

**Inside the Cycle: Understanding and Overcoming
Decomposition of Key Intermediates in Olefin Metathesis**

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Abstract

Ru-catalyzed olefin metathesis is an exceptionally powerful, versatile methodology for the assembly of carbon–carbon bonds. The *N*-heterocyclic carbene (NHC)-stabilized, “second-generation” Ru catalysts have enabled groundbreaking recent advances, ranging from the RCM assembly of cyclic peptides as hepatitis C virus therapeutics, to the elaboration of renewable seed oils and phenylpropanoids into value-added products and chemicals. However, key limitations arise from facile catalyst decomposition. Despite a plethora of studies on the synthesis of new catalysts, and on the decomposition processes accessible to the precatalyst and resting-state species, the underlying principles that govern decomposition of the active intermediates have been surprisingly little examined. One important reason for this is their incredible reactivity: the four-coordinate methyldiene intermediate $\text{RuCl}_2(\text{H}_2\text{IMes})(=\text{CH}_2)$ is too short-lived to be observed, while the metallacyclobutane (MCB) intermediate $\text{RuCl}_2(\text{H}_2\text{IMes})(\kappa^2\text{-C}_3\text{H}_6)$ can only be observed below $-40\text{ }^\circ\text{C}$. This makes them extremely challenging, but also fascinating targets for study. Understanding the underlying chemistry that dictates their reactivity and decomposition is essential for informed catalyst and process redesign, and is thus of fundamental interest, but also considerable practical importance.

This thesis work thus aims at understanding the decomposition of active intermediates relevant to the highly-active, second-generation class of catalysts. Emphasis is placed on examining a variety of metathesis contexts, as well as providing solutions. Treated first are the decomposition pathways that arise during metathesis of electron-deficient olefins, a frontier area in organic synthesis, and in the utilization of renewable resources. An unexpected correlation is revealed between rapid catalyst decomposition, and the presence of a stabilizing PCy_3 ligand in the standard catalyst for this reaction. The nucleophilic phosphine ligand is shown to attack an acrylate olefin, forming enolates that function as potent Brønsted bases. Literature evidence suggests that such strong bases are innocuous towards the precatalyst, pointing towards a key role for the active intermediates in Brønsted base-induced catalyst decomposition.

Precisely which intermediate is involved, as well as the site of deprotonation, is elucidated next. Prior to this work, the NHC ligand was widely believed to be the target for attack. However, through labelling experiments, analysis of the Ru and organic byproducts, and computational studies, deprotonation is shown to occur at the MCB ring. Moreover, MCB deprotonation is

revealed to be unexpectedly general, and not contingent on the presence of either an exceptionally strong base, or an electron-deficient substrate. This understanding is key, given recent reports from pharma highlighting the adverse impact of base contaminants, as well as current interest in metathesis of amine-containing substrates.

Next examined are the *intrinsic* decomposition pathways operative for the MCB and four-coordinate methyldiene. Prior to this work, the only reported pathway for decomposition of these two species involved β -elimination of the MCB ring as propene. However, β -elimination is shown to play an unexpectedly minor role in catalyst decomposition: less than 40% propenes are observed, even under conditions expected to favour MCB elimination. Bimolecular coupling of the methyldiene, with loss of the methyldiene moiety as ethylene, is proposed to account for the difference. Thus, transiently-stabilized adducts $\text{RuCl}_2(\text{H}_2\text{IMes})(=\text{CH}_2)(\text{L})_n$ ($\text{L} = o$ -dianiline or pyridine) are synthesized at temperatures down to -120°C . On warming, these adducts lose L_n and rapidly decompose via bimolecular coupling, with loss of the methyldiene moiety as ethylene. These experiments provide the first unambiguous evidence for bimolecular coupling in the important "second-generation" Ru systems, nearly two decades after which this pathway was dismissed in leading papers and reviews.

The last two sections focus on solutions. First, a powerful, straightforward solution to the "enolate problem" is developed, whereby the acrylate enolates are quenched and sequestered via reaction with a polyphenol resin. Then, methods for preventing catalyst decomposition during matrix-assisted laser desorption / ionization mass spectrometry (MALDI-MS) are developed, via elucidation of the instrumental and experimental factors that promote successful analysis. As one of the only MS methods capable of affording insight into neutral metal complexes and catalysts, MALDI has unique potential to enable routine analysis of catalyst speciation and decomposition in situ, under real catalytic conditions, for a wide range of catalytic reactions.

Collectively, the findings in this thesis offer a much more complete understanding of the fundamental pathways accessible to the important, highly-active metathesis intermediates, and offer strategies likely to inform practice in both academic and industrial settings. This understanding is key to harnessing the full potential of metathesis methodologies.

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*I take as my guide the hope of a saint: in crucial things, unity—in important things, diversity—
but in all things, generosity.* – George W. Bush, Inaugural Address

Abbreviations

ATR	attenuated total reflectance
ax	axial (hydrogen atom)
BHT	butylated hydroxytoluene (i.e., 2,6-di- <i>tert</i> -butyl-4-methylphenol)
Bu	butyl
CAAC	cyclic alkyl amino carbene
CHCA	α -cyano-4-hydroxycinnamic acid
CI	chemical ionization
CM	cross-metathesis
COSY	correlation spectroscopy
Cp	cyclopentadienyl anion, C ₅ H ₅ ⁻
CT	charge transfer
Cy	cyclohexyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DCTB	trans-2-[3-(4- <i>tert</i> -butylphenyl)-2-methyl-2-propenylidene]malononitrile
DEPT	distortionless enhancement by polarization transfer
DFT	density functional theory
DHB	2,5-dihydroxybenzoic acid
DMAP	4-dimethylaminopyridine
DMT	dimethyl terephthalate
dppe	1,2-bis(diphenylphosphino)ethane
DT	dithranol
e	equatorial (hydrogen atom)
EHA	2-ethylhexyl acrylate
ESI	electrospray ionization
Et	ethyl
equiv	equivalents
ϵ_A	analyte molar absorptivity at the laser wavelength
ϵ_M	matrix molar absorptivity at the laser wavelength

ϵ_{rel}	relative molar absorptivity at the laser wavelength; i.e., $\epsilon_{\text{M}}/\epsilon_{\text{A}}$
FID	flame-ionization detector
GC	gas chromatography
GC/MS	gas chromatography/mass spectrometry
H ₂ IMes	1,3-bis-(2,4,6-trimethylphenyl)imidazolin-2-ylidene
HMBC	heteronuclear multiple bond coherence
HMQC	heteronuclear multiple quantum coherence
HPLC	high-performance liquid chromatography
IR	infrared
ISD	in-source decay
KTp	potassium tris(1-pyrazolyl)borate
LDI	laser desorption/ionization (i.e., matrix-free)
MALDI	matrix-assisted laser desorption/ionization
MCB	metallacyclobutane
Me	methyl
Mes	mesityl (i.e., 1,3,5-trimethylphenyl)
MMA	methyl methacrylate
MS	mass spectrometry
N.D.	not determined
Nd:YAG	neodymium-doped yttrium aluminum garnet
Nd:YLF	neodymium-doped yttrium lithium fluoride
NHC	<i>N</i> -heterocyclic carbene
NMR	nuclear magnetic resonance
NOESY	nuclear overhauser effect spectroscopy
N.R.	not reported
ORTEP	Oak Ridge thermal ellipsoid plot
Ph	phenyl
PSD	post-source decay
PTFE	poly(tetrafluoroethylene)
py	pyridine
PVP	poly(4-vinylphenol)

Q-TOF	quadrupole time-of-flight
RCM	ring-closing metathesis
RMS	root-mean-square
SA	sinapinic acid
SCF	self-consistent field
Tf	trifluoromethanesulfonate
THF	tetrahydrofuran
TMB	trimethoxybenzene
TMS	trimethylsilyl
TOF	time-of-flight
TTP	2,2':5',2''-terthiophene
UHP	ultra-high purity
XRD	X-ray diffraction

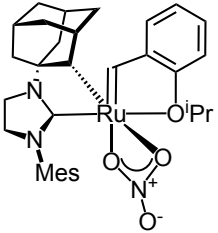
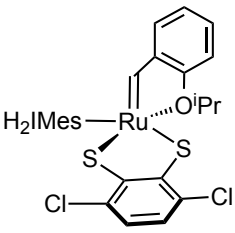
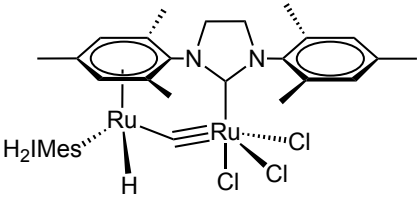
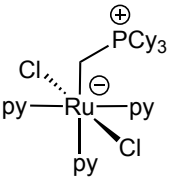
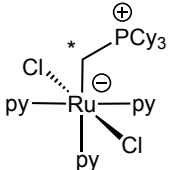
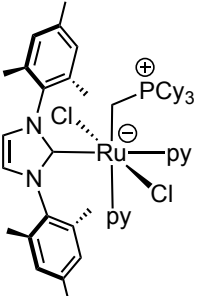
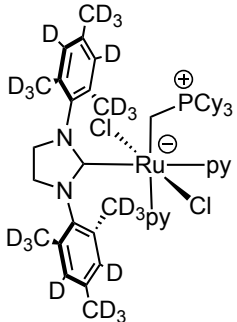
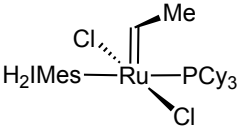
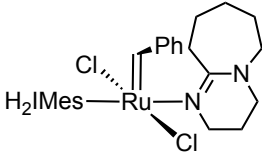
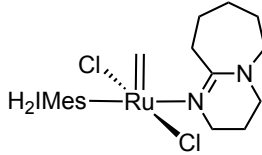
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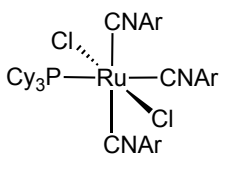
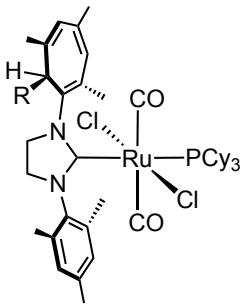
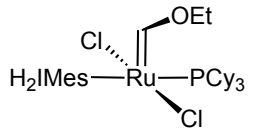
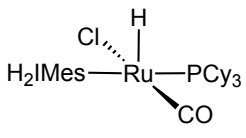
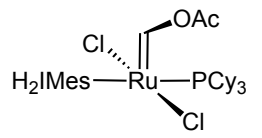
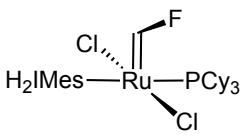
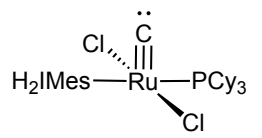
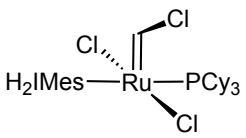
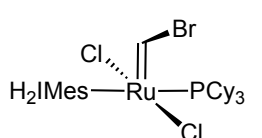
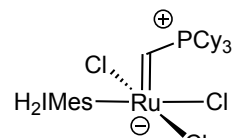
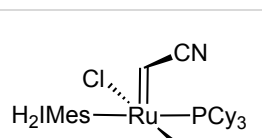
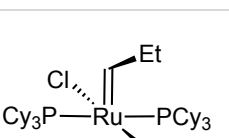
Ruthenium Complexes

#	Structure	#	Structure
G0		G1	
GII		GII-IMes	
GII-PPh3		M2	
M20		GIm	
GIIIm		GIIIm-IMes	
GII-d22		GIIIm-d22	

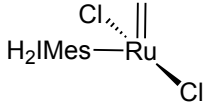
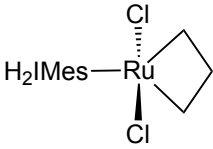
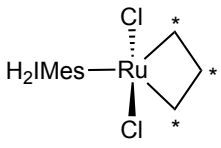
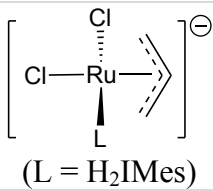
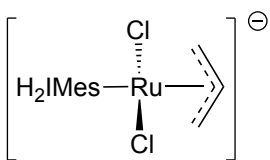
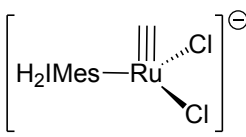
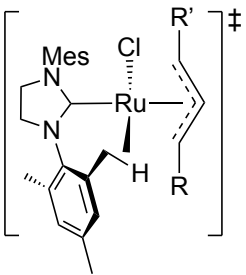
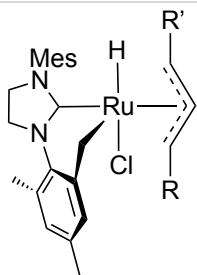
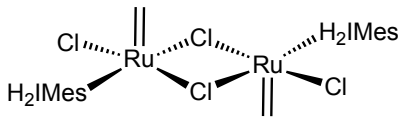
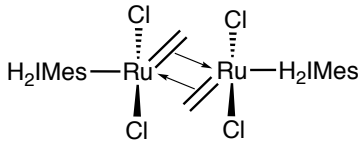
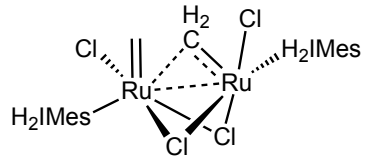
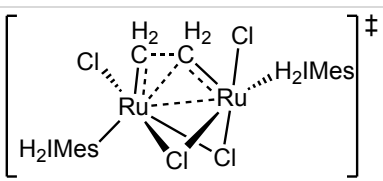
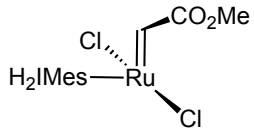
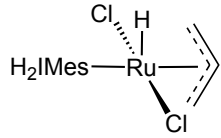
GIIIm*		III	
III-PCy3		nG	
nG-CAAC		M51	
Zhan1B		GIII	
GIII'		GIII^{Br}	
GIIIIm		GIIIIm'	
GIIIe		PII	

PII'		DA	
Ru-1a		Ru-1b	
Ru-1c		Ru-2	
Ru-2'		Ru-3	
Ru-4		Ru-5	
Ru-6		Ru-7	

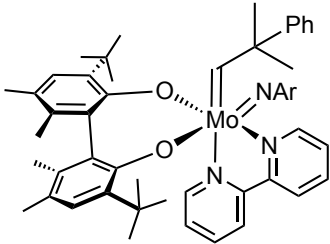
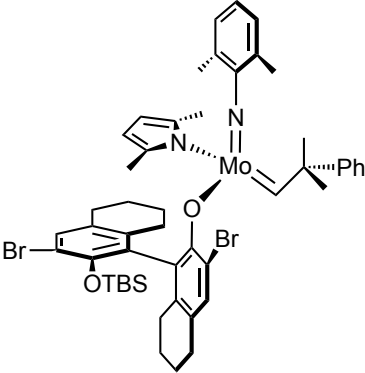
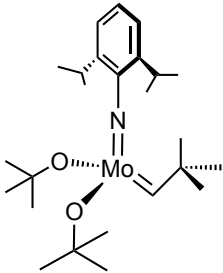
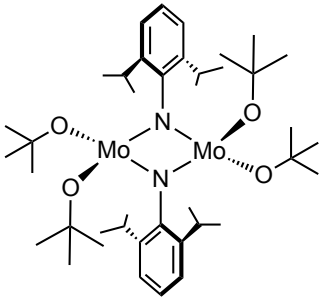
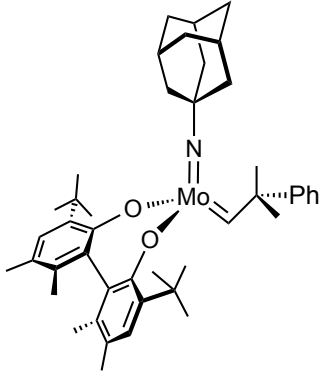
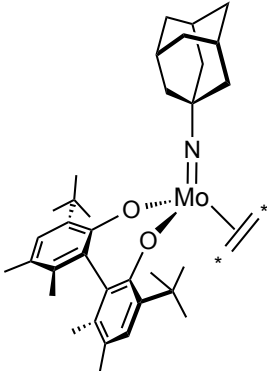
Ru-8		Ru-9	
Ru-10		Ru-11	
Ru-11*		Ru-12	
Ru-13		Ru-14	
Ru-15a		Ru-15b	

Ru-16		Ru-17	
Ru-18		Ru-19	
Ru-20		Ru-21	
Ru-22		Ru-23a	
Ru-23b		Ru-24	
Ru-25		Ru-26	

Ruthenium Intermediates and Transition States

#	Structure	#	Structure
Ru-A		Ru-B	
Ru-B*		Ru-C	 (L = H ₂ IMes)
Ru-C'		Ru-D	
Ru-F		Ru-I	
Ru-Q		Ru-R	
Ru-S		TS-T	
Ru-U		Ru-V	

Other Transition Metal Complexes

#	Structure	#	Structure
Mo-bipy		Mo-MAP	
Mo-1		Mo-2	
Mo-3		Mo-4*	

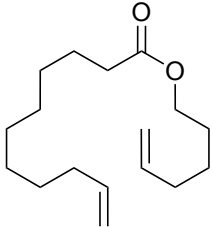
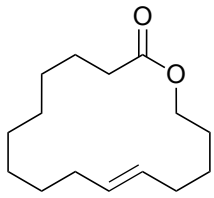
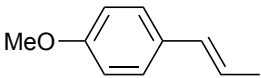
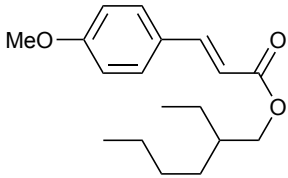
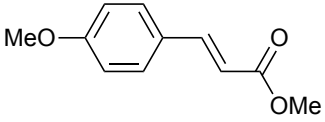
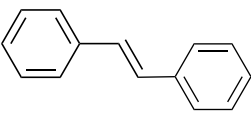
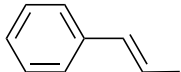
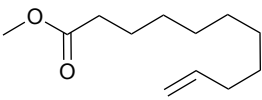
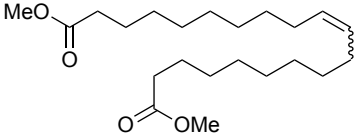
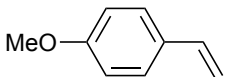
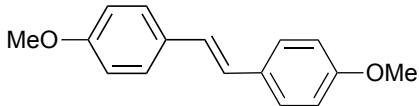
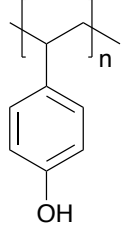
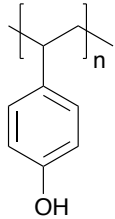
Ligands

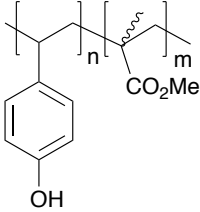
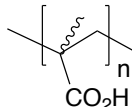
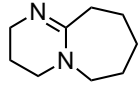
#	Structure	#	Structure
H₂IMes		H₂IMes-d₂₂	
IMes		IPr	
H₂IPr		H₂ITol	
o-Dianiline (ODA)			

Phosphonium Zwitterions and Salts

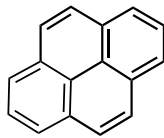
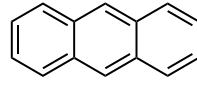
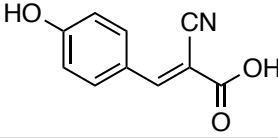
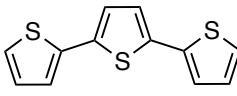
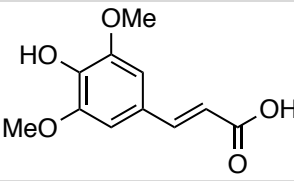
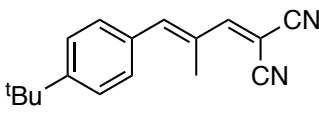
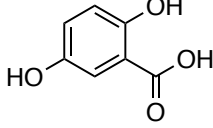
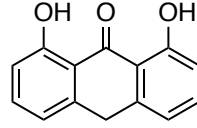
#	Structure	#	Structure
A		[A]Cl	
[B]Cl		B	
[C]Cl			

