* = kF_c[1 + x\{0.001F_c^2\lambda^3/\sin(2\theta)\}]^{-1/4}$ where *k* is the overall scale factor.

$$gS = [\Sigma w(F_o^2 - F_c^2)^2 / (n - p)]^{1/2} \quad (n = \text{number of data; } p = \text{number of parameters varied; } w = [\sigma^2(F_o^2) + (0.0490P)^2]^{-1} \text{ where } P = [\text{Max}(F_o^2, 0) + 2F_c^2]/3).$$

$$^hR_1 = \Sigma ||F_o| - |F_c|| / \Sigma |F_o|; \quad wR_2 = [\Sigma w(F_o^2 - F_c^2)^2 / \Sigma w(F_o^4)]^{1/2}.$$

Table C.2. Crystallographic parameters for **S-GIIIm**.

<i>A. Crystal data</i>	
formula	C ₄₆ H ₆₇ Cl ₂ N ₂ PRu
formula weight	850.96
crystal dimensions (mm)	0.48 × 0.45 × 0.19
crystal system	monoclinic
space group	<i>P</i> 2 ₁ / <i>n</i> (an alternate setting of <i>P</i> 2 ₁ / <i>c</i> [No. 14])
unit cell parameters ^a	
<i>a</i> (Å)	11.7908 (5)
<i>b</i> (Å)	21.2371 (9)
<i>c</i> (Å)	17.6139 (8)
β (deg)	94.2194 (5)
<i>V</i> (Å ³)	4398.6 (3)
<i>Z</i>	4
ρ_{calcd} (g cm ⁻³)	1.285
μ (mm ⁻¹)	0.547
<i>B. Data collection and refinement</i>	
Diffractionmeter	Bruker D8/APEX II CCD ^b
radiation (λ [Å])	graphite-monochromated Mo K α (0.71073)
temperature (°C)	−100
scan type	ω scans (0.3°) (20 s exposures)
data collection 2θ limit (deg)	55.02
total data collected	38769 ($-15 \leq h \leq 15$, $-27 \leq k \leq 27$, $-22 \leq l \leq 22$)
independent reflections	10101 ($R_{\text{int}} = 0.0277$)
number of observed reflections (<i>NO</i>)	9108 [$F_o^2 \geq 2\sigma(F_o^2)$]
structure solution method	direct methods (<i>SHELXS</i> –97 ^c)
refinement method	full-matrix least-squares on F^2 (<i>SHELXL</i> –97 ^c)
absorption correction method	Gaussian integration (face-indexed)
range of transmission factors	0.9041–0.7788
data/restraints/parameters	10101 / 0 / 483
extinction coefficient (κ) ^f	0.00016(3)
goodness-of-fit (<i>S</i>) ^d [all data]	1.040
final <i>R</i> indices ^e	
R_1 [$F_o^2 \geq 2\sigma(F_o^2)$]	0.0280
wR_2 [all data]	0.0721
largest difference peak and hole	0.498 and −0.444 e Å ⁻³

^aObtained from least-squares refinement of 9912 reflections with $4.30^\circ < 2\theta < 49.50^\circ$.

^bPrograms for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

^cSheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112–122.

^d $S = [\Sigma w(F_o^2 - F_c^2)^2 / (n - p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.0276P)^2 + 3.1363P]^{-1}$ where $P = [\text{Max}(F_o^2, 0) + 2F_c^2]/3$).

$$^eR_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|; wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}.$$

Table C.3. Crystallographic parameters for **Ru-6**.