Organic Compounds and Polymers

#	Structure	#	Structure
1		2	
3		4a	
4b		5	
6		7	
8		9	
10		11	
PVP-11	 PVP-11 $\overline{M}_w = 11,000$	PVP-25	 PVP-25 $\overline{M}_w = 25,000$

PVP-MMA	 PVP-MMA $\overline{M}_w = 8,000-12,000$	Amberlite CG-50	
DBU			

MALDI matrices

#	Structure	#	Structure
pyrene		anthracene	
CHCA		TTP	
SA		DCTB	
DHB		DT	

Chapter 1. Introduction

Homogeneous transition-metal catalysis has reached a remarkable level of development. The range of transformations that can now be promoted with high efficiency and selectivity using metal complexes is tremendous, and important advances continue to be made daily (Figure 1.1).^{1,2} Applications of transition-metal catalysis span a wide range of industrial, academic, and human interests, including synthesis of pharmaceuticals, polymers, materials, and other consumer products;³⁻⁵ construction of novel and elaborate molecular structures and natural products;^{3,6} degradation of environmental contaminants and pollutants;^{7,8} and storage or release of energy via small-molecule, multielectron transformations critical to the mitigation of global warming and climate change.^{9,10} An important example of a catalytically-enabled transformation is olefin metathesis, today one of the most heavily relied-upon transformations for the assembly of carbon–carbon bonds.^{11,12} Like other metal-catalyzed reactions, olefin metathesis has reached new heights even in the past decade, with pioneering advances in the deployment of metathesis

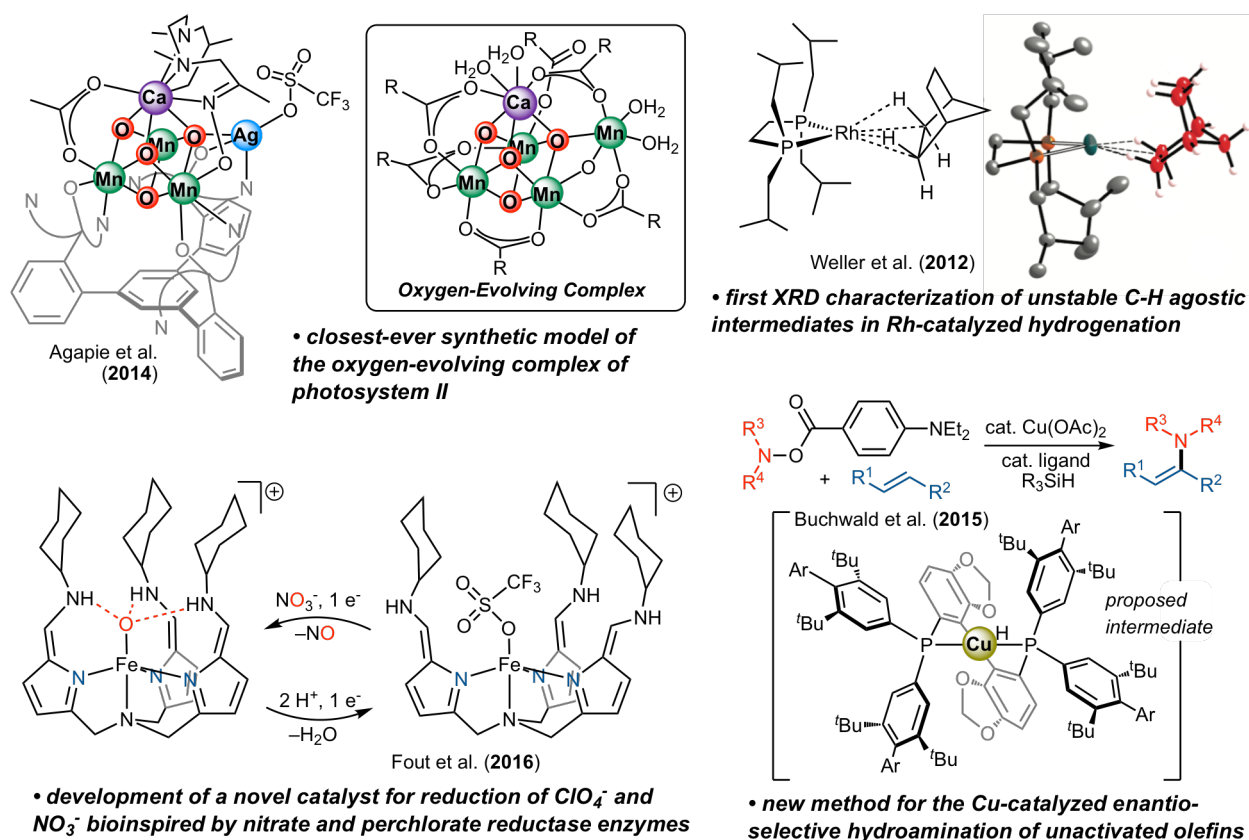


Figure 1.1. Selected high-profile advances in the construction, discovery, and understanding of transition-metal catalysts over the past 5 years.²

in industry;¹³⁻¹⁷ discovery of new catalysts that exhibit unprecedented productivity, Z-selectivity, and functional group tolerance;¹⁸⁻²² development of renewable metathesis methodologies;^{14,17,23-25} realization of base-metal metathesis;²⁶⁻³¹ and more (Figure 1.2). Even with all of these achievements, chemists continue to aspire to higher levels, and many further advances can be expected in the coming years.³²

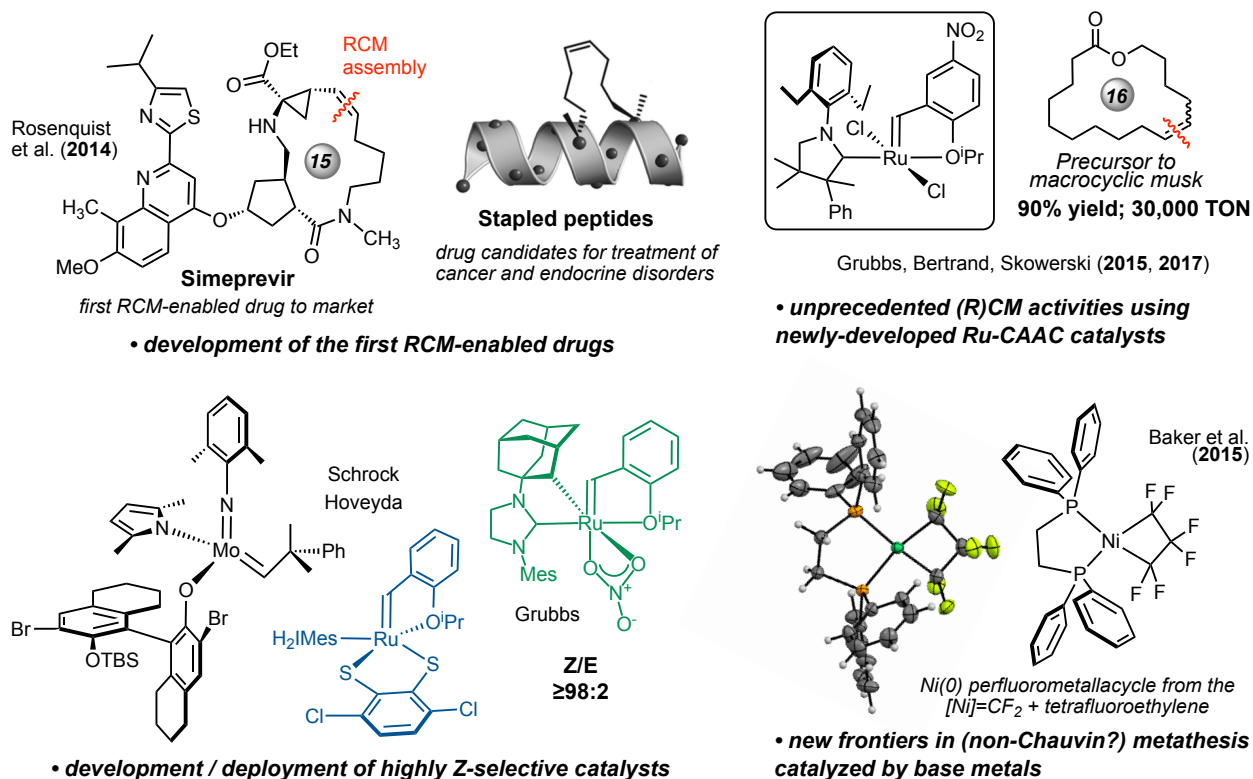


Figure 1.2. Selected advances in olefin metathesis over the past decade.^{19,20,22,27,33,34}

Our ability to reap the fruits of catalysis (e.g., Figures 1.1 and 1.2) critically depends on understanding the fundamental processes involved. For transition-metal catalysts, such insight has been built up over many decades; and so in many ways, the achievements of today are a result of the hard labours of our scientific predecessors. This is especially true for olefin metathesis. Olefin metathesis has been practiced industrially since the late 1950s, when chemists at DuPont, Standard Oil, and Phillips Petroleum reported that homogeneous Mo oxides or $Mo(CO)_6$ on alumina very capably transformed propene into ethylene and 2-butene at high temperatures.^{35,36} However, the actual structure of the active sites were unknown until Chauvin's perceptive mechanistic proposal for olefin metathesis appeared. Chauvin proposed that metathesis occurs via a series of [2+2] cycloaddition / cycloreversion sequences involving the incoming olefin and

a metal alkylidene species ($[M]=CHR$; Figure 1.3a).³⁷ As a result, chemists began to tackle the interesting fundamental question of how to construct well-defined alkylidene and metallacyclobutane (MCB) complexes. This led to a flurry of effort, and a plethora of very interesting and useful alkylidene and MCB complexes that might not have been discovered otherwise (Figure 1.3b).³⁸⁻⁴⁷ Synthesis of the first metathesis-active MCB complexes from Tebbe's reagent $Ti(\eta^5-Cp)_2(\mu^2-CH_2)(\mu^2-Cl)(AlMe_2)$ (see Figure 1.3b)⁴⁴ led to the sequential identification of all of the proposed intermediates in the Chauvin cycle.⁴⁵ All of these efforts culminated in the development of the first well-defined, molecular metathesis catalysts.^{46,47}

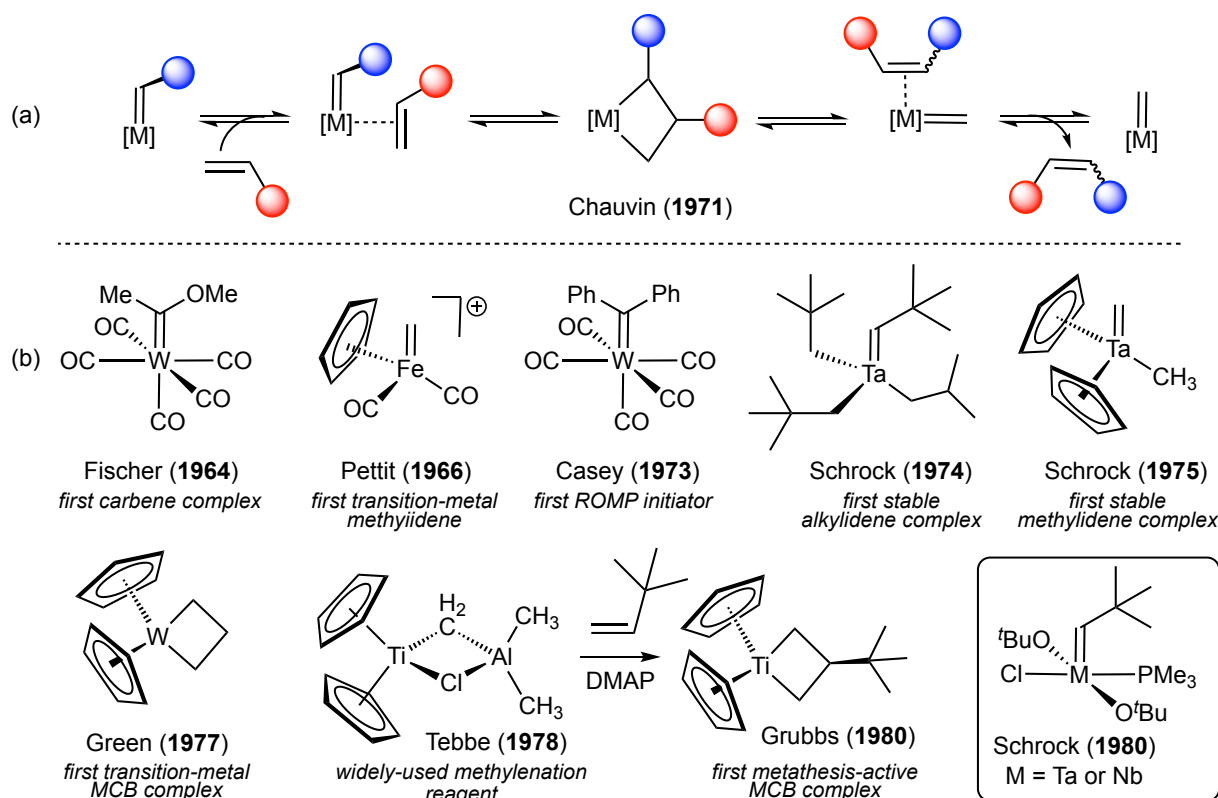
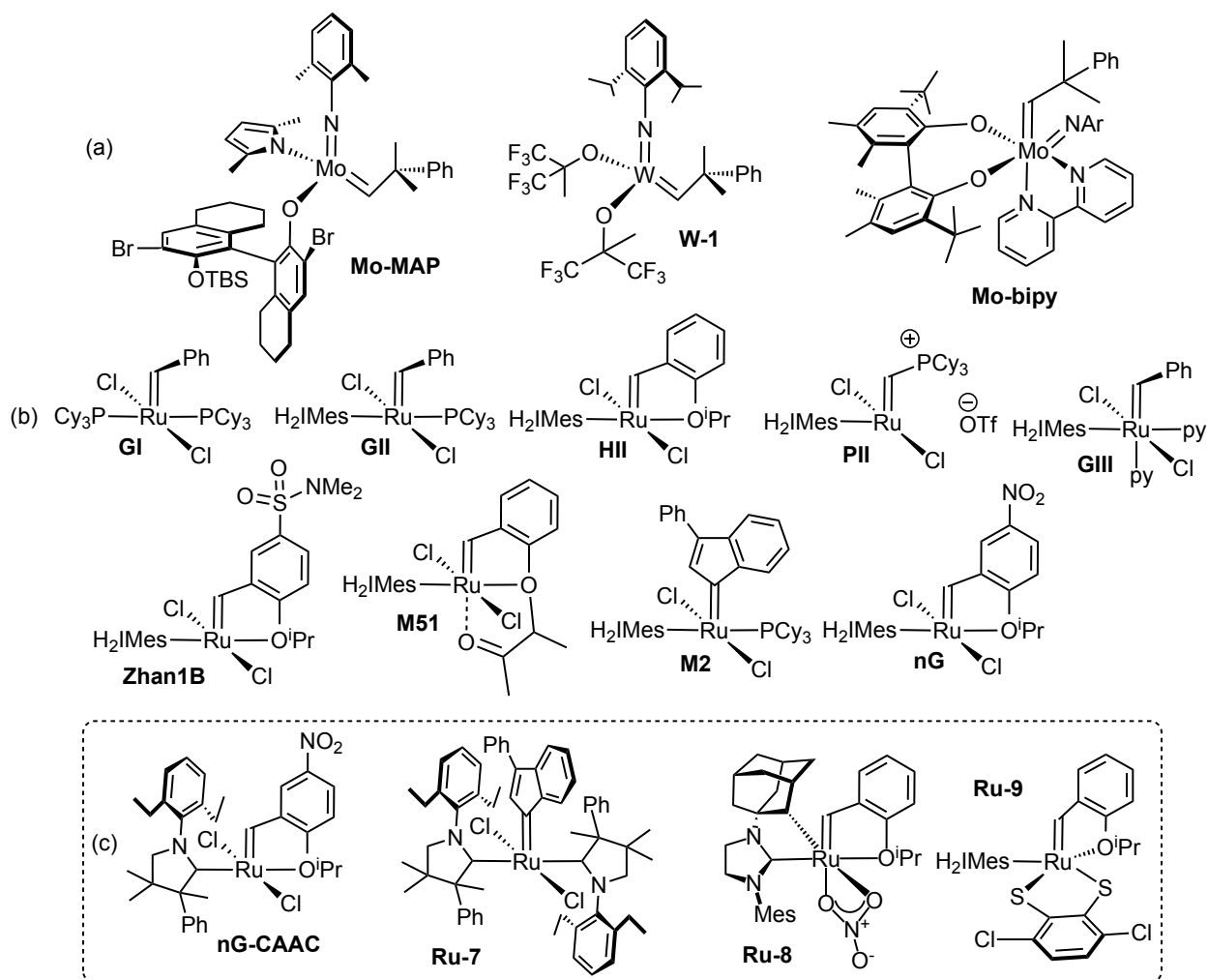


Figure 1.3. Key advances in metathesis, circa 1975. (a) The Chauvin mechanism for olefin metathesis.³⁷ (b) Some of the first-ever metallacyclobutane and alkylidene complexes synthesized,³⁸⁻⁴⁵ including (inset) the first well-defined molecular metathesis catalyst.^{46,47}

Additional challenges arise in the refinement of catalyst structures for improved activity and robustness. In olefin metathesis, unlike many other metal-catalyzed reactions (such as, for example, addition of $H-X$ across a double bond),^{48,49} the active ligands are not regenerated in every cycle. Instead, processes that lead to loss of the $[M]=CHR$ or MCB ligand result in irreversible catalyst deactivation. Possible consequences include (i) the need for higher catalyst

loadings (resulting in inflated catalyst costs); (ii) greater demands on product purification, to remove the spent catalyst;⁵⁰⁻⁵² and (iii) undesired side-reactions promoted by the decomposed catalyst.^{15,16,53-55} Catalyst decomposition studies are therefore urgently required to inform catalyst redesign efforts.⁵⁶⁻⁵⁸ Such studies have already been integral to the development of the state-of-the-art catalysts in current use (see, e.g., Chart 1.1). However, catalyst productivity remains one of the major barriers preventing broad uptake of metathesis methodologies, both in industry and in academia. There is much greater potential to be realized before the full power of metathesis methodologies can be brought to fruition.

Chart 1.1. Leading metathesis catalysts in current use. (a) Group 6 catalysts, or (Mo-bipy) catalyst precursors. (b) Commercially available Ru catalysts (and parent “first-generation” catalyst GI). (c) Recently-developed highly-active and Z-selective Ru catalysts.



Beyond catalyst redesign, however, decomposition studies have the potential to offer much broader insight (Figure 1.4). Most notably, such studies may reveal strategies for the installation of the alkylidene or MCB ligand, via the reverse process for ligand loss.⁵⁹ Besides the tantalizing potential capacity for reinstallation of the alkylidene ligand in situ *during* catalysis,^{57,60} the discovery of new and improved strategies for alkylidene installation would alleviate one of the most cumbersome, costly, and (potentially) dangerous^{61,62} steps of the catalyst synthesis.⁶³ Meanwhile, methods for installation of metathesis-active MCBs would open up new avenues for catalyst synthesis. Decomposition studies may also offer predictive power in terms of which functional groups, contaminants, and/or conditions are likely to be problematic. They may therefore inform *process* and/or *reactor* redesign.^{15,16,53,64,65} Finally, there are important fundamental insights to be gained. The non-Chauvin behaviour of the key MCB and $[M]=CHR$ entities for the groups 4-7 systems is already relatively well understood,⁵⁹ for the important second-generation Ru systems, however, it is a frontier for discovery. Loss of the MCB / $[M]=CHR$ ligand results in the formation of highly reactive, coordinatively unsaturated species that can participate in additional pathways, such as C=C isomerization⁶⁶⁻⁶⁸ and nanoparticle formation.⁶⁹ Such processes are generally undesired, in the context of metathesis; however, learning how to control them could lead to important tandem processes that are inherently more efficient, atom-economic, and green.⁷⁰⁻⁷² Understanding of catalyst decomposition processes can

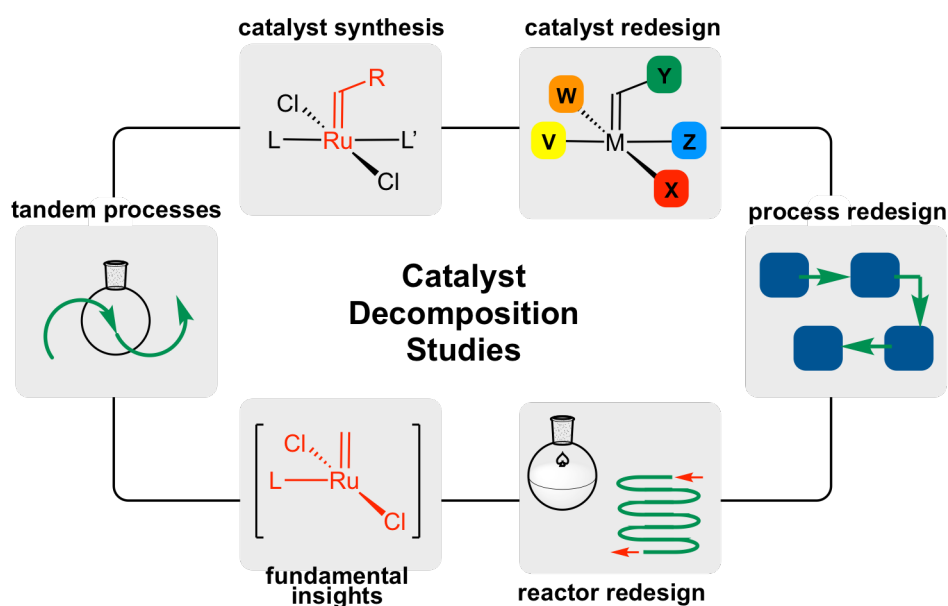
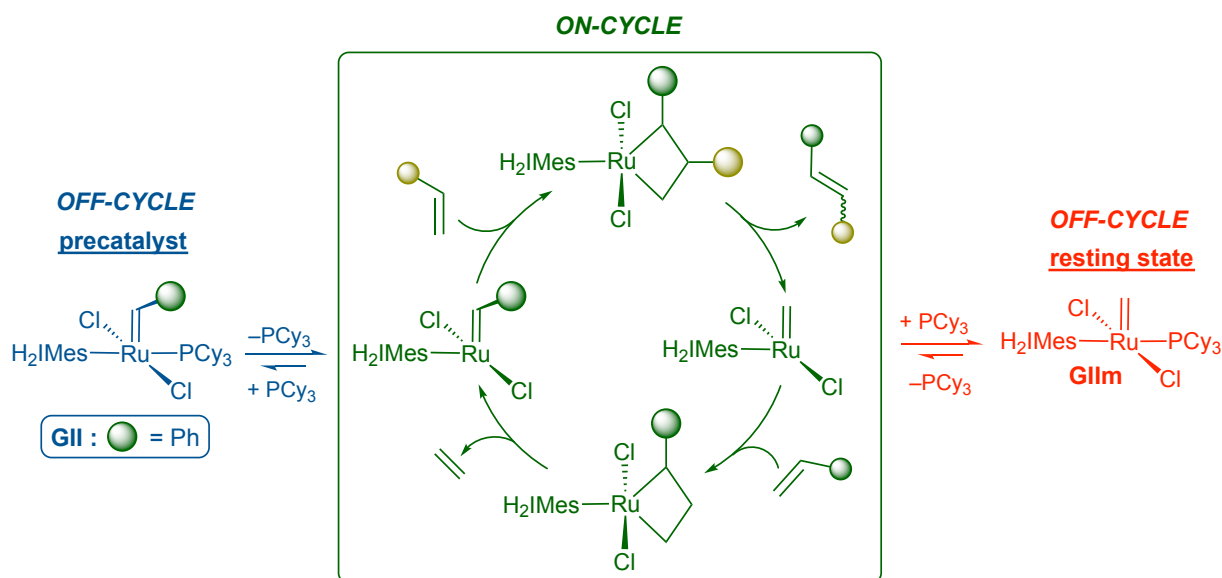


Figure 1.4. Potential insights arising from catalyst decomposition studies.

therefore not only inform the practice of metathesis, but also lead to new and unexpected advances for transition-metal catalysis as a whole.

This thesis work focuses chiefly on the decomposition of highly active, “second-generation” Ru catalysts (Chart 1.1b), as the most widely-used catalysts in metathesis. Prior work in this area has been devoted principally to understanding decomposition of the *off-cycle* precatalyst and resting state species, or on developing an essentially phenomenological understanding of the factors that limit catalyst performance. Here, emphasis is placed on revealing the underlying processes involved in decomposition of the *on-cycle* active Ru-MCB and four-coordinate $[\text{Ru}]=\text{CHR}$ species, as the most vulnerable species present during catalysis (Scheme 1.1). Outlined below are the major decomposition pathways known for the second-generation catalysts, prior to this thesis work. Decomposition processes for the group 4-7 catalysts are briefly summarized, as context to the present work on the Ru systems (Section 1.1). Decomposition processes involving the Grubbs resting-state species **GIIIm** and precatalysts **GII**, **III**, and **nG** are treated next (Sections 1.2–1.5). Prior work on catalyst decomposition during metathesis of directly functionalized olefins is then considered (Section 1.6). Finally, decomposition processes known to involve the active Ru-MCB and four-coordinate $[\text{Ru}]=\text{CHR}$ species are examined (Section 1.7), in order to set the stage for the key advances reported herein, summarized in Section 1.8).

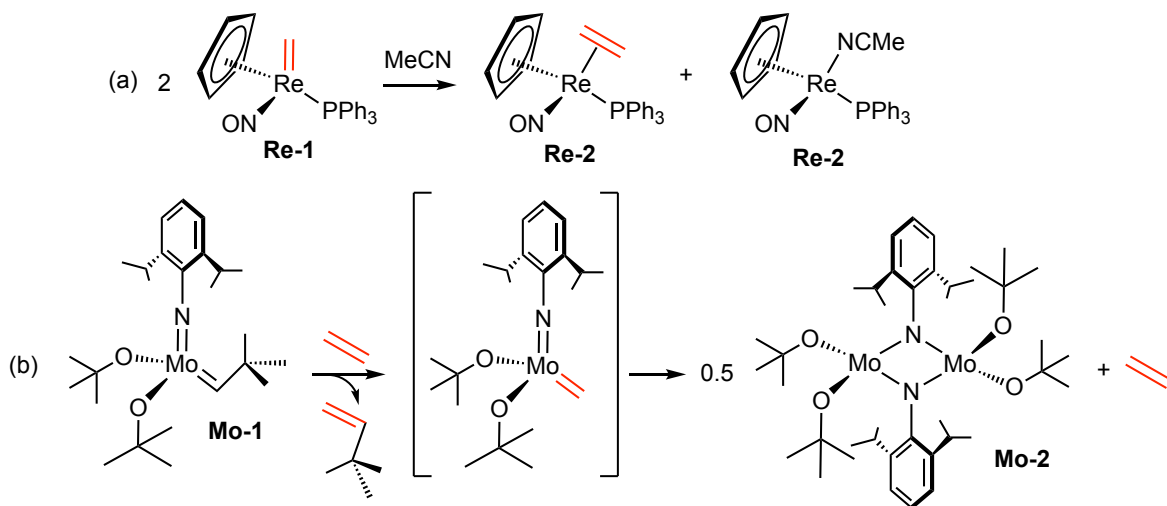
Scheme 1.1. Understanding decomposition in olefin metathesis: on- vs. off-cycle species. Catalytic cycle shown with precatalyst **GII as an exemplar.**



1.1 Catalyst Decomposition in the Group 4-7 Systems

Catalyst decomposition in the group 4-7 systems occurs according to two principal pathways: (i) bimolecular coupling of $[M]=CHR$ intermediates, with elimination of the alkylidene as an olefin of the form $RHC=CHR$; and (ii) β -H elimination of metallacyclobutane to yield propenes.^{59,73} Bimolecular coupling was first studied in detail for the early Re and Ta methylidenes,^{74,75} and was later extended to the highly-active Mo and W catalysts (Scheme 1.2).⁷⁶⁻⁸⁰ Within the early systems, quantification of the key marker for coupling, ethylene, was facilitated by its high affinity for the low-coordinate metal complexes formed. Ethylene binding prevented its loss into the headspace, and enabled its detection and quantitation as the metal-olefin complex.^{74,75,78-80}

Scheme 1.2. Bimolecular coupling of representative early-metal methylidenes.^{75,76}



Insight into the mechanism for coupling was provided by detailed kinetic and labelling studies.^{74,75} Kinetic studies confirmed clean, second-order behaviour over a wide range of concentrations and temperatures. Studies with labelled $[Re]=CD_2$ analogs of **Re-1** revealed an *inverse* secondary isotope effect ($k_H / k_D = 0.79$), consistent with a partial hybridization change from sp^2 to sp^3 during the rate-limiting coupling step.⁷⁵ Experiments with enantiomerically pure (R)- and (S)-**Re-1** revealed a significant kinetic preference for homochiral over heterochiral coupling.⁷⁵ The observed preference could not be rationalized assuming a 1,3-dimetallacyclic transition state, which would predict significant steric repulsion between the two incoming Cp ligands (Figure 1.5a). A 1,2-dimetallacyclic transition state is a possible alternative (Figure 1.5b), but this solution was not considered by the authors.

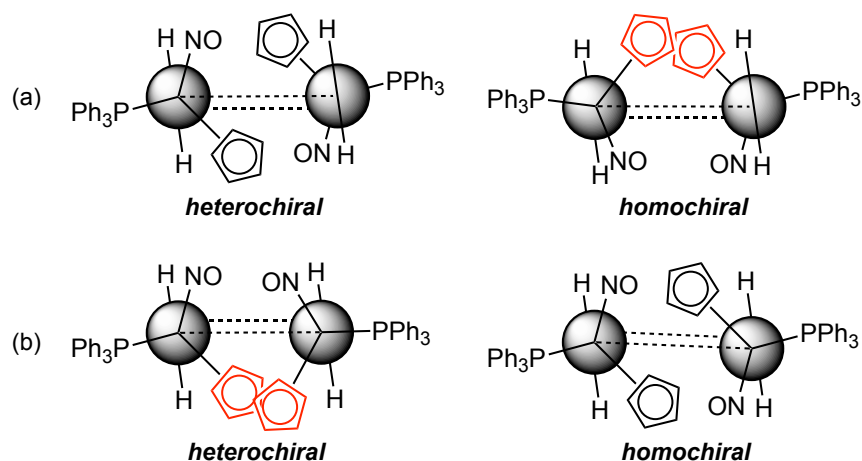
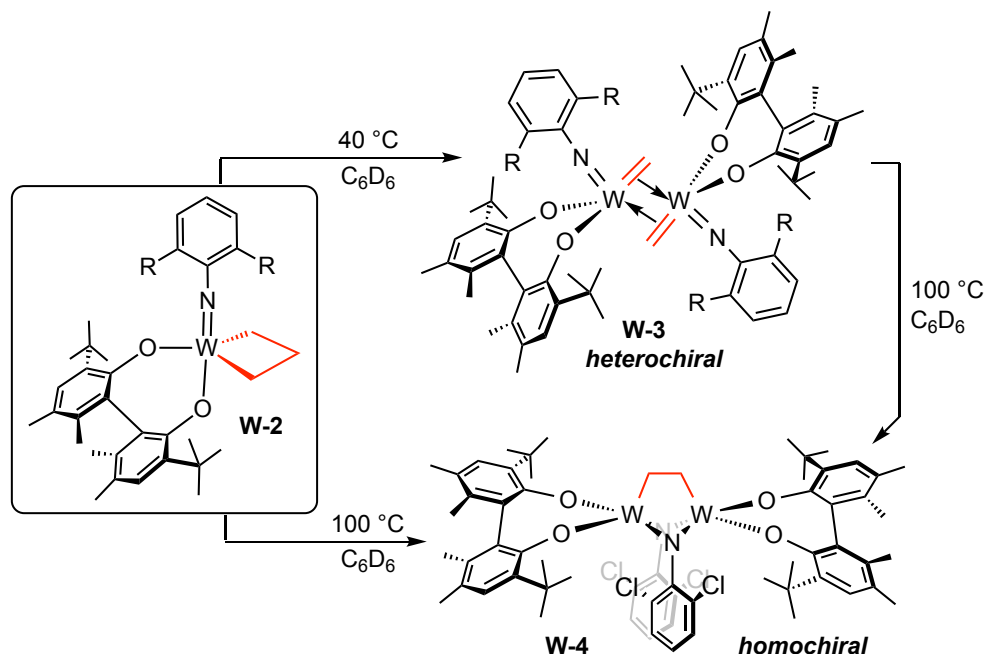


Figure 1.5. Newman projections for homochiral and heterochiral coupling of **Re-1**, assuming (a) a 1,3-dimetallacyclic transition state; and (b) a 1,2-dimetallacyclic transition state. Steric repulsion is emphasized in red. The largest ligand present, PPh₃, is assumed to occupy the position *anti* to the coupling methylidene.

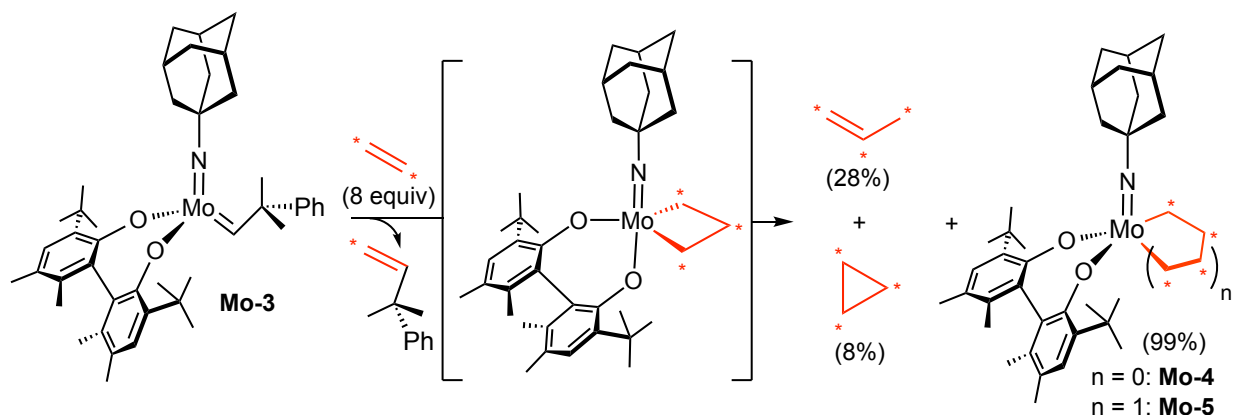
More recently, the isolation and crystallographic characterization of stable dimetallacyclobutane complexes on decomposition of a chiral MCB **W-2** provided further insight (Scheme 1.3).^{78,80} Thus, heterochiral 1,3-dimetallacyclobutane **W-3** formed on decomposition of MCB **W-2** at 40 °C in C₆D₆, while homochiral 1,2-dimetallacyclobutane **W-4** was produced at 100 °C.⁸⁰ **W-4** was also observed on thermolysis of **W-3** at 100 °C, albeit in limited yields (ca. 25%). Reversible ethylene loss was observed from **W-4**, with formation of an ethylene-free W=W dimer.⁷⁹ The homochirality of 1,3-dimetallacyclobutane **W-4**, in contrast to heterochiral **W-3**, demonstrated that **W-3** is not an intermediate en route to **W-4**. Rather, **W-3** likely dedimerizes, and then recombines with another W-methylidene of identical chirality. **W-3** and **W-4** are important in demonstrating the viability of both 1,2- and 1,3-dimetallacyclic intermediates in bimolecular coupling of **W-2**. Methylidene coupling in these systems is proposed to proceed either via a homochiral analog of **W-3**, or homochiral **W-4**, or a combination of the two.

Scheme 1.3. Observation of 1,2- and 1,3-dimetallacyclobutane complexes on decomposition of chiral MCB W-2.⁸⁰



In the Mo and W catalysts bearing bulky aryloxy and/or imido ligands, bimolecular coupling is slowed, and β -H elimination begins to compete (Scheme 1.4).^{78,80-82} While the organometallic fragments formed on ligand loss are identical for both bimolecular coupling and β -H elimination, propene can be used as a diagnostic marker for the latter. β -H elimination is accelerated in the presence of excess ethylene, which shuttles the active catalyst into the MCB state.⁷⁸

Scheme 1.4. β -H Elimination of the MCB ligand in a representative Mo catalyst.^a

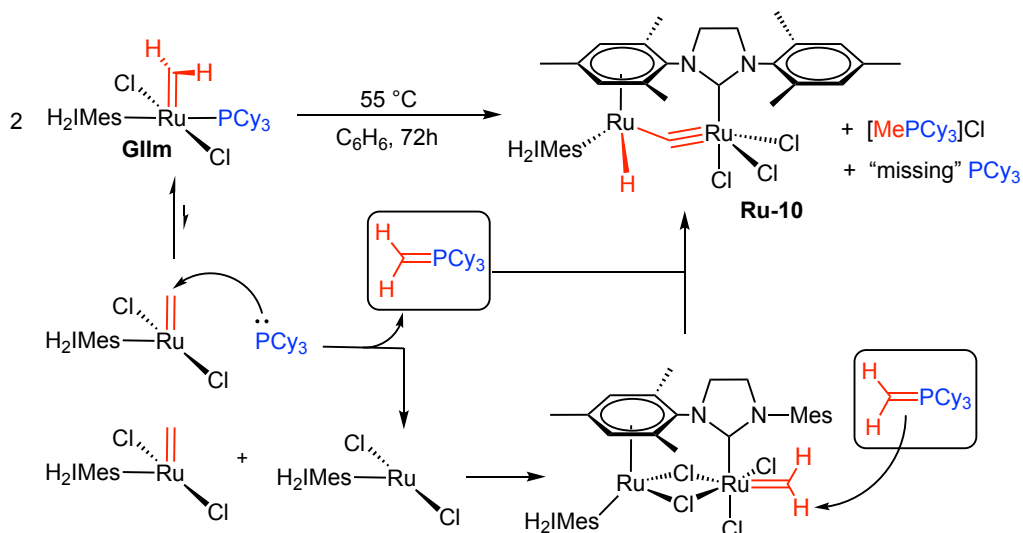


^a Molybdacyclopentane **Mo-5** originates from addition of ethylene to Mo-C₂H₄ complex **Mo-4**.

1.2 Decomposition of the Grubbs Resting-State Species, **GIIm**

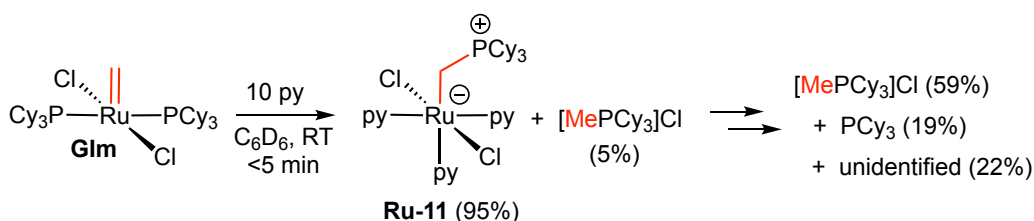
Low productivity for the second-generation Grubbs catalyst **GII** stems from the poor lability and potent nucleophilicity of the stabilizing PCy_3 ligand. Low PCy_3 lability impedes catalyst turn-on and shunts the active catalyst off-cycle as resting-state species **GIIm**.^{83,84} PCy_3 loss from **GIIm** is dramatically reduced vs. **GII** (ca. 280x),⁸⁴ a consequence of the limited steric pressure exerted by the methylidene on the bulky PCy_3 ligand.⁸⁵⁻⁸⁷ Even more problematic than low lability, however, is facile catalyst decomposition by PCy_3 . Notwithstanding the slow initiation of **GII** (which results in a very low effective concentration of PCy_3 and active catalyst), PCy_3 acts as a voracious nucleophile, readily abstracting the methylidene ligand and HCl from the catalyst, and forming phosphonium salt $[\text{MePCy}_3]\text{Cl}$ as a byproduct (Scheme 1.5).^{88,89} In thermolysis studies with **GIIm**, dimer **Ru-10** was isolated as a byproduct, leading Hong and Grubbs to propose a mechanism whereby the ylide $\text{H}_2\text{C}=\text{PCy}_3$ formed on nucleophilic abstraction deprotonates a second methylidene equivalent. However, none of the proposed intermediates in the pathway were conclusively identified.^{88,89} Moreover, the implied resistance of H_2IMes to providing a proton is unexpected, given the growing list of reports demonstrating facile NHC cyclometallation in these and related complexes.⁸⁹⁻⁹⁸ Finally, the low yield and slow rate of formation of **Ru-10** (ca. 45%, over 3 d at 55 °C; cf. catalysis on the timescale of hours), as well as the curious “missing” PCy_3 balance that arises (highlighted in blue in Scheme 1.5, but not mentioned by the authors) suggest that other pathways may be involved.