<i>A. Crystal data</i>	
formula	C ₃₄ H ₅₀ Cl ₂ N ₃ PRu
formula weight	703.71
crystal dimension (nm)	0.41 × 0.35 × 0.22
crystal system	monoclinic
space group	<i>P</i> 2 ₁ / <i>c</i> (No. 14)
unit cell parameters ^a	
<i>a</i> (Å)	17.3322 (12)
<i>b</i> (Å)	10.9026 (8)
<i>c</i> (Å)	17.5380 (12)
β (deg)	93.0376 (8)
<i>V</i> (Å ³)	3309.4 (4)
<i>Z</i>	4
ρ_{calcd} (g cm ⁻³)	1.412
μ (mm ⁻¹)	0.712
diffractometer	Bruker D8/APEX II CCD ^b
radiation (λ [Å])	graphite-monochromated Mo K α (0.71073)
temperature (°C)	−100
scan type	ω scans (0.3°) (15 s exposures)
data collection 2θ limit (deg)	56.64
total data collected	28446 ($-22 \leq h \leq 22$, $-14 \leq k \leq 14$, $-23 \leq l \leq 23$)
independent reflections	8002 ($R_{\text{int}} = 0.0215$)
number of observed reflections (<i>NO</i>)	7494 [$F_o^2 \geq 2\sigma(F_o^2)$]
structure solution method	direct methods (<i>SHELXS-2013</i> ^c)
refinement method	full-matrix least-squares on F^2 (<i>SHELXL-2013</i> ^c)
absorption correction method	Gaussian integration (face-indexed)
range of transmission factors	0.9136–0.7961
data/restraints/parameters	8002 / 0 / 424
goodness-of-fit (<i>S</i>) ^d [all data]	1.064
final <i>R</i> indices ^e	
R_1 [$F_o^2 \geq 2\sigma(F_o^2)$]	0.0231
wR_2 [all data]	0.0636
largest difference peak and hole	0.663 and −0.568 e Å ⁻³

^aObtained from least-squares refinement of 9207 reflections with $4.42^\circ < 2\theta < 56.04^\circ$.

^bPrograms for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

^cSheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112–122.

^d $S = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.0329P)^2 + 1.3492P]^{-1}$ where $P = [\text{Max}(F_o^2, 0) + 2F_c^2]/3$).

^e $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

D. Handling of isotopically-labelled ethylene

A needle valve was installed on lecture bottles of labelled gases to permit controlled dispensing of small gas volumes. Once the bottle pressure dropped below 1 atm (14.7 ± 1 psi local value), the lecture bottle was warmed in a hot-water bath to increase the pressure to the 1 atm level required for continued dispensing. Labelled gases were transferred to evacuated flasks via a delivery system of minimum volume (**Figure D.1**).

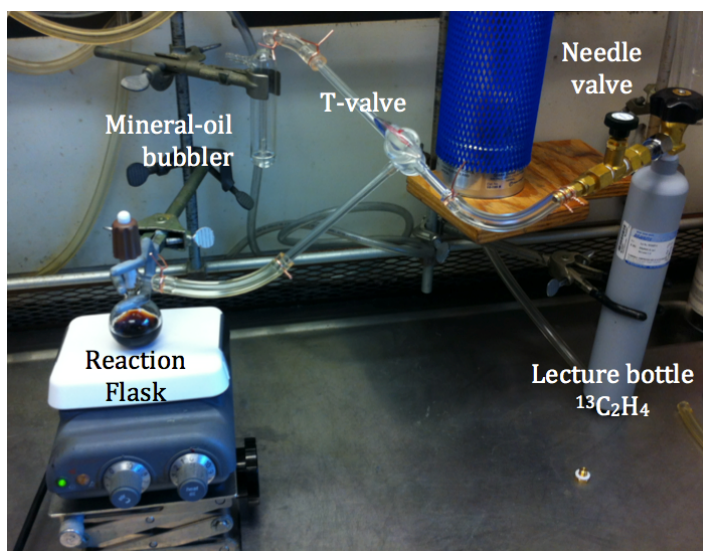


Figure D.1. Transferring isotopically-labelled ethylene from lecture bottle to reaction flask using a T-valve connected to an oil bubbler. Load position: T-valve open to flask and lecture bottle; Pressure check position: T-valve open to oil bubbler.

E. References

- (1) Gallagher, M. M.; Rooney, A. D.; Rooney, J. J. *J. Organomet. Chem.* **2008**, 693, 1252–1260.
- (2) Kotyk, M. W.; Gorelsky, S. I.; Conrad, J. C.; Carra, C.; Fogg, D. E. *Organometallics* **2009**, 28, 5424–5431.