Scheme 1.5. First proposed pathway for formation of dimer Ru-10 and $[\text{MePCy}_3]\text{Cl}$ on thermolysis of isolated methylidene complex **GIIm.⁸⁸**



Observation of σ -Alkyl Intermediates. Insight into the PCy_3 attack step was facilitated by recently-developed, high-yield routes to methylenes **GIm** and **GIIIm**,⁹⁹ and their isotopically labelled derivatives.^{100,101} Attack of PCy_3 at the *methyldiene* carbon was unequivocally demonstrated in experiments with **GIIIm***, which bears a ^{13}C label at the methyldiene carbon.¹⁰⁰ Labelled $[\text{}^{13}\text{CH}_3\text{PCy}_3]\text{Cl}$ was liberated, confirming that the phosphonium methyl group originates from the Ru-methyldiene. Additional insights were obtained from experiments in which **GIm** was treated with an excess of pyridine. In this system, C-H activation is slowed, and near-quantitative formation of σ -alkyl species **Ru-11** is observed (Scheme 1.6).¹⁰² **Ru-11** was identified by single crystal X-ray diffraction, and by its diagnostic ^{13}C and ^{31}P NMR shifts (confirmed by analysis of a ^{13}C -labelled derivative **Ru-11***: δ_{P} 55.7, $^1J_{\text{PC}} = 9.8$ Hz; δ_{H} -12.3, $^1J_{\text{PC}} = 9.8$ Hz).¹⁰⁰ **Ru-11** liberates $[\text{MePCy}_3]\text{Cl}$ in ca. 60% yield over a period of days. In contrast, the corresponding experiment with **GIIIm** liberated $[\text{MePCy}_3]\text{Cl}$ in nearly 90% yield within 5 min, without observable intermediates.

Scheme 1.6. Identification of σ -alkyl species formed on nucleophilic attack of PCy_3 on **GIm.**^{102 a}

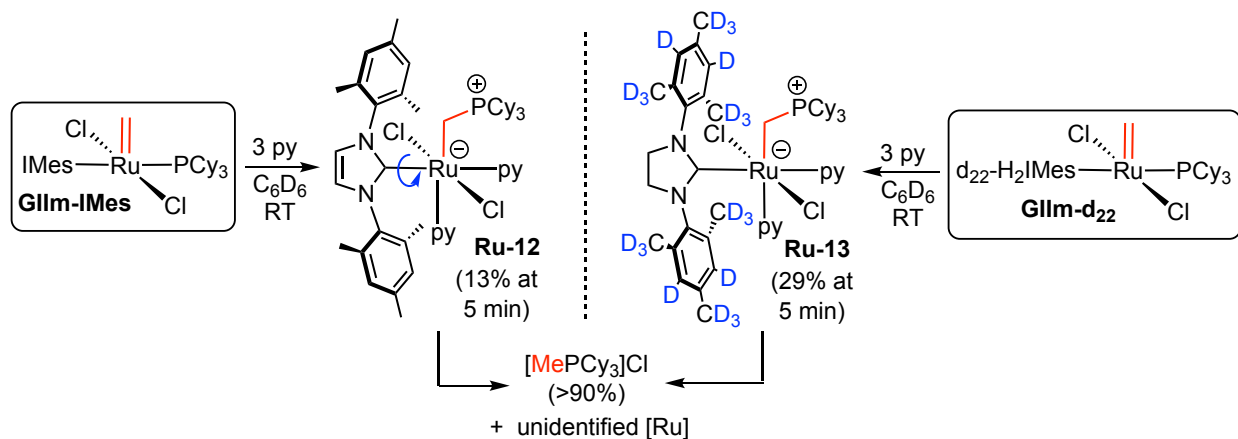


^a The Ru precipitates at least in part as $\text{RuCl}_2(\text{py})_4$, though other products cannot be ruled out.

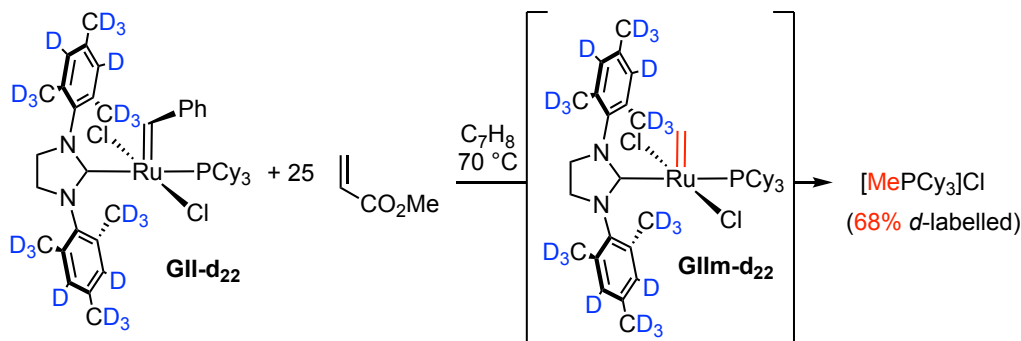
Further experiments confirmed the relevance of σ -alkyl intermediates to the second-generation catalysts, and confirmed that C-H activation occurs at least partially at the NHC. In a clever series of experiments, McClennan and Fogg deployed analogs of **GIIIm** bearing the backbone-saturated **IMes** and the labelled carbene **H₂IMes-d₂₂** (Scheme 1.7).¹⁰¹ NHC rotation about the Ru-C_{NHC} bond is much faster for **IMes** vs. **H₂IMes**, a consequence of the limited degree of Ru-NHC backbonding in **IMes**.⁸⁴ Suspecting that the absence of observable intermediates for **GIIIm** was due to facile C-H activation of **H₂IMes**, McClennan hypothesized that rapid rotation may retard activation for **GIIIm-IMes**. Indeed, σ -alkyl species **Ru-12** was observed in up to 13% yield at short reaction times, on treatment of **GIIIm-IMes** with 3 py at RT (Scheme 1.7a). Moreover, on switching to **GIIIm-d₂₂**, σ -alkyl species **Ru-13** was observed in up to 29% yield at

5 min, with near-quantitative liberation of the phosphonium salts after 10 min (Scheme 1.7b). A kinetic isotope effect of 1.5 was measured in analogous experiments with DMSO as donor, for which decomposition was slower, and the rate constants could be measured.

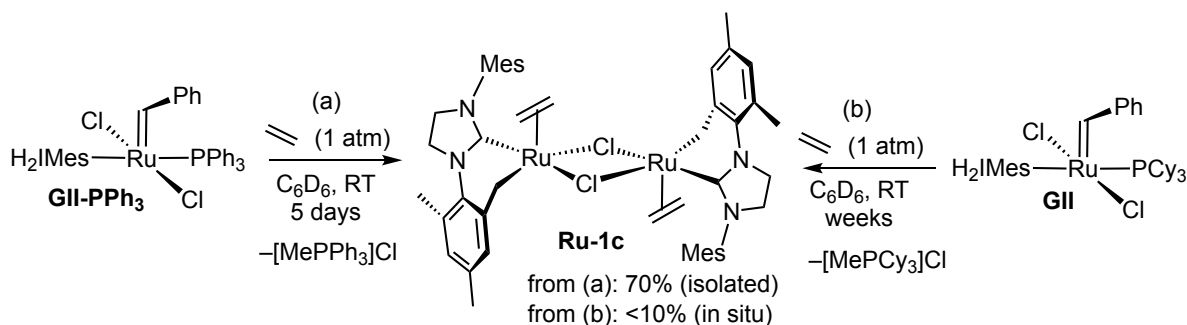
Scheme 1.7. Observation of σ -alkyl intermediates in the second-generation systems.



C-H activation step. The presence of an observable (albeit small) primary kinetic isotope effect when the NHC ligand in **IIIm** is deuterated is highly suggestive that mesityl activation is a key step, at least in the presence of added donor. However, MALDI-MS analysis of the resulting phosphonium salts formed on decomposition of **IIIm-d₂₂** was inconclusive, with roughly equal proportions of $[\text{CH}_2\text{DPCy}_3]\text{Cl}$ and non-labelled $[\text{CH}_3\text{PCy}_3]\text{Cl}$ observed, accompanied by smaller proportions of the d_2 - and d_3 -labelled isotopologues.¹⁰¹ The mixture of isotopologues observed may reflect facile H/D scrambling,¹⁰³⁻¹⁰⁵ perhaps promoted by the pyridine base. In contrast, methylphosphonium salts liberated from experiments with **IIIm-d₂₂** and methyl acrylate were predominantly labelled (68%; Scheme 1.8).¹⁰⁶ These experiments confirm the importance of NHC activation in liberation of the σ -alkyl ligand as a phosphonium salt, even in the absence of base.

Scheme 1.8. Observation of labelled $[\text{CH}_2\text{DPCy}_3]\text{Cl}$ on treatment of **GII-d₂₂ with methyl acrylate.¹⁰⁶**

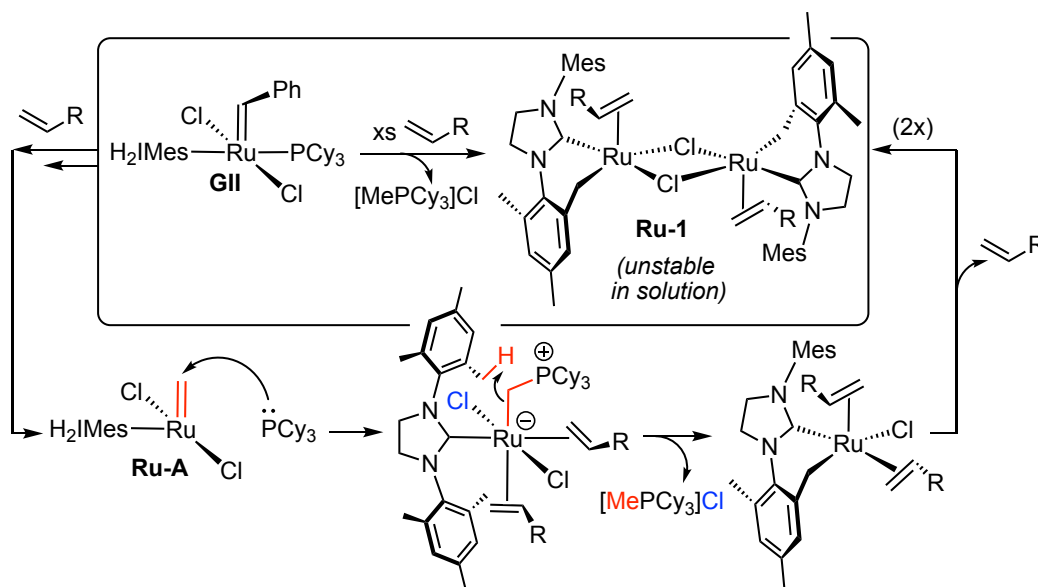
Nature of the Ru products. Dimeric hydride **Ru-10** was isolated in 46% yield on thermolysis of **GIIIm** at 55°C , as noted earlier (Scheme 1.5 above).⁸⁸ During metathesis, however, a different picture emerges. Thus, reaction of **GII-PPh₃** with ethylene at RT results in quantitative formation of $[\text{MePPh}_3]\text{Cl}$, with deposition of X-ray-quality crystals of dimer **Ru-1c** in 70% yield.⁸⁹ The same product (recently prepared by a convergent, high-yield route and fully characterized by NMR methods)¹⁰⁶ is observed in situ on treating **GII** with 1 atm ethylene.¹⁰⁷ Yields are limited to ca. 10%, however, likely owing to competing decomposition of **Ru-1c** ($t_{1/2} \approx 24$ h, vs. > 7 d for complete consumption of **GII** at RT).¹⁰⁷ (We will return to a discussion of olefin dimers **Ru-1**, and the convergent pathways by which they form, in Chapter 3.)

Scheme 1.9. Observation of cyclometallated dimer **Ru-1c on treatment of **GII-PPh₃** with ethylene.^{89,107}**

Revised Mechanism for Decomposition of **GII During Metathesis.** Based on all of the evidence described above, a revised mechanism for the decomposition of **GII** during metathesis of terminal olefins is presented (Scheme 1.10). Reaction of **GII** with terminal olefin generates four-coordinate intermediate **Ru-A** after the first cycle of metathesis. **Ru-A** is readily attacked by the liberated PCy_3 ligand to give a σ -alkyl species, which is likely stabilized by coordination of

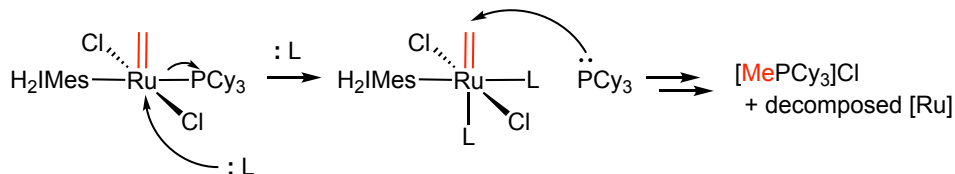
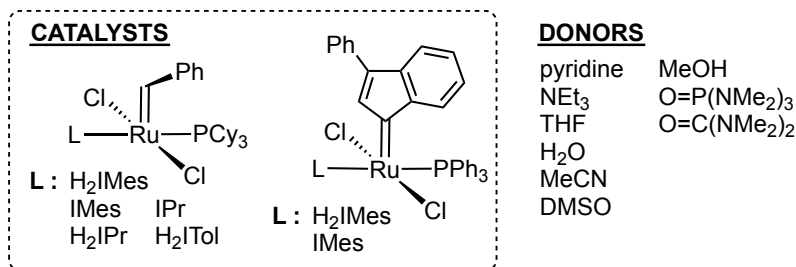
ethylene or another donor olefin. NHC cyclometallation, together with loss of the methylidene and a chloride counterion as $[\text{MePCy}_3]\text{Cl}$, yields fragment $\text{RuCl}(\kappa^2\text{-H}_2\text{IMes-H})$, again probably stabilized by donor olefins. Dimerization produces **Ru-1**, an unstable intermediate that ultimately decomposes to less well-defined products, likely following loss of olefin.

Scheme 1.10. Revised mechanism for nucleophilic abstraction of methylidenes during metathesis.

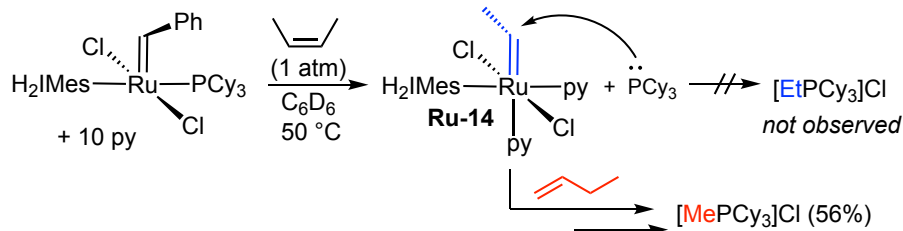


1.3 Impact of Lewis Bases on Decomposition of **GII**

The deleterious impact of bases on metathesis performance has been widely noted in both academia and industry.^{14-16,53,108-110} Lewis bases were long suspected to act as poisons, by binding to the open coordination sites and preventing olefin binding.^{108,111} However, more recent studies by our group outlined a role for Lewis donors in accelerating decomposition for the phosphine-stabilized metathesis catalysts.^{101,102,112} Thus, Lewis bases accelerate ejection of PCy_3 from **GII**, but do not confer sufficient steric protection to prevent methylidene abstraction (Scheme 1.11). PCy_3 displacement is associative in donor, and is therefore accelerated at higher donor concentrations.¹⁰¹ Such “donor-accelerated” decomposition was observed to be general for a wide range of catalysts and bases (Chart 1.2). Importantly, experiments with RCM substrate diethyl diallylmalonate (DDM) established the relevance of such pathways under real catalytic conditions, and confirmed that $[\text{MePCy}_3]\text{Cl}$ was the major product of decomposition formed.¹⁰¹

Scheme 1.11. Donor-accelerated decomposition of GII_m.**Chart 1.2. Generality of donor-accelerated decomposition for catalysts and donors.****1.4 Catalyst Decomposition by Brønsted Bases and Nucleophiles**

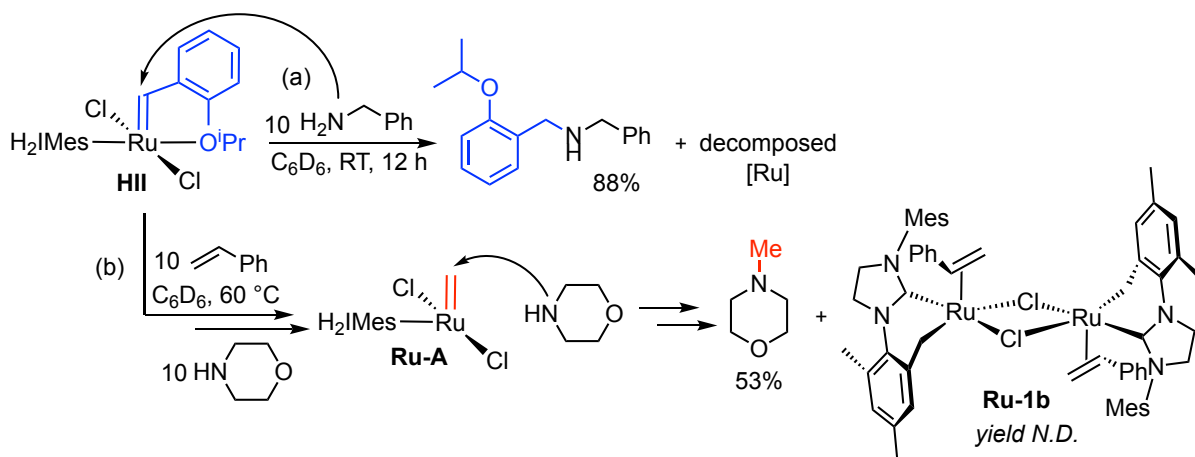
Nucleophilic attack of PCy₃ on [Ru]=CHR is shut down for bulkier R groups, except in special circumstances (see, e.g., section 1.5).^{101,113,114} Even ethylenes (R = Me) are resistant to attack. In experiments where **GII** was treated with *cis*-2-butene, the expected ethylphosphonium salt [EtPCy₃]Cl from nucleophilic attack on ethylidene **Ru-14** was not observed (Scheme 1.12).¹⁰¹ Instead, [MePCy₃]Cl was the major ³¹P-containing product, indicating olefin isomerization to 1-butene, followed by PCy₃ attack on the methylidene. Accordingly, strategies aimed at improving catalyst longevity via use of alpha-olefins offer only a partial solution.^{17,115,116} The reduced binding affinity of the more sterically encumbered alpha-olefins likely also limits achievable performance.¹¹⁷

Scheme 1.12. Resistance of ethylidene Ru-14 to nucleophilic abstraction by PCy₃.¹⁰¹

The alkylidene ligand can be abstracted from [Ru]=CHR by smaller nucleophiles, however. Primary amines such as *n*-butylamine can abstract even benzylidenes, generating benzylamines

as byproducts (Scheme 1.13a).^{100,112,118} Secondary amines are capable *methylidene* abstractors, though they do not readily compete with PCy₃ for abstraction of methylidene.¹¹² Treating **III** with styrene in the presence of 10 equiv each styrene and morpholine at 60 °C resulted in complete loss of **III** over 6 h, together with formation of *N*-methylmorpholine (the latter accounting for ca. 55% of the starting **III** charge; Scheme 1.13b).¹¹⁹ Reexamination of the NMR spectrum in the present work (see Chapter 3) revealed **Ru-1b** in significant proportions, indicating proton abstraction from H₂IMes.

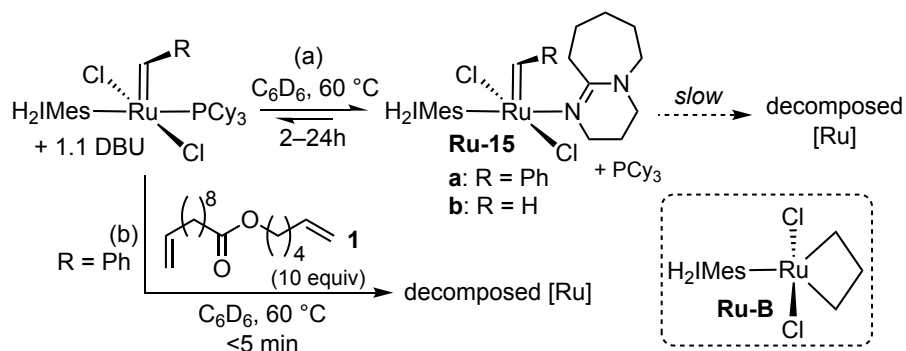
Scheme 1.13. Abstraction of [Ru]=CHR by amine nucleophiles.^{118,119}



Also formed in 26% yield from the reaction in Scheme 1.13b was β -methylstyrene, suggesting competing MCB decomposition by morpholine. The potency of Brønsted bases in promoting decomposition of MCB intermediates was demonstrated in a recent study by Lummiss and Fogg.¹⁰² Thus, DBU superbase (pK_a 24) was relatively innocuous towards precatalyst **GII**, instead forming stable DBU adduct **Ru-15a**, which decomposed only minimally over 24 h at 60 °C (<10% [Ru]=CHR loss; Scheme 1.14a). **GII**m was likewise resistant to decomposition by DBU, with only ca. 40 % loss after 2 h (cf. 50% loss in the absence of base). DBU may indeed play a *protective* role for **GII**m, via formation of bulky adducts that are sterically protected against PCy₃ attack (e.g., **Ru-15b**). In the presence of prolactone **1**, however, complete loss of **GII** was evident in <5 min, indicating rapid decomposition of active intermediates, such as unsubstituted **Ru-B** (Scheme 1.14b). The ability of Brønsted bases to decompose MCB intermediates was corroborated by a recent study demonstrating formation of propenes on

catalyst decomposition in the presence of amine bases.¹¹⁸ We will return to the pathway by which bases decompose MCB intermediates in Chapter 3.

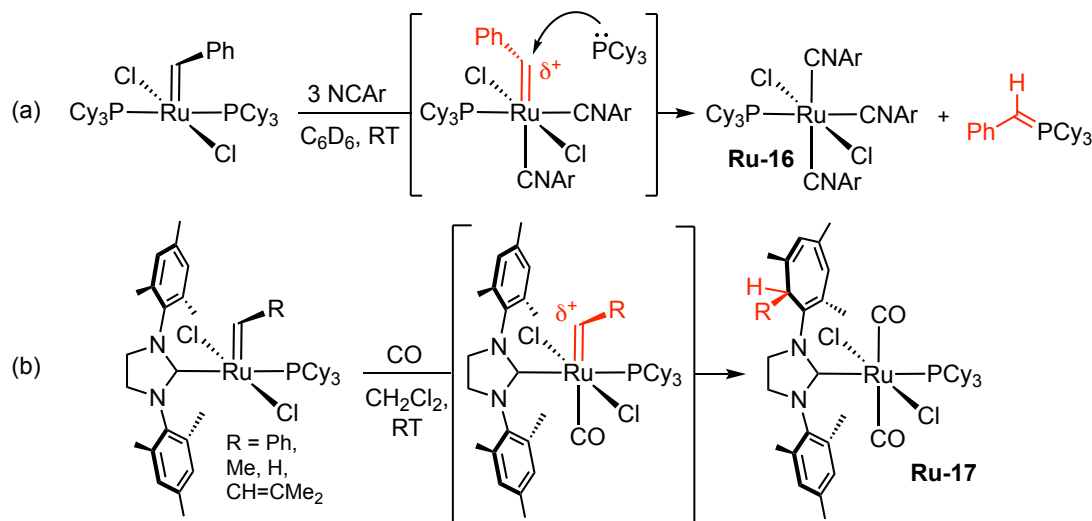
Scheme 1.14. Decomposition of **GI and **GIIm** by DBU superbases.¹¹²**



1.5 Catalyst Decomposition by π -Acids

π -Acids such as CO and isocyanides render the $[\text{Ru}]=\text{CHR}$ moiety more electrophilic. Two consequences emerge: (i) enhanced susceptibility of $[\text{Ru}]=\text{CHR}$ to attack by nucleophiles,¹¹⁴ and (ii) decomposition via alkylidene insertion into a mesityl ring on the NHC.¹²⁰⁻¹²² Case (i) is dramatically exemplified by the nucleophilic abstraction of the *benzylidene* ligand by PCy_3 on treatment of **GI** with isocyanide (Scheme 1.15a).¹¹⁴ Isocyanide-ligated **Ru-16** is liberated, along with ylide $\text{PhHC}=\text{PCy}_3$. A related pathway was observed for **GI** in neat acetonitrile.¹²³ Case (ii) is a general pathway for H_2IMes -stabilized methylidenes, ethylidenes, vinylidenes, and benzylidenes (Scheme 1.15b).¹²¹

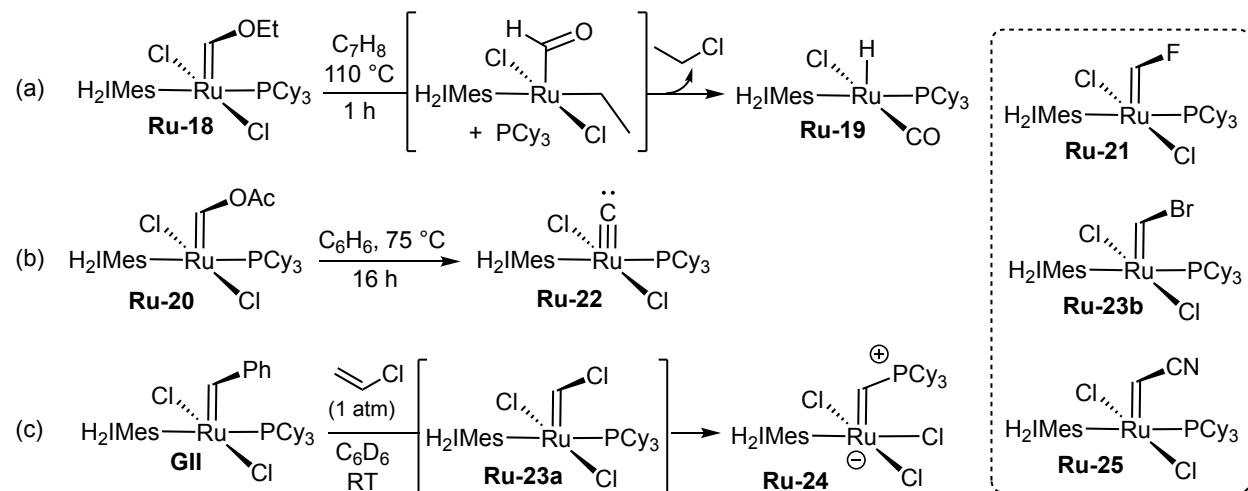
Scheme 1.15. Catalyst decomposition pathways proposed to result from binding π -acids to Ru. (a) PCy_3 attack on $[\text{Ru}]=\text{CHR}$; (b) Ylidene transfer to *o*-Mes.



1.6 Catalyst Decomposition by Directly-Functionalized Olefins

Metathesis of directly-functionalized olefins is a frontier area of research. Beyond the appeal of methodologies that offer direct access to functionalized C=C bonds,⁵³ the functionalized olefins can be subsequently transformed into valuable products and polymers.^{124,125} Notwithstanding exciting recent advances in the cross-metathesis of fluorinated olefins with acrylonitrile,^{26,27,125} metathesis yields are generally limited by formation of stable Fischer carbenes,¹²⁶ and/or catalyst decomposition. Fischer carbenes are thermodynamically stable, but are not necessarily inert. Thus, ethoxycarbene **Ru-18**^{127,128} (and related derivatives^{128,129}) decompose readily to Ru-hydrides such as **Ru-19**, possibly via a formyl intermediate formed on β -alkyl elimination (Scheme 1.16a). Acetoxycarbene **Ru-20** and fluorocarbene **Ru-21** are susceptible to loss of HX, with formation of carbide **Ru-22**,^{130,131} as are the unobservable halocarbenes **Ru-23**.¹³² A competing pathway for halocarbenes such as **Ru-23a** is nucleophilic attack on the carbene, and formation of phosphonium alkylidene **Ru-24** (which, unlike four-coordinate Piers catalyst **PII** in Chart 1.1b, is metathesis-inactive).^{132,133}

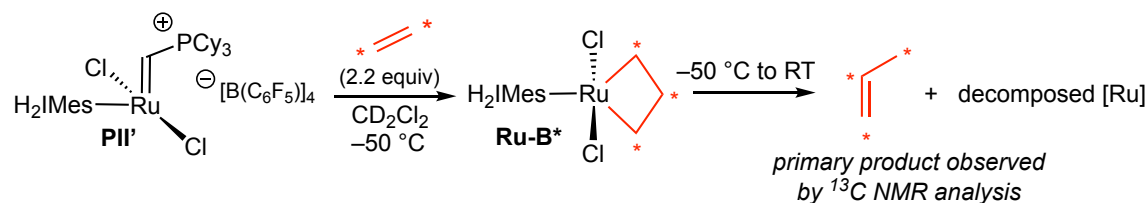
Scheme 1.16. Decomposition of directly-functionalized [Ru]=CHR: (a) R = OEt; (b) R = OAc; (c) R = Cl. (Inset) Other directly-functionalized alkylidene complexes discussed.



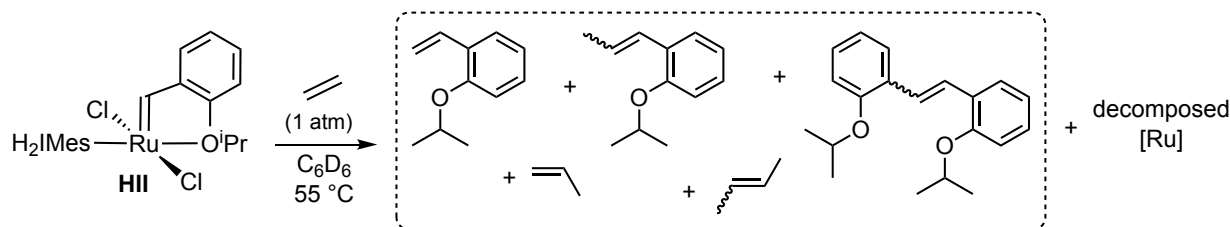
In contrast, the decomposition pathways promoted by electron-deficient olefins are poorly understood. The only known electron-deficient alkylidene complex is cyanoalkylidene **Ru-25**, which is a feeble metathesis catalyst.¹¹⁵ The origin of poor catalyst performance during metathesis of electron-deficient olefins by **GII** will be treated in Chapter 2.

1.7 Spontaneous Decomposition Pathways for the Active Intermediates

Study of the decomposition pathways accessible to Ru-MCBs was facilitated by Piers' discovery of four-coordinate phosphonium alkylidene complexes such as **PII'**, which initiate readily at temperatures down to $-50\text{ }^\circ\text{C}$.¹³⁴⁻¹³⁷ Thus, treatment of CD_2Cl_2 solutions of **PII'** with ethylene at $-50\text{ }^\circ\text{C}$ results in formation of unsubstituted MCB **Ru-B** (Scheme 1.17). Insight into the decomposition pathways accessible to **Ru-B** was provided by labelling studies with ^{13}C -labelled ethylene.¹³⁶ Warming solutions of **Ru-B*** results in complete disappearance of the NMR signals for **Ru-B***, together with formation of propylene- $^{13}\text{C}_3$ as the major organic product observable in the ^{13}C NMR spectrum. Spontaneous MCB decomposition was therefore proposed to proceed via β -H elimination, a process analogous to that seen in the group 4-7 systems discussed above.

Scheme 1.17. Synthesis and decomposition of unsubstituted MCB Ru-B* at -40 °C.

Further evidence for decomposition via β -H elimination during metathesis was provided by the van Rensburg and Bessalova groups, who observed formation of propene on ethenolysis of **GII**m and **III**, respectively (Scheme 1.18).^{138,139} (Generation of propene from **GII** is unexpected, given the well-established methylidene abstraction pathways outlined above. Incomplete air-exclusion, with oxidation of phosphine to O=PCy₃, may have affected these results, although MCB β -elimination as a minor pathway cannot be ruled out. O=PCy₃ was indeed evident in ³¹P NMR spectra given in the supporting information, and propene was not quantified.) DFT calculations predicted that MCB elimination is energetically accessible, with an energy barrier of 24.3 kcal / mol from **Ru-B** (Figure 1.6).¹³⁹ Key to MCB elimination is formation of allyl-hydride intermediate **Ru-V**, which is predicted to be slightly more stable than **Ru-B**. Two related Ru-allyl intermediates discovered in the present work will be discussed in Chapter 3.

Scheme 1.18. Observation of propene and butenes on ethenolysis of **III.**¹³⁸

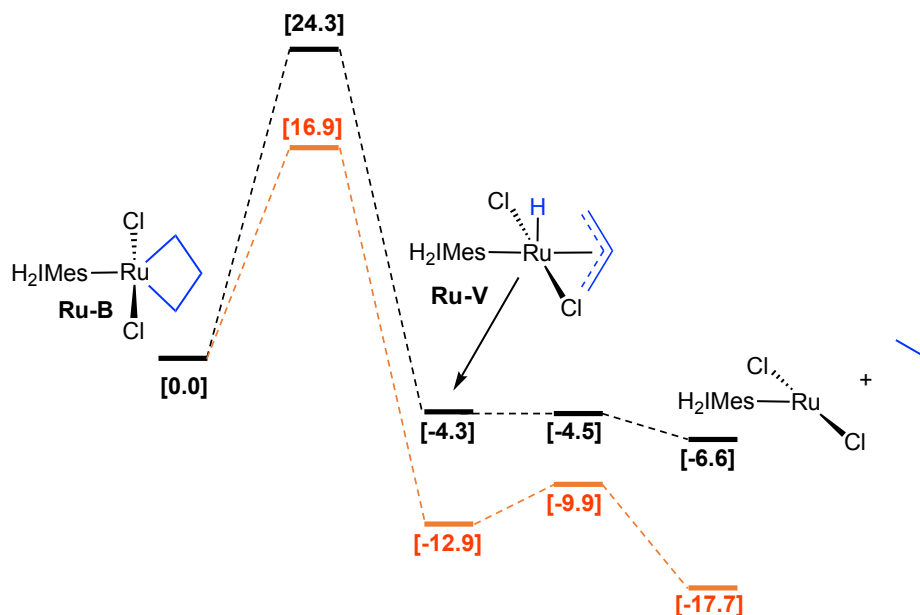
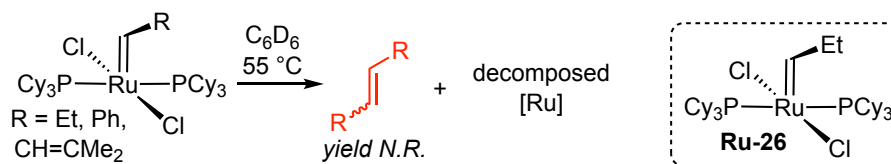


Figure 1.6. Computed pathway for β -elimination of unsubstituted MCB **Ru-B** (black). Shown in orange are the energy values for the corresponding decomposition of PCy_3 derivative $\text{RuCl}_2(\text{PCy}_3)(\kappa^2\text{-C}_3\text{H}_6)$ **Ru-B'**; structures not shown. Gibbs free energies vs. **Ru-B** / **Ru-B'** (kcal / mol).¹³⁹

Beyond MCB elimination, few pathways for the spontaneous decomposition of NHC-stabilized intermediates have been proposed. Bimolecular coupling pathways (see also Section 1.1) are apparently operative for certain *first-generation* alkylidene complexes, but coupling is slow on the timescale of metathesis (e.g. propylidene **Ru-26**: $t_{1/2} = 8$ h at 55 °C).^{61,103,140-142} Importantly, methylidene **GIm** was shown to decompose by a divergent, *unimolecular* pathway (see Section 1.2),¹⁰³ although evidence exists for bimolecular coupling as a minor pathway for **GIm**¹⁴⁰ (or related derivatives)¹⁴³ as well as another, metathetically inactive methylidene complex.¹⁴⁴

Scheme 1.19. Decomposition of first-generation catalysts via bimolecular coupling.¹⁰³



Despite the precedents from the first-generation Ru catalysts, bimolecular coupling of the NHC-stabilized catalysts has been widely viewed as improbable. The discovery of phosphine-mediated decomposition pathways for **GII** and its derivatives probably diverted attention from the possibility of bimolecular coupling pathways.^{88,89} Moreover, the widespread belief that the NHC-

stabilized catalysts initiate slowly led to the inference that bimolecular coupling pathways are impeded.^{57,83,145,146} However, isotopic labelling and kinetics studies by our group and Diver's recently overturned the view that **HII** is slow to initiate,^{147,148} after nearly two decades of debate.¹⁴⁹⁻¹⁵³ The NHC-stabilized catalysts also exhibit enhanced affinity for olefins, relative to their first-generation congeners.^{83,154} High olefin affinity is expected to favour formation of MCB intermediates, and thus reduce the concentration of four-coordinate intermediates.¹⁴⁶ But ultimately, one of the major factors impeding investigation of bimolecular coupling pathways in the Ru systems is probably the paucity of synthetic routes to phosphine-free methylidene complexes. Isolable methylidenes are required to prove the operation of bimolecular coupling pathways, because any ethylene generated from coupling is otherwise indistinguishable from the ethylene generated via metathesis.^{74,75} This challenge is addressed in Chapter 4.

1.8 Scope of This Thesis

The literature precedents discussed above reveal clear opportunities for discovery. Enormous research effort in Ru-catalyzed olefin metathesis has focused on the synthesis of new catalysts,^{11,155} without a complete understanding of the factors that undermine catalyst performance. Studies of the group 4-7 systems illustrate the clear value of an informed approach to catalyst redesign, and indeed some of the most productive of the Mo/W catalysts known to date were designed with inhibition of bimolecular coupling in mind.^{57,156} For the widely-used Ru catalysts, such an approach is only starting to take hold.^{157,158} Especially for the active on-cycle species, much deeper understanding is required before decomposition chemistry can inform practice.

This thesis therefore places an emphasis on uncovering the fundamental, non-Chauvin behaviour of the key Ru metathesis intermediates. Chapter 2 explores the root cause of a long-standing curiosity in renewable metathesis: the remarkably poor performance of **GII** in the metathesis of electron-deficient olefins. An active intermediate is implicated, prompting closer examination. Chapters 3 and 4 advance a mechanistic basis for decomposition of the MCB and [Ru]=CHR intermediates, in the presence or absence of base. As described in Sections 1.4 and 1.7 above, the underlying chemistry of these important intermediates has been little studied. Improved understanding is paramount: all of the NHC-stabilized catalysts shown in Chart 1.1 converge on

these same active intermediates. The findings in Chapters 3 and 4 are thus generally applicable to all of these catalysts, which are also the most widely-used catalysts in current use.