F. List of Contributions

PUBLICATIONS (C = communication, F= full paper, B = book chapter, [†]*equal contributions*)

- 10C. J.A.M. Lummiss, W.L. McClennan, R. McDonald, D.E. Fogg (2014) "Donor-Induced Decomposition of Grubbs Catalysts: An Intercepted Intermediate" *Organometallics* 33, 6738–6741.
- 9F. J.A.M. Lummiss, A.G.G. Botti, D.E. Fogg (2014) "¹³C-labeled Grubbs catalysts" *Catal. Sci. Technol.* 4, 4210–4218 (selected for inside cover, designated as "Hot Article").
- 8F. J.B. Bates,[†] J.A.M. Lummiss,[†] G.A. Bailey, D.E. Fogg (2014) "Operation of the Boomerang Mechanism in Olefin Metathesis Reactions Promoted by the Second-Generation Hoveyda Catalyst" *ACS Catal.* 4(7), 2387–2394 (Highlighted on "All Things Metathesis").
- 7C. J.A.M. Lummiss, B.J. Ireland, J.M. Sommers, D.E. Fogg (2014) "Amine-Mediated Degradation in Olefin Metathesis Reactions that Employ the Second-Generation Grubbs Catalyst" *ChemCatChem* 6(2) 459–463.
- 6B. B.J. van Lierop,[†] J.A.M. Lummiss,[†] D.E. Fogg, Ring Closing Metathesis: A How-To Guide. In: K. Grela (editor) "Olefin Metathesis: Theory and Practice" Weinheim:Wiley 2014 p 85–151.
- 5C. J.A.M. Lummiss, K.C. Oliveira, A.M.T. Prankevicius, A.G. Santos, E.N. dos Santos, D.E. Fogg (2012) "Chemical Plants: High-Value Molecules from Essential Oils." *J. Am. Chem. Soc.* 134 (46), 18889–18891 (Highlighted by ACS News service).
- 4F. B.J. van Lierop, A.M. Reckling, J.A.M. Lummiss, D.E. Fogg (2012) "High-Yield, High-Purity Routes to Second-Generation Ru Metathesis Catalysts from Commercially Available Precursors." *ChemCatChem*, 4 (12), 2020–2025 (selected as Cover Article).
- 3C. J.A.M. Lummiss, N.J. Beach, J. Smith, D.E. Fogg (2012) "Targeting an Achilles Heel in Olefin Metathesis: A Strategy for High-Yield Synthesis of Second-Generation Grubbs Methylidene Catalysts." *Catal. Sci. Technol.* 2, 1630–1632 (Designated as "Hot Article").
- 2F. N.J. Beach, J.A.M. Lummiss, J.M. Bates, D.E. Fogg (2012) "Reactions of Grubbs Catalysts with Excess Methoxide: Novel Methoxyhydride Complexes of Ruthenium." *Organometallics*, 31 (16), 2349–2356 (Highlighted on "All Things Metathesis").
- 1C. A.G.D. Grotevendt, J.A.M. Lummiss, M.L. Mastrodardi, D.E. Fogg (2011) "Ethylene-Promoted versus Ethylene-Free Enyne Metathesis." *J. Am. Chem. Soc.* 133 (40), 15918–15921.

MANUSCRIPTS IN PREPARATION (C = communication, F = full paper, R = review)

- 4R. J.A.M. Lummiss, D.E. Fogg "Ruthenium catalyzed olefin metathesis: recent insights and current understanding" (**invited**) *Acc. Chem. Res.*
- 3C. J.A.M. Lummiss, D.E. Fogg "Morphing a Ru-metathesis catalyst into a cyclopropanation catalyst through ligand exchange" *Organometallics*.
- 2F. F.A. Perras, J.A.M. Lummiss, D.L. Bryce, D.E. Fogg "Origin of the reactivity difference between the Grubbs catalyst and its methylidene resting state: A solid-state NMR study" *Organometallics*.
- 1R. J.A.M. Lummiss, C.S. Higman, D.E. Fogg "Molecular Metathesis Comes of Age: Emerging Applications in Fine Chemicals and Pharmaceutical Manufacturing" (**invited**) *Angew. Chem. Int. Ed.*

PRESENTATIONS (^ presenting author; P = poster presentation; O = oral presentation)