An ultimate goal of these studies, however, is also to improve practice. Therefore, a second core focus is improving catalyst productivity through informed choice. Chapter 5 presents a solution to the “enolate problem” delineated in Chapters 2 and 3. The choice of acrylate metathesis as a target for improvement is strategic, given enormous current interest in acrylate metathesis for construction of functionalized natural products and renewable chemicals,^{124,159} as well as the poor metathesis performance of the most widely-used catalysts for this transformation.¹⁶⁰ Finally, Chapter 6 presents solutions to a related problem: *gas-phase* catalyst decomposition during MALDI-MS analysis. The practices outlined are expected to facilitate routine MS deployment for analysis of highly-reactive and labile metal complexes and catalysts, and hence to enable important further studies of catalyst decomposition, and transition-metal chemistry and catalysis as a whole.

1.9 References

- (1) Selected recent reviews: (a) Ping, L.; Chung, D. S.; Bouffard, J.; Lee, S.-G. *Chem. Soc. Rev.* **2017**, *46*, 4299–4328. (b) Janssen-Muller, D.; Schlepphorst, C.; Glorius, F. *Chem. Soc. Rev.* **2017**, *46*, 4845–4854. (c) Park, Y.; Kim, Y.; Chang, S. *Chem. Rev.* **2017**, *117*, 9247–9301. (d) Twilton, J.; Le, C.; Zhang, P.; Shaw, M. H.; Evans, R. W.; MacMillan, D. W. C. *Nature Rev. Chem.* **2017**, *1*, 0052. (e) Grice, K. A. *Coord. Chem. Rev.* **2017**, *336*, 78–95.
- (2) Selected examples depicted in Figure 1.1: (a) Kanady, J. S.; Lin, P.-H.; Carsch, K. M.; Nielsen, R. J.; Takase, M. K.; Goddard, W. A.; Agapie, T. *J. Am. Chem. Soc.* **2014**, *136*, 14373–14376. (b) Pike, S. D.; Thompson, A. L.; Algarra, A. G.; Apperley, D. C.; Macgregor, S. A.; Weller, A. S. *Science* **2012**, *337*, 1648–1651. (c) Ford, C. L.; Park, Y. J.; Matson, E. M.; Gordon, Z.; Fout, A. R. *Science* **2016**, *354*, 741–743. (d) Yang, Y.; Shi, S.-L.; Niu, D.; Liu, P.; Buchwald, S. L. *Science* **2015**, *349*, 62–66.
- (3) 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.
- (4) Busacca, C. A.; Fandrick, D. R.; Song, J. J.; Senanayake, C. H. *Adv. Synth. Catal.* **2011**, *353*, 1825–1864.
- (5) Hoff, R.; Mathers, R. T., *Handbook of Transition Metal Polymerization Catalysts*. Wiley: Hoboken, NJ, 2010.
- (6) Cossy, J.; Arseniyadis, S.; Meyer, C., *Metathesis in Natural Product Synthesis: Strategies, Substrates and Catalysts*. Wiley-VCH: Weinheim, 2010.

- (7) Wang, C.-C.; Li, J.-R.; Lv, X.-L.; Zhang, Y.-Q.; Guo, G. *Energy Environ. Sci.* **2014**, *7*, 2831–2867.
- (8) Lai Lyu, C. H. *Prog. Chem.* **2017**, *29*, 981–999.
- (9) Crabtree, R. H., *Energy Production and Storage: Inorganic Chemical Strategies for a Warming World*. Wiley: Hoboken, NJ, 2010.
- (10) Olah, G. A.; Goeppert, A.; Prakash, G. K. S. *J. Org. Chem.* **2009**, *74*, 487–498.
- (11) Grela, K., *Olefin Metathesis-Theory and Practice*. Wiley: Hoboken, NJ, 2014.
- (12) Grubbs, R. H.; Wenzel, A. G., *Handbook of Metathesis*. 2nd ed.; Wiley-VCH: Weinheim, 2015.
- (13) Hughes, D. L. *Org. Process Res. Dev.* **2016**, *20*, 1008–1015.
- (14) Higman, C. S.; Lummiss, J. A. M.; Fogg, D. E. *Angew. Chem., Int. Ed.* **2016**, *55*, 3552–3565.
- (15) Farina, V.; Horváth, A., Ring-Closing Metathesis in the Large-Scale Synthesis of Pharmaceuticals. In *Handbook of Metathesis*, Grubbs, R. H.; Wenzel, A. G., Eds. Wiley-VCH: Weinheim, 2015; Vol. 2, pp 633–658.
- (16) 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. Wiley: Hoboken, 2014; pp 349–366.
- (17) Pederson, R. L.; Nickel, A., Commercial Potential of Olefin Metathesis of Renewable Feedstocks. In *Olefin Metathesis-Theory and Practice*, Grela, K., Ed. Wiley: Hoboken, NJ, 2014; pp 335–348.
- (18) Lam, J. K.; Zhu, C.; Bukhryakov, K. V.; Müller, P.; Hoveyda, A.; Schrock, R. R. *J. Am. Chem. Soc.* **2016**, *138*, 15774–15783.
- (19) Gawin, R.; Tracz, A.; Chwalba, M.; Kozakiewicz, A.; Trzaskowski, B.; Skowerski, K. *ACS Catal.* **2017**, *7*, 5443–5449.
- (20) Yu, M.; Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2015**, *54*, 215–220.
- (21) Herbert, M. B.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2015**, *54*, 5018–5024.
- (22) Marx, V. M.; Sullivan, A. H.; Melaimi, M.; Virgil, S. C.; Keitz, B. K.; Weinberger, D. S.; Bertrand, G.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2015**, *54*, 1919–1923.
- (23) Higman, C. S.; de Araujo, M. P.; Fogg, D. E. *Catal. Sci. Technol.* **2016**, *6*, 2077–2084.
- (24) Lummiss, J. A. M.; Oliveira, K. C.; Prankevicius, A.; Santos, A.; dos Santos, E. N.; Fogg, D. E. *J. Am. Chem. Soc.* **2012**, *134*, 18889–18891.
- (25) Bilel, H.; Hamdi, N.; Zagrouba, F.; Fischmeister, C.; Bruneau, C. *RSC Adv.* **2012**, *2*, 9584–9589.
- (26) Harrison, D. J.; Lee, G. M.; Leclerc, M. C.; Korobkov, I.; Baker, R. T. *J. Am. Chem. Soc.* **2013**, *135*, 18296–18299.
- (27) Harrison, D. J.; Daniels, A. L.; Korobkov, I.; Baker, R. T. *Organometallics* **2015**, *34*, 5683–5686.

- (28) Lee, G. M.; Leung, A. S. C.; Harrison, D. J.; Korobkov, I.; Hughes, R. P.; Baker, R. T. *Organometallics* **2017**, *36*, 2853–2860.
- (29) de Brito Sá, E.; Rodríguez-Santiago, L.; Sodupe, M.; Solans-Monfort, X. *Organometallics* **2016**, *35*, 3914–3923.
- (30) Mauksch, M.; Tsogoeva, S. B. *Chem. Eur. J.* **2017**, *23*, 10264–10269.
- (31) Levine, D. S.; Tilley, T. D.; Andersen, R. A. *Organometallics* **2017**, *36*, 80–88.
- (32) Zhou, Q.-L. *Angew. Chem. Int. Ed.* **2016**, *55*, 5352–5353.
- (33) Rosenquist, Å.; Samuelsson, B.; Johansson, P.-O.; Cummings, M. D.; Lenz, O.; Raboisson, P.; Simmen, K.; Vendeville, S.; de Kock, H.; Nilsson, M.; Horvath, A.; Kalmeijer, R.; de la Rosa, G.; Beumont-Mauviel, M. *J. Med. Chem.* **2014**, *57*, 1673–1693.
- (34) 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.
- (35) Banks, R. L.; Bailey, G. C. *Ind. Eng. Chem. Prod. Res. Dev.* **1964**, *3*, 170–173.
- (36) Eleuterio, H. S. *J. Mol. Catal.* **1991**, *65*, 55–61.
- (37) Hérisson, J. L.; Chauvin, Y. *Makromol. Chem.* **1971**, *141*, 161–176.
- (38) Fischer, E. O.; Maasbol, A. *Angew. Chem., Int. Ed.* **1964**, *3*, 580–581.
- (39) Jolly, P. W.; Pettit, R. *J. Am. Chem. Soc.* **1966**, *88*, 5044–5045.
- (40) Casey, C. P.; Burkhardt, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 5833–5834.
- (41) Schrock, R. R. *J. Am. Chem. Soc.* **1974**, *96*, 6796–6797.
- (42) Schrock, R. R. *J. Am. Chem. Soc.* **1975**, *97*, 6577–6578.
- (43) Ephritikhine, M.; Francis, B. R.; Green, M. L. H.; Mackenzie, R. E.; Smith, M. J. *J. Chem. Soc., Dalton Trans.* **1977**, 1131–1135.
- (44) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611–3613.
- (45) Howard, T. R.; Lee, J. B.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 6876–6878.
- (46) Schrock, R.; Rocklage, S.; Wengrovius, J.; Rupprecht, G.; Fellmann, J. *J. Mol. Catal.* **1980**, *8*, 73–83.
- (47) Wengrovius, J. H.; Schrock, R. R.; Churchill, M. R.; Missert, J. R.; Youngs, W. J. *J. Am. Chem. Soc.* **1980**, *102*, 4515–4516.
- (48) Köhler, K.; Wussow, K.; Wirth, A. S., Palladium-Catalyzed Cross-Coupling Reactions. In *Palladium-Catalyzed Coupling Reactions*, Wiley-VCH: Weinheim, 2013; pp 1–30.
- (49) Ager, D. J.; de Vries, A. H. M.; de Vries, J. G. *Chem. Soc. Rev.* **2012**, *41*, 3340–3380.
- (50) Wheeler, P.; Phillips, J. H.; Pederson, R. L. *Org. Process Res. Dev.* **2016**, *2*, 1182–1190.
- (51) Cho, J. H.; Kim, B. M. *Org. Lett.* **2003**, *5*, 531–533.

- (52) Conrad, J. C.; Parnas, H. H.; Snelgrove, J. L.; Fogg, D. E. *J. Am. Chem. Soc.* **2005**, *127*, 11882–11883.
- (53) 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.
- (54) Larionov, E.; Li, H.; Mazet, C. *Chem. Commun.* **2014**, *50*, 9816–9826.
- (55) Alcaide, B.; Almendros, P.; Luna, A. *Chem. Rev.* **2009**, *109*, 3817–3858.
- (56) Crabtree, R. H. *Chem. Rev.* **2015**, *115*, 127–150.
- (57) Schrodi, Y., Mechanisms of Olefin Metathesis Catalyst Decomposition and Methods of Catalyst Reactivation. In *Handbook of Metathesis*, Grubbs, R. H.; Wenzel, A. G., Eds. Wiley-VCH: Weinheim, 2015; pp 323–342.
- (58) Chadwick, J. C.; Duchateau, R.; Freixa, Z.; van Leeuwen, P. W. N. M., *Homogeneous Catalysts: Activity – Stability – Deactivation*. Wiley-VCH: Weinheim, 2011.
- (59) Schrock, R. R.; Copéret, C. *Organometallics* **2017**, *36*, 1884–1892.
- (60) Tabari, D. S.; Tolentino, D. R.; Schrodi, Y. *Organometallics* **2013**, *32*, 5–8.
- (61) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100–110.
- (62) Creary, X. *Org. Synth.* **1986**, *64*, 207–216.
- (63) 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.
- (64) Monfette, S.; Eyholzer, M.; Roberge, D. M.; Fogg, D. E. *Chem. – Eur. J.* **2010**, *16*, 11720–11725.
- (65) Skowerski, K.; Czarnocki, S. J.; Knapkiewicz, P. *ChemSusChem* **2014**, *7*, 536–542.
- (66) Engel, J.; Smit, W.; Foscatto, M.; Occhipinti, G.; Törnroos, K. W.; Jensen, V. R. *J. Am. Chem. Soc.* **2017**, *139*, 16609–16619.
- (67) Nelson, D. J.; Percy, J. M. *Dalton Trans.* **2014**, *43*, 4674–4679.
- (68) Higman, C. S.; Plais, L.; Fogg, D. E. *ChemCatChem* **2013**, *5*, 3548–3551.
- (69) Higman, C. S.; Lanterna, A. E.; Marin, M. L.; Scaiano, J. C.; Fogg, D. E. *ChemCatChem* **2016**, *8*, 2446–2449.
- (70) Nam, Y. H.; Snapper, M. L., Ruthenium-Catalyzed Tandem Metathesis/Non-Metathesis Processes. In *Handbook of Metathesis*, Grubbs, R. H.; Wenzel, A. G., Eds. Wiley-VCH: Weinheim, 2015; pp 311–380.
- (71) Schmidt, B.; Krehl, S., Domino and Other Olefin Metathesis Reaction Sequences In *Olefin Metathesis-Theory and Practice*, Grela, K., Ed. Wiley: Hoboken, NJ, 2014; pp 187–232.
- (72) For selected examples of tandem metathesis-isomerization, see: (a) J. R. Clark, J. R. Griffiths and S. T. Diver, *J. Am. Chem. Soc.*, 2013, **135**, 3327–3330; (b) B. Schmidt and S. Hauke, *Org. Biomol. Chem.*, 2013, **11**, 4194–4206; (c) B. Schmidt and O. Kunz, *Synlett*, 2012, **23**, 851–854; (d) A. D. Wadsworth, D. P. Furkert, J. Sperry and M. A. Brimble, *Org. Lett.*, 2012, **14**, 5374–5377; (e) Ascic, J. F. Jensen and T. E. Nielsen, *Angew. Chem., Int. Ed.*, 2011, **50**, 5188

- 5191; (f) B. Schmidt, R. Berger and F. Holter, *Org. Biomol. Chem.*, 2010, **8**, 1406–1414; (g) A. Mallagaray, G. Dominguez, A. Gradillas and J. Perez-Castells, *Org. Lett.*, 2008, **10**, 597–600; (h) D. Finnegan, B. A. Seigal and M. L. Snapper, *Org. Lett.*, 2006, **8**, 2603–2606.
- (73) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592–4633.
- (74) Schrock, R. R.; Sharp, P. R. *J. Am. Chem. Soc.* **1978**, *100*, 2389–2399.
- (75) Merrifield, J. H.; Lin, G.-Y.; Kiel, W. A.; Gladysz, J. A. *J. Am. Chem. Soc.* **1983**, *105*, 5811–5819.
- (76) Robbins, J.; Bazan, G. C.; Murdzek, J. S.; O'Regan, M. B.; Schrock, R. R. *Organometallics* **1991**, *10*, 2902.
- (77) Fox, H. H.; Schrock, R. R.; O'Dell, R. *Organometallics* **1994**, *13*, 635–639.
- (78) 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.
- (79) Lopez, L. P. H.; Schrock, R. R. *J. Am. Chem. Soc.* **2004**, *126*, 9526–9527.
- (80) Arndt, S.; Schrock, R. R.; Muller, P. *Organometallics* **2007**, *26*, 1279–1290.
- (81) Tsang, W. C. P.; Schrock, R. R.; Hoveyda, A. H. *Organometallics* **2001**, *20*, 5658–5669.
- (82) Tsang, W. C. P.; Jamieson, J. Y.; Aeilts, S. L.; Hultsch, K. C.; Schrock, R. R.; Hoveyda, A. H. *Organometallics* **2004**, *23*, 1997–2007.
- (83) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543–6554.
- (84) Lummiss, J. A. M.; Higman, C. S.; Fyson, D. L.; McDonald, R.; Fogg, D. E. *Chem. Sci.* **2015**, *6*, 6739–6746.
- (85) Straub, B. F. *Angew. Chem., Int. Ed.* **2005**, *44*, 5974–5978.
- (86) Yang, H.-C.; Huang, Y.-C.; Lan, Y.-K.; Luh, T.-Y.; Zhao, Y.; Truhlar, D. G. *Organometallics* **2011**, *30*, 4196–4200.
- (87) Lummiss, J. A. M.; Perras, F. A.; Bryce, D. L.; Fogg, D. E. *Organometallics* **2016**, *35*, 691–698.
- (88) Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2004**, *126*, 7414–7415.
- (89) Hong, S. H.; Wenzel, A. G.; Salguero, T. T.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2007**, *129*, 7961–7968.
- (90) Trnka, T. M.; Morgan, J. P.; Sanford, M. S.; Wilhelm, T. E.; Scholl, M.; Choi, T.-L.; Ding, S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 2546–2558.
- (91) Leitao, E. M.; Dubberley, S. R.; Piers, W. E.; Wu, Q.; McDonald, R. *Chem. – Eur. J.* **2008**, *14*, 11565–11572.
- (92) Endo, K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2011**, *133*, 8525–8527.
- (93) Endo, K.; Herbert, M. B.; Grubbs, R. H. *Organometallics* **2013**, *32*, 5128–5135.
- (94) Phillips, N.; Tang, C. Y.; Tirfoin, R.; Kelly, M. J.; Thompson, A. L.; Gutmann, M. J.; Aldridge, S. *Dalton Trans.* **2014**, *43*, 12288–12298.

- (95) Abdur-Rashid, K.; Fedorkiw, T.; Lough, A. J.; Morris, R. H. *Organometallics* **2004**, *23*, 86–94.
- (96) Huang, J.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2000**, *19*, 1194.
- (97) Chilvers, M. J.; Jazzar, R. F. R.; Mahon, M. F.; Whittlesey, M. K. *Adv. Synth. Catal.* **2003**, *345*, 1111–1114.
- (98) Burling, S.; Paine, B. M.; Nama, D.; Brown, V. S.; Mahon, M. F.; Prior, T. J.; Pregosin, P. S.; Whittlesey, M. K.; Williams, J. M. J. *J. Am. Chem. Soc.* **2007**, *129*, 1987–1995.
- (99) Lummiss, J. A. M.; Beach, N. J.; Smith, J. C.; Fogg, D. E. *Catal. Sci. Technol.* **2012**, *2*, 1630–1632.
- (100) Lummiss, J. A. M.; Botti, A. G. G.; Fogg, D. E. *Catal. Sci. Technol.* **2014**, *4*, 4210–4218.
- (101) McClelland, W. L.; Rufh, S. A.; Lummiss, J. A. M.; Fogg, D. E. *J. Am. Chem. Soc.* **2016**, *138*, 14668–14677.
- (102) Lummiss, J. A. M.; McClelland, W. L.; McDonald, R.; Fogg, D. E. *Organometallics* **2014**, *33*, 6738–6741.
- (103) Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 7202–7207.
- (104) Courchay, F. C.; Sworen, J. C.; Ghiviriga, I.; Abboud, K. A.; Wagener, K. B. *Organometallics* **2006**, *25*, 6074–6086.
- (105) Giunta, D.; Hoelscher, M.; Lehmann, C. W.; Mynott, R.; Wirtz, C.; Leitner, W. *Adv. Synth. Catal.* **2003**, *345*, 1139–1145.
- (106) Bailey, G. A.; Lummiss, J. A. M.; Foscatto, M.; Occhipinti, G.; McDonald, R.; Jensen, V. R.; Fogg, D. E. *J. Am. Chem. Soc.* **2017**, *139*, 16446–16449.
- (107) Bailey, G.A.; Fogg, D.E. Unpublished results.
- (108) Compain, P. *Adv. Synth. Catal.* **2007**, *349*, 1829–1846.
- (109) Compain, P.; Hazeldard, D. *Top. Heterocyclic Chem.* **2015**, 1–43.
- (110) Lafaye, K.; Bosset, C.; Nicolas, L.; Guérinot, A.; Cossy, J. *Beilstein J. Org. Chem.* **2015**, *11*, 2223–2241.
- (111) Wilson, G. O.; Porter, K. A.; Weissman, H.; White, S. R.; Sottos, N. R.; Moore, J. S. *Adv. Synth. Catal.* **2009**, *351*, 1817–1825.
- (112) Lummiss, J. A. M.; Ireland, B. J.; Sommers, J. M.; Fogg, D. E. *ChemCatChem* **2014**, *6*, 459–463.
- (113) Hansen, S. M.; Rominger, F.; Metz, M.; Hofmann, P. *Chem. – Eur. J.* **1999**, *5*, 557–566.
- (114) Galan, B. R.; Pitak, M.; Keister, J. B.; Diver, S. T. *Organometallics* **2008**, *27*, 3630–3632.
- (115) Vancompernelle, T.; Vignon, P.; Trivelli, X.; Mortreux, A.; Gauvin, R. M. *Cat. Commun.* **2016**, *77*, 75–78.
- (116) Vignon, P.; Vancompernelle, T.; Couturier, J.-L.; Dubois, J.-L.; Mortreux, A.; Gauvin, R. M. *ChemSusChem* **2015**, *8*, 1143–1146.

- (117) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.
- (118) Ireland, B. J.; Dobigny, B. T.; Fogg, D. E. *ACS Catal.* **2015**, *5*, 4690–4698.
- (119) Ireland, B. J.; Fogg, D. E. Unpublished results.
- (120) Galan, B. R.; Gembicky, M.; Dominiak, P. M.; Keister, J. B.; Diver, S. T. *J. Am. Chem. Soc.* **2005**, *127*, 15702–15703.
- (121) Galan, B. R.; Pitak, M.; Gembicky, M.; Keister, J. B.; Diver, S. T. *J. Am. Chem. Soc.* **2009**, *131*, 6822–6832.
- (122) Poater, A.; Ragone, F.; Correa, A.; Cavallo, L. *J. Am. Chem. Soc.* **2009**, *131*, 9000–9006.
- (123) Zhao, Z.-X.; Wang, H.-Y.; Guo, Y.-L. *Rapid Commun. Mass Spectrom.* **2011**, *25*, 3401–3410.
- (124) Dixneuf, P. H.; Bruneau, C.; Fischmeister, C. *Oil Gas Sci. Technol.* **2016**, *71*, 19.
- (125) Takahira, Y.; Morizawa, Y. *J. Am. Chem. Soc.* **2015**, *137*, 7031–7034.
- (126) Trnka, T. M.; Day, M. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 3441–3444.
- (127) Louie, J.; Grubbs, R. H. *Organometallics* **2002**, *21*, 2153–2164.
- (128) Arisawa, M.; Terada, Y.; Takahashi, K.; Nakagawa, M.; Nishida, A. *J. Org. Chem.* **2006**, *71*, 4255–4261.
- (129) Wu, Z.; Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1995**, *117*, 5503–5511.
- (130) Caskey, S. R.; Stewart, M. H.; Kivela, J. E.; Sootsman, J. R.; Johnson, M. J. A.; Kampf, J. W. *J. Am. Chem. Soc.* **2005**, *127*, 16750.
- (131) MacNaughtan, M. L.; Johnson, M. J. A.; Kampf, J. W. *Organometallics* **2007**, *26*, 780–782.
- (132) MacNaughtan, M. L.; Johnson, M. J. A.; Kampf, J. W. *J. Am. Chem. Soc.* **2007**, *129*, 7708–7709.
- (133) Leitao, E. M.; van der Eide, E. F.; Romero, P. E.; Piers, W. E.; McDonald, R. *J. Am. Chem. Soc.* **2010**, *132*, 2784–2794.
- (134) Romero, P. E.; Piers, W. E.; McDonald, R. *Angew. Chem., Int. Ed.* **2004**, *43*, 6161–6165.
- (135) Romero, P. E.; Piers, W. E. *J. Am. Chem. Soc.* **2005**, *127*, 5032–5033.
- (136) Romero, P. E.; Piers, W. E. *J. Am. Chem. Soc.* **2007**, *129*, 1698–1704.
- (137) van der Eide, E. F.; Piers, W. E. *Nature Chem.* **2010**, *2*, 571–576.
- (138) Nizovtsev, A. V.; Afanasiev, V. V.; Shutko, E. V.; Bespalova, N. B. *NATO Sci. Ser. II* **2007**, *243*, 125–135.
- (139) van Rensburg, W. J.; Steynberg, P. J.; Meyer, W. H.; Kirk, M. M.; Forman, G. S. *J. Am. Chem. Soc.* **2004**, *126*, 14332–14333.
- (140) Dias, E. L.; Grubbs, R. H. *Organometallics* **1998**, *17*, 2758–2767.

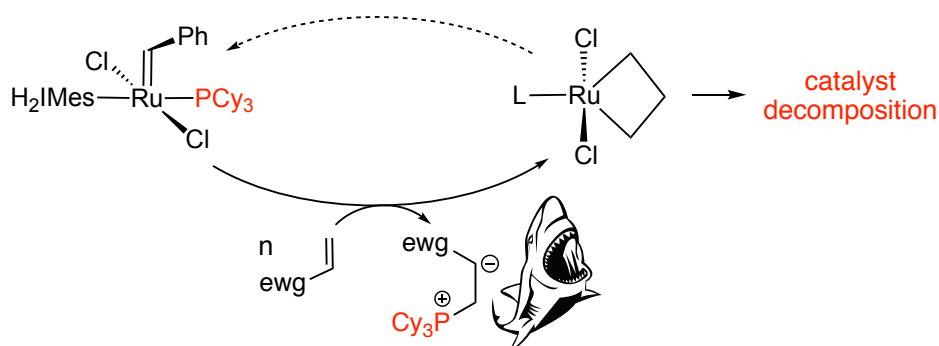
- (141) Dinger, M. B.; Mol, J. C. *Organometallics* **2003**, *22*, 1089–1095.
- (142) Wang, H.; Metzger, J. O. *Organometallics* **2008**, *27*, 2761–2766.
- (143) Forman, G. S.; McConnell, A. E.; Hanton, M. J.; Slawin, A. M. Z.; Tooze, R. P.; van Rensburg, W. J.; Meyer, W. H.; Dwyer, C.; Kirk, M. M.; Serfontein, D. W. *Organometallics* **2004**, *23*, 4824–4827.
- (144) Werner, H.; Stuer, W.; Weberndorfer, B.; Wolf, J. *Eur. J. Inorg. Chem.* **1999**, 1707–1713.
- (145) 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.
- (146) 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.
- (147) Bates, J. M.; Lummiss, J. A. M.; Bailey, G. A.; Fogg, D. E. *ACS Catal.* **2014**, *4*, 2387–2394.
- (148) Griffiths, J. R.; Keister, J. B.; Diver, S. T. *J. Am. Chem. Soc.* **2016**, *138*, 5380–5391.
- (149) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791–799.
- (150) Bieniek, M.; Michrowska, A.; Usanov, D. L.; Grela, K. *Chem. – Eur. J.* **2008**, *14*, 806–818.
- (151) Kingsbury, J. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 4510–4517.
- (152) Vorfalt, T.; Wannowius, K. J.; Thiel, V.; Plenio, H. *Chem. – Eur. J.* **2010**, *16*, 12312–12315.
- (153) Núñez-Zarur, F.; Solans-Monfort, X.; Pleixats, R.; Rodríguez-Santiago, L.; Sodupe, M. *Chem. – Eur. J.* **2013**, *19*, 14553–14565.
- (154) Adlhart, C.; Chen, P. *Helv. Chim. Acta* **2003**, *86*, 941–949.
- (155) Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Rev.* **2010**, *110*, 1746–1787.
- (156) Pietraszuk, C., Well-Defined Olefin Metathesis Catalysts Based on Metals of Group 4–7. In *Olefin Metathesis–Theory and Practice*, Wiley 2014; pp 367–396.
- (157) Koh, M. J.; Khan, R. K. M.; Torker, S.; Yu, M.; Mikus, M. S.; Hoveyda, A. H. *Nature* **2015**, *517*, 181–186.
- (158) Chung, C. K.; Grubbs, R. H. *Org. Lett.* **2008**, *10*, 2693–2696.
- (159) For recent applications in the synthesis of natural products of medicinal relevance, see: (a) Plummer, C. W.; Wei, C. S.; Yozwiak, C. E.; Soheili, A.; Smithback, S. O.; Leighton, J. L. *J. Am. Chem. Soc.* **2014**, *136*, 9878–9881; (b) Chatterjee, S.; Ghadigaonkar, S.; Sur, P.; Sharma, A.; Chattopadhyay, S. *J. Org. Chem.* **2014**, *79*, 8067–8076; (c) Xiao, Q.; Jackson, J. J.; Basak, A.; Bowler, J. M.; Miller, B. G.; Zakarian, A. *Nature Chem.* **2013**, *5*, 410–416; (d) Willwacher, J.; Fürstner, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 4217–4221; (e) Fuwa, H.; Saito, A.; Sasaki, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 3041–3044; (f) Brewitz, L.; Llaveria, J.; Yada, A.; Fürstner, A. *Chem. – Eur. J.* **2013**, *19*, 4532–4537.

(160) The superior performance of **HII** relative to **GII** for acrylate metathesis has since been confirmed in multiple reports. See, for example, Refs. 8, 10, and: (a) Schweitzer, D.; Snell, K. D. *Org. Process Res. Dev.* **2015**, *19*, 715–720; (b) Lafaye, K.; Nicolas, L.; Guérinot, A.; Reymond, S. b.; Cossy, J. *Org. Lett.* **2014**, *16*, 4972–4975; (c) Meng, X.; Matson, J. B.; Edgar, K. J. *Biomacromolecules* **2014**, *15*, 177–187; (d) Bilel, H.; Hamdi, N.; Zagrouba, F.; Fischmeister, C.; Bruneau, C. *Green Chem.* **2011**, *13*, 1448–1452; (e) Djigoué, G. B.; Meier, M. A. R. *Appl. Catal. A* **2009**, *368*, 158–162.

Chapter 2. Catalyst Decomposition During Acrylate Metathesis: Unexpected Pathways Enabled by a PCy₃-Generated Enolate

2.1 Published Contributions

Acrylate Metathesis via the Second-Generation Grubbs Catalyst: Unexpected Pathways Enabled by a PCy₃-Generated Enolate. Gwendolyn A. Bailey and Deryn E. Fogg, *J. Am. Chem. Soc.* **2015**, 7318–7321. (Communication)



Abstract: The diverse applications of acrylate metathesis range from synthesis of high-value α,β -unsaturated esters to depolymerization of unsaturated polymers. Examined here are unexpected side reactions promoted by the important Grubbs catalyst **GII**. Evidence is presented for attack of PCy_3 on the acrylate olefin to generate a reactive carbanion, which participates in multiple pathways, including further Michael addition, proton abstraction, and catalyst deactivation. Related chemistry may be anticipated whenever labile metal–phosphine complexes are used to catalyze reactions of substrates bearing an electron-deficient olefin.

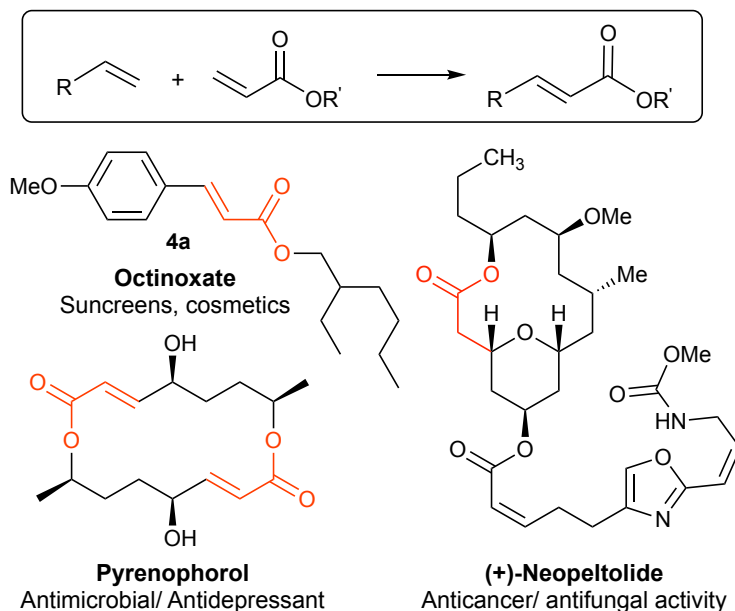
Author Contributions: This manuscript was written, edited, and revised by GAB and DEF. The key role of the liberated PCy_3 ligand in catalyst decomposition was discovered by GAB, as were the phosphonium salt byproducts $[\text{A}]\text{Cl}-[\text{C}]\text{Cl}$. The mechanistic pathway involving catalyst deprotonation by enolates was proposed and refined by GAB and DEF.^a

^a The contributions of Drs. Justin Lummiss and Cédric Fischmeister are gratefully acknowledged. JL suggested the key PCy_3 spiking experiment shown in Figure 2.1a. Discussions with Dr. Cédric Fischmeister were instrumental in refining the proposed mechanistic pathway shown in Scheme 2.2.

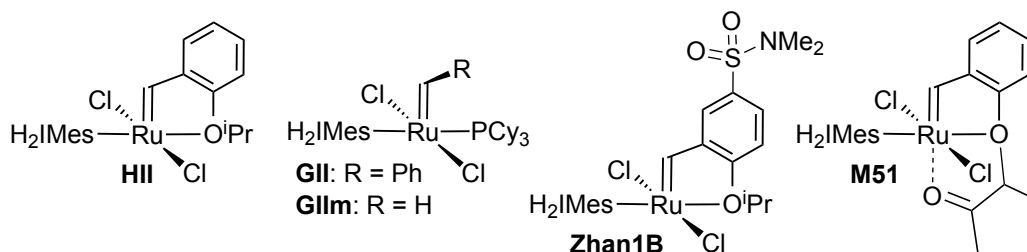
2.2 Introduction

Olefin metathesis offers powerful methodologies for the synthesis of α,β -unsaturated carbonyl compounds.¹⁻⁴ High-profile targets accessed via acrylate metathesis range from the high-value antioxidant **4a** to natural products of medicinal relevance (Scheme 2.1).^{5,6} Cross-metathesis (CM) of acrylates with plant-oil triglycerides or fatty acid esters is likewise key to the transformation of unsaturated fats and oils into renewable platform chemicals, including novel building blocks for high-performance surfactants.^{2-4,7} In materials applications, related strategies have recently been deployed for depolymerization of polybutadiene⁸ or, alternatively, assembly of bio-based polyesters⁹ and polyamides.¹⁰⁻¹²

Scheme 2.1. Acrylate metathesis and selected products.



An influential report by Meier et al. described 50-fold higher productivity for the Hoveyda catalyst **III** in oleate–acrylate CM, relative to the second-generation Grubbs catalyst **GII** (Chart 2.1).^{9,13} Related catalysts (**Zhan1B**, **M51**) likewise show improved performance.¹⁴ Phosphine-free catalysts are now the standard for acrylate metathesis applied to renewable feedstocks, although **GII** remains commonly used in target-directed synthesis of α,β -unsaturated carbonyl derivatives.¹⁵

Chart 2.1. Key catalysts used in acrylate metathesis, and the resting-state species **GIIIm for the Grubbs catalyst.**

While several explanations for the superiority of phosphine-free catalysts have been advanced,^{16,17} the mechanistic basis remains speculative. Given the large number of metathesis catalysts now based on the archetypal structures **GII** and **HII**,¹⁸ and the limited understanding of the factors governing relative performance, this system affords an important target for study. Here we demonstrate that the performance of **GII** in acrylate metathesis is undermined by Michael addition pathways enabled by free PCy₃, which limit yields, promote side reactions, and cause catalyst decomposition. These findings offer informed insight into catalyst choice for acrylate metathesis. In the broader context, they highlight hazards in the use of metal–phosphine complexes to promote reactions of electron-deficient olefins.

2.3 Results and Discussion

We recently noted that the excellent performance of **HII** in acrylate–anethole metathesis is completely suppressed by added PCy₃ (Figure 2.1a).¹⁹ Here we use the combination of fast-initiating **HII** and mid-metathesis addition of PCy₃ to simulate highly initiated **GII**. By amplifying the concentration of the metallacyclobutane (MCB) intermediate relative to the off-cycle species **GII** and **GIIIm** which otherwise dominate, this experimental approach permits us to dissect out the impact of PCy₃ on the MCB intermediate: that is, on the active species central to the olefin metathesis reaction.

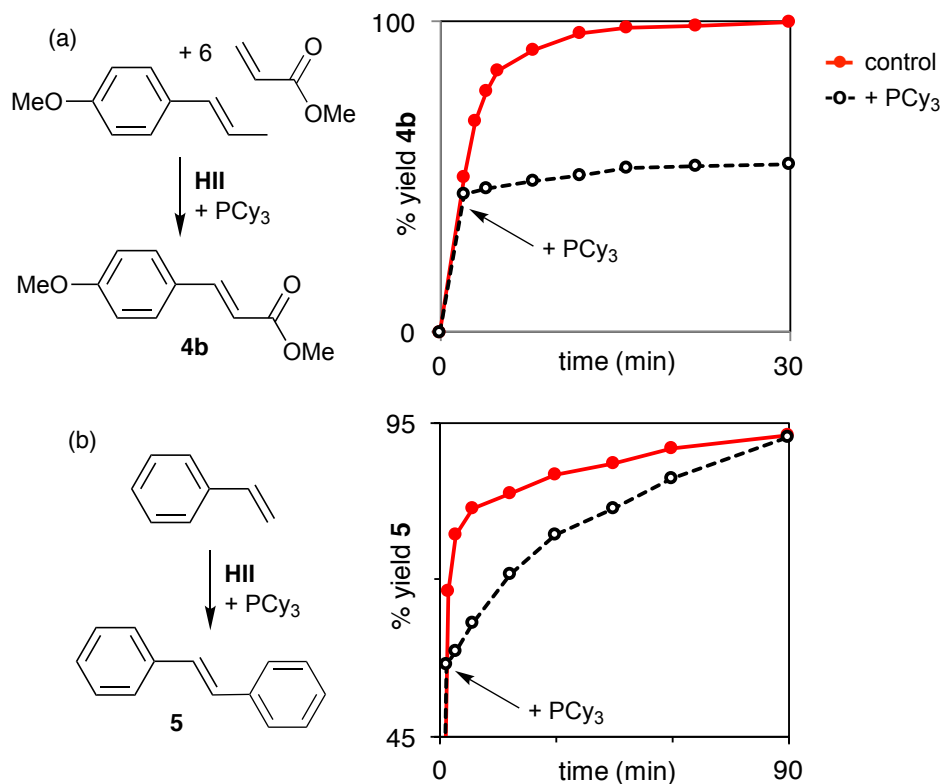


Figure 2.1. (a) Termination of CM by added PCy₃ in anethole–acrylate CM (Ar = 4-methoxyphenyl). (b) Rate retardation by added PCy₃ for CM in the absence of acrylate (0.5 mol % Ru, 70 °C, toluene).

To confirm that the rapid knockdown seen in Figure 2.1a is due to the electron-withdrawing ester moiety, we repeated the reaction with styrene in the absence of acrylate (Figure 2.1b). Styrene was chosen in place of anethole to ensure formation of the key methylenide species **GII_m** (the dominant species observed on treating **GII** with methyl acrylate), while subtracting ester-functionalized intermediates. In sharp contrast with the acrylate experiment, the ultimate yield of stilbene **5** was unaffected. That is, addition of PCy₃ merely slowed the reaction, by trapping the catalyst as the off-cycle species **GII_m** and **GII** (ratio 2:3 at 0.5 h). This experiment pinpoints the acrylate ester functionality as key to the deactivating effect of PCy₃, and we therefore examined the companion reaction, in which acrylate is retained but its coupling partner is omitted.

In these experiments, **HII** and PCy₃ were added to excess acrylate in C₆D₆, and the reaction was heated open to N₂ to permit ethylene loss.²⁰ Periodic analysis revealed formation of the phosphonium salts **A**⁺ and **B**⁺, in parallel with loss of **HII** and its PCy₃ adduct **HII-PCy₃** (Figure

2.2a).²¹ The simplicity of the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum suggests that one decomposition process predominates (Figure 2.2b).