- 24P W.L. McClennan,^ J.A.M. Lummiss, D.E. Fogg (2014), Inorganic Discussion Weekend, Montreal, Nov 14-16 (Regional).
- 23P A.G.G. Botti,^ J.A.M. Lummiss, K.A. Campbell, D.E. Fogg (2014), Inorganic Discussion Weekend, Montreal, Nov 14-16 (Regional).
- 22O D.E.Fogg,^ J.A.M. Lummiss (2014) 20th Molecular Complexity in Modern Chemistry, Moscow, Sep. 13-19 (International).
- 21P A.G.G. Botti,^ J.A.M. Lummiss, D.E. Fogg (2014), 19th International Symposium on Homogenous Catalysis, Ottawa, Jul. 6-11 (International) .
- 20P F.A. Perras,^ J.A.M. Lummiss, D.E. Fogg, D.L. Bryce (2014), 19th International Symposium on Homogenous Catalysis, Ottawa, Jul. 6-11 (International).
- 19P J.A.M. Lummiss^, J.M. Bates, G.A. Bailey, D.E. Fogg (2014), 19th International Symposium on Homogenous Catalysis, Ottawa, Jul. 6-11 (International).
- 18O J.A.M. Lummiss, K.A. Campbell, D.E. Fogg^ (2014) 97th Canadian Society for Chemistry Conference, Vancouver, June 1-5 (National).
- 17O J.A.M. Lummiss^, D.E. Fogg (2013) Center for Catalysis Research and Innovation: Lunch-time technical talk, uOttawa June 20 (Regional).
- 16O J.A.M. Lummiss^, D.E. Fogg (2013) 95th Canadian Society for Chemistry Conference, Quebec City, May 26-30 (National).
- 15O J.A.M. Lummiss^, D.E. Fogg (2013) Atlantic Inorganic Discussion Weekend, Moncton, Mar. 22-24 (Regional).
- 14O J.A.M. Lummiss^, D.E. Fogg (2012) Inorganic Discussion Weekend, Ottawa, Nov. 2-4 (Regional).
- 13P J.A.M. Lummiss, D.E. Fogg^ (2012) 18th International Symposium on Homogenous Catalysis, France, Jul. 9-13 (International).
- 12O J.A.M. Lummiss, E.N. dos Santos, K.C. Oliveira, D.E. Fogg^ (2012) 95th Canadian Society for Chemistry Conference, Calgary, May 26-30 (National).
- 11O J.A.M. Lummiss^, D.E. Fogg (2012) 95th Canadian Society for Chemistry Conference, Calgary, May 26-30 (National).
- 10O J.A.M. Lummiss^, D.E. Fogg (2012) Ottawa-Carleton Chemistry Symposium, Ottawa, May 18 (Institutional).
- 9P A. Reckling^, J.A.M. Lummiss, D.E. Fogg (2011) 24^{ième} Entretiens Jacques Cartier, Ottawa, Sep. 29-30 (International).
- 8P J.A.M. Lummiss^, D.E. Fogg (2011) 24^{ième} Entretiens Jacques Cartier, Ottawa, Sep. 29-30 (International).
- 7P J.A.M. Lummiss^, D.E. Fogg (2011) Center for Catalysis Research and Innovation Annual Meeting, Ottawa, Sep. 15 (Institutional).
- 6P A. Reckling^, J.A.M. Lummiss, D.E. Fogg (2011) 94th Canadian Society for Chemistry Conference, Montreal, Jun. 5-9 (Institutional).
- 5P J.A.M. Lummiss^, D.E. Fogg (2011) 94th Canadian Society for Chemistry Conference, Montreal, Jun. 5-9 (National).
- 4P J.A.M. Lummiss^, D.E. Fogg (2011) Ottawa-Carleton Chemistry Symposium, Ottawa, May 27 (Institutional).
- 3P J.A.M. Lummiss^, D.E. Fogg (2010); 93rd Canadian Society for Chemistry Conference, Toronto, May 29- Jun. 2 (National).
- 2P J.A.M. Lummiss^, D.E. Fogg. (2010); Ottawa-Carleton Chemistry Symposium,

- Ottawa, May 21 (Institutional).
- 1P. J.A.M. Lummiss[^], D.E. Fogg. (2009); 92nd Canadian Society for Chemistry Conference, Hamilton, May 30-Jun. 3 (National).