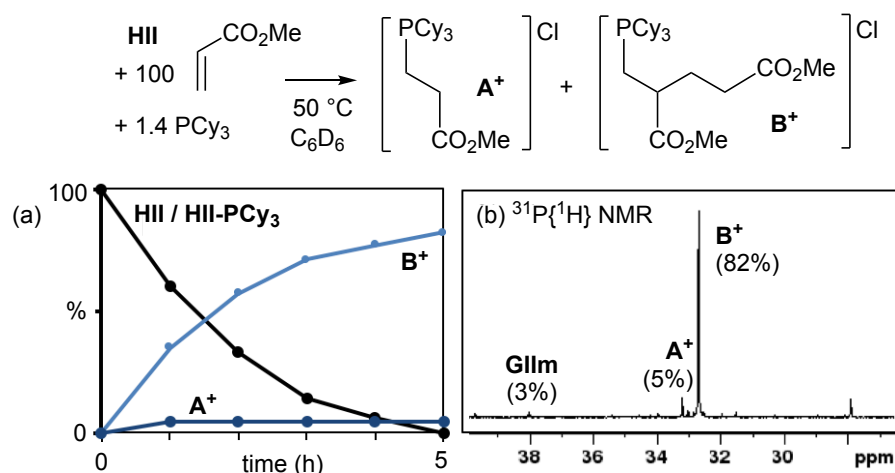
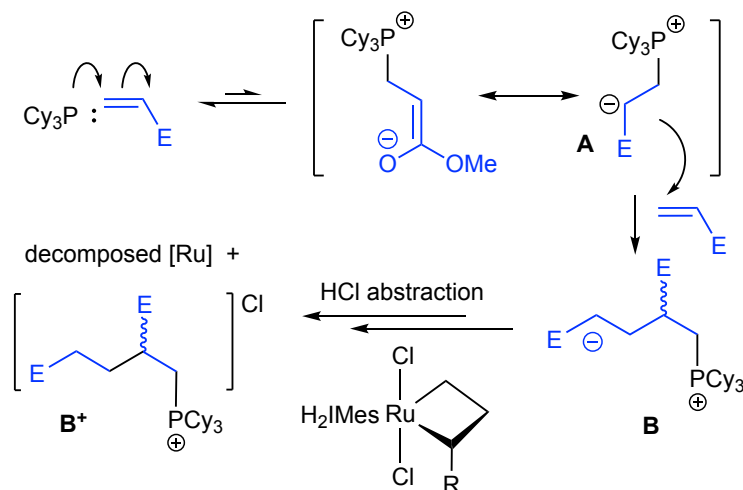


Figure 2.2. (a) Rate of loss of **HII** / **HII-PCy₃** (^1H NMR analysis) and formation of phosphonium salts ($^{31}\text{P}\{^1\text{H}\}$ NMR analysis); curve for **GIIIm** omitted for clarity (<5%). (b) $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of the reaction mixture at 5 h.

We propose that the phosphonium salts are generated by initial attack of PCy₃ on the electron-deficient olefin, forming zwitterionic **A**, which can participate in multiple subsequent pathways (Scheme 2.2). Ample precedent exists for this phosphonium enolate, both in phosphine-catalyzed Michael reactions²²⁻²⁵ and in the Morita–Baylis–Hillman reaction, in which **A** participates in further nucleophilic attack on aldehyde substrates.^{26,27}

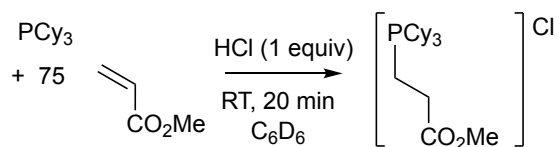
Scheme 2.2. Proposed mechanism for acrylate-induced catalyst decomposition (E = CO₂Me; R = H, CO₂Me)



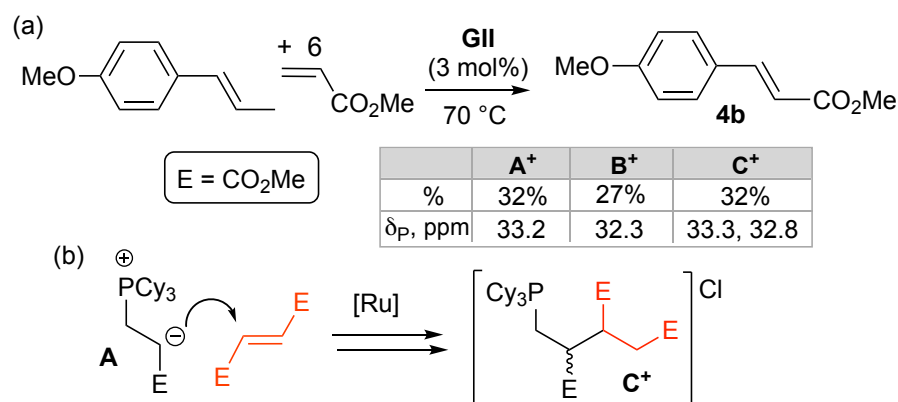
In the present context, the dominant reaction involves attack of **A** on further acrylate, followed by proton abstraction to liberate [**B**]X. No reaction is seen in the absence of **HII**, indicating that the ruthenium species present supplies the required proton and counter-anion.²⁸ Chloride abstraction may provide the anion, given the absence of additional signals in NMR spectra of isolated **B**⁺. An MCB intermediate is suggested as the likely target of attack. We recently reported that MCB intermediates formed during styrene metathesis are rapidly decomposed by base, including amines.²⁹ (The mechanism of catalyst decomposition by Brønsted base will be discussed in more detail in Chapter 3.) Competing attack on **GIIIm** (Scheme 1.10 above) is not unequivocally excluded, but is sterically less favorable.

Co-formation of **A**⁺ indicates competing reaction of the carbon nucleophile in **A** with a proton source. MCB species are again candidates for attack. Adventitious water is another, and indeed the proportion of **A**⁺ was increased on use of acrylate that was not dried over molecular sieves.³⁰ Stronger acids promote this reaction: thus, treating PCy₃ with methyl acrylate in the presence of HCl (Scheme 2.3) resulted in quantitative formation of [**A**]Cl. This behaviour offers a new explanation for the long-established capacity of phenols to improve the productivity of the Grubbs catalysts in acrylate metathesis:³¹⁻³⁵ in short, the phenol functions as a proton source, protecting the catalyst.

Scheme 2.3. Formation of [A**]Cl in the presence of HCl, with no metal species present**



The relevance of this chemistry to **GII** is supported by analysis of the anethole–acrylate CM reaction shown in Scheme 2.4a. Four species account for ca. 90% of the total ³¹P{¹H} NMR integration at 1 h, and for the three major ESI-MS signals. Of these species, **B**⁺ and **A**⁺ account for 60%. The balance is due to the new diastereomers **C**⁺, generated by attack of **A** on the re and si faces of methyl fumarate (Scheme 2.4b). Fumarate formation is due in part to the higher temperatures employed: **C**⁺ is likewise observed at 70 °C in acrylate metathesis using the **HII**/PCy₃ system (16%, vs <2% at 50 °C). Also notable is the higher proportion of **A**⁺, which may suggest that both the MCB and the resting-state species **GIIIm** are deprotonated by **A**. Precedents for the accessibility of the methyldiene ligand of **GIIIm** were noted above.

Scheme 2.4. (a) Decomposition of GII during anethole–acrylate CM. (b) Formation of C⁺

2.4 Conclusions

The foregoing demonstrates that the superiority of **III** over **GII** in acrylate metathesis reactions is due to elimination of reaction pathways triggered by the ancillary PCy₃ ligand. The potent nucleophilicity of the latter enables efficient reaction with electron-deficient olefins, leading to unwanted byproducts and to catalyst deactivation. The well-established versatility of nucleophilic phosphines in organocatalysis points toward the broad scope of this pathway. Substrates at risk, where a phosphine ligand is liberated—whether in metathesis or other catalytic chemistry—include those bearing α,β -unsaturated carbonyl and cyano functionalities, including acrylates, acrylamides, acrylonitriles, and α,β -unsaturated ketones. In all of these cases, a phosphine-free catalyst is likely to offer the simplest means of achieving the desired selectivity and catalyst productivity.

2.5 Experimental Details

2.5.1 General Procedures

Reactions were carried out in an N₂-filled glovebox at room temperature (25 ± 2 °C), unless otherwise indicated. Solvents were dried and degassed using a Glass Contour solvent purification system, then stored under N₂ in the glovebox over 4 Å molecular sieves for at least 16 h prior to use, unless otherwise indicated. Literature procedures were used to prepare the second-generation Hoveyda (**III**) and Grubbs (**GII**) catalysts.³⁶ Liquid reagents, including methyl acrylate (Aldrich: 99%; contains ≤100 ppm *p*-methoxyphenol as inhibitor) were degassed by five consecutive freeze/pump/thaw cycles, and then stored under N₂ in the glovebox freezer (-35 °C). Except where otherwise indicated (see text), methyl acrylate was dried over molecular sieves for

at least 16 h prior to use. NMR spectra were recorded at 23 ± 2 °C, and referenced against the residual proton signals of the deuterated solvents (¹H) or 85% H₃PO₄ (³¹P). ¹³C{¹H} NMR spectra in D₂O were referenced against the residual ¹H NMR signals of the deuterated solvent using the IUPAC-recommended method.³⁷ Mass spectra were recorded on a Waters Micromass quadrupole time-of-flight mass spectrometer equipped with a standard electrospray ionization (ESI) source. 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). Calibration curves (peak areas vs. concentration for solutions with ca. 1:1 w/w decane/analyte) in the relevant concentration regimes were constructed using commercial samples (styrene, *trans*-stilbene, anethole), or samples synthesized by literature methods (cinnamate **4b**).⁵ Yields in catalytic runs were determined from the integrated peak areas (referenced against decane), compared to the substrate/decane ratio at time zero (*t*₀). GC samples were quenched using ca. 10 equiv of potassium tris(pyrazolyl)borohydride (KTp)³⁸ in THF prior to analysis.

2.5.2 Suppression of acrylate cross-metathesis by added PCy₃

Stock solutions of **III** (12.5 mg in 800 μL C₇H₈; 19.9 μmol, 24.9 μM) and PCy₃ (35.0 mg in 2.5 mL C₇H₈; 125 μmol, 49.9 μM) were prepared. A 20 mL Schlenk tube containing a magnetic stir bar was charged with anethole (74 μL, 0.5 mmol), decane (98 μL, 0.5 mmol), methyl acrylate (272 μL, 3 mmol), and toluene (1.96 mL). A ca. 10 μL aliquot was removed for GC analysis to determine the ratio of anethole to decane at *t*₀. A stock solution of **III** (100 μL, 0.5 mol%) was added to the stirred solution to give a final anethole concentration of 200 mM, and the flask was immediately heated to 70 °C in a pre-heated, thermostatted oil bath while open to the glovebox atmosphere. After 2 min reaction (ca. 50% yield of cinnamate **4b**), PCy₃ was added (50 μL of the 50 mM stock solution, 2.50 μmol, 0.5 mol%). A colour change from green-brown to orange occurred within 5 min, and an orange solid precipitated over 0.5 h.

2.5.3 Observation of GII and GIIm during metathesis of styrene by **III** in the presence of PCy₃

As above, except with 200 mM styrene as the sole olefinic substrate. An aliquot was removed at 0.5 h to assess the alkylidene and phosphine-containing products present (Table 2.1). See Figure 2.1a above.

Table 2.1. Alkylidene and phosphorus-containing products formed during metathesis of styrene in the presence of added PCy₃.

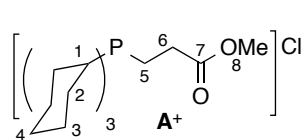
	¹ H (δ _H , ppm)		³¹ P{ ¹ H} (δ _P , ppm)		Relative proportion ^b
	expected ^a (C ₇ D ₈)	observed (C ₇ H ₈)	expected ^a (C ₇ D ₈)	observed (C ₇ H ₈)	
GII	19.55	19.51	30.0	29.9	3
GIIIm	18.29	18.25	38.0	37.9	2
III-PCy₃	20.3	—	30.4	—	0

^a Values observed for isolated complexes (**GII**, **GIIIm**) or in situ-generated adduct (**III-PCy₃**) formed from a 1:1 mixture of **III** and PCy₃. ^b Assessed by ³¹P{¹H} NMR integration.

2.5.4 NMR study of PCy₃-induced deactivation during acrylate metathesis

See Figure 2.2 above. Stock solutions of **III** and PCy₃ were prepared as above, at concentrations sufficient to observe catalyst speciation over time by NMR analysis (ca. 20 sec acquisition for ¹H, 2 min for ³¹P). **III**: 24.0 mg in 1.70 mL C₆D₆, 38.3 μmol, 22.5 μM; PCy₃: 17.7 mg in 250 μL C₆D₆, 63.1 μmol, 252 μM. A 20 mL Schlenk tube containing a stir-bar was charged with dry methyl acrylate (326 μL, 3.6 mmol), dimethyl terephthalate (internal ¹H NMR standard; ca. 2 mg), and C₆D₆ (874 μL). From the stock solutions, PCy₃ (200 μL, 0.05 mmol) and **III** (1.600 mL, 0.036 mmol) were added. The flask was immediately transferred to a thermostatted oil bath pre-warmed to 50 °C. The stirred reaction was left open to the glovebox atmosphere to enable loss of ethylene. Aliquots were removed at regular intervals for ¹H and ³¹P{¹H} NMR analysis in J. Young tubes, to quantify loss of the alkylidene signals for **III** (16.7 ppm) and **III-PCy₃** adduct (20.3 ppm) relative to internal standard, and to assess ³¹P speciation. The aliquots were returned promptly to the reaction flask after analysis.

2.5.5 Isolation and characterization of phosphonium salts

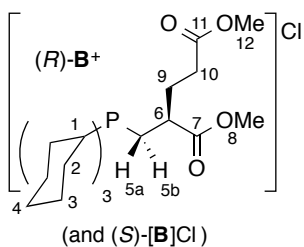


Synthesis of [Cy₃PCH₂CH₂CO₂Me]⁺Cl⁻, [A]Cl. In the glovebox, methyl acrylate (1.45 mL, 16.0 mmol), guaiacol (1.00 g, 0.80 mmol), and PCy₃ (33.6 mg, 0.12 mmol) were dissolved in toluene (9.5 mL) in

a 100 mL Schlenk tube equipped with a magnetic stir bar. **III** (50 mg) was added, the catalyst vessel was rinsed with 2.5 mL toluene to ensure complete transfer, and the reaction was transferred to an oil bath pre-heated to 70 °C. The stirred reaction was left open to the glovebox atmosphere to enable loss of ethylene. A colour change from green to brown occurred. After 1 h, the reaction was extracted with H₂O (3 x 2 mL), and the combined aqueous phase was extracted

with hexanes (3 x 2 mL), and stripped to dryness, affording [A]Cl as an air-stable yellow solid. Yield 43 mg (97%). ³¹P{¹H} NMR (D₂O, 121.5 MHz): δ 32.7 ppm (s, 99%, [A]Cl), 33.5 (s, 1%, unassigned). ¹H NMR (D₂O, 300.1 MHz, ax = axial, e = equatorial): δ 3.75 (s, 3H, H₈), 2.71 (m, 2H, H₆), 2.53 (m, 5H, H₁, H₅), 1.92 (br m, 12H, H_{2e}, H_{3e}), 1.75 (br d, 3H, H_{4e}), 1.57 (br q, 6H, H_{3ax}), 1.35 (br m, 9H, H_{2ax}, H_{4ax}) ppm. ¹³C{¹H} NMR (D₂O, 75.5 MHz): δ 173.4 (d, ³J_{PC} = 15 Hz, C₇), 52.8 (s, C₈), 29.0 (d, ¹J_{PC} = 41 Hz, C₁), 26.4 (d, ²J_{PC} = 3 Hz, C₆), 26.2 (d, ²J_{PC} = 4 Hz, C₂), 25.9 (d, ³J_{PC} = 12 Hz, C₃), 24.9 (s, C₄), 10.2 (d, ¹J_{PC} = 47 Hz, C₅) ppm. (+)-ESI-MS (*m/z*): 367.3 (calc'd for [C₂₂H₄₀O₂P]⁺: 367.3). (+)-ESI-MS/MS (CID, 50 eV, *m/z*): 285.2 ([M-C₆H₁₀]⁺), 203.1 ([M-2C₆H₁₀]⁺), 143.1 ([M-2C₆H₁₀-HCOOMe]⁺). A minor impurity (ca. 1% of total ³¹P integration) was also present, as was the case for all phosphonium salts investigated (all of which resist separation by chromatography, precipitation, washing, etc.) No signals for the aryloxide counterion were observable in the ¹H NMR spectrum (see Figure A1), consistent with formation of [A]Cl as the dominant product.

Synthesis of [A]Cl in the absence of Ru. A 100 μL aliquot of a PCy₃ stock solution (22.6 mg, 80.5 μmol, 357 μM in 226 μL C₆D₆) was combined with methyl acrylate (242 μL, 2.67 mmol, 75 equiv) and 358 μL C₆D₆ in a Rotaflo NMR tube. A dioxane solution of HCl (9 μL of a 3.7 M solution, ca. 1 equiv) was injected, the puncture was sealed immediately with electrical tape, and the NMR tube was shaken briefly. NMR analysis after 20 min showed no remaining PCy₃. ³¹P{¹H} NMR (C₆D₆, 300.1 MHz): δ_P 33.3 ppm (s, 96%, [A]Cl), 33.1 ppm (s, 4%, unknown). Extraction into D₂O gave ¹H and ³¹P{¹H} NMR spectra identical to those above.



Synthesis of phosphonium salt (±)-[B]Cl. In the glovebox, a 100 mL Schlenk tube containing a stir-bar was charged with dry methyl acrylate (1.15 mL, 12.7 mmol), toluene (7 mL), PCy₃ (21.4 mg, 0.076 mmol), and **III** (40 mg, 0.063 mmol). The catalyst vessel was rinsed with 2.5 mL toluene to ensure complete transfer. The reaction was

stirred open at RT for 5 h to permit loss of ethylene, then sealed to minimize odours associated with the acrylate. The solution changed colour from green-brown to bright orange over 24 h, and deposited an orange solid containing unidentified Ru products and [B]Cl. This was filtered off. The dark orange filtrate contained [B]Cl and [A]Cl (the chloride counter-ion is presumed, on the basis of the absence of additional NMR signals for the isolated salts; see below). [B]Cl was

isolated by re-dissolving the orange solid in a minimum volume of CH₂Cl₂ (2.5 mL), precipitating the Ru species with hexanes (35 mL), filtering these off, and extracting the filtrate with H₂O (3 x 2 mL) in the glovebox (an inert atmosphere was essential to prevent decomposition of Ru species into water-soluble products). The aqueous extracts were combined and stripped to dryness, affording [**B**]Cl (10 mg, 29%) as an air-stable colourless solid. ¹H NMR (D₂O, 300.1 MHz, ax = axial, e = equatorial; Figure A2): δ 3.81 (s, 3H, *H*8), 3.72 (s, 3H, *H*12), 3.06 (p, ³*J*_{HH} = 8 Hz, ³*J*_{HP} = 8 Hz, 1H, *H*6), 2.84 (ddd, ²*J*_{PH} = 11 Hz, 1H, *H*5b), 2.45 (m, 6H, *H*10, *H*1, *H*5a), 2.08 (m, 2H, *H*9), 1.92 (br t, 12 H, *H*2e, *H*3e), 1.76 (br d, 3H, *H*4e), 1.56 (br p, 6H, *H*3ax), 1.33 (br m, 9H, *H*2ax, *H*4ax) ppm. ³¹P{¹H} NMR (D₂O, 121.5 MHz): δ 32.9 ppm (s). ¹³C{¹H} NMR (D₂O, 75.5 MHz): δ 175.7 (d, ³*J*_{PC} = 2 Hz, C7), 175.5 (s, C11), 53.3 (s, C8), 52.4 (s, C12), 38.2 (d, ²*J*_{PC} = 4 Hz, C6), 30.5 (s, C10), 29.9 (d, ¹*J*_{PC} = 40 Hz, C1), 29.8 (d, ³*J*_{PC} = 10 Hz, C9), 26.3 (2d, C2), 26.1 (d, ³*J*_{PC} = 12 Hz, C3), 25.1 (s, C4), 17.4 (d, ¹*J*_{PC} = 44 Hz, C5) ppm. (+)ESI-MS (*m/z*): 453.3 (calc'd for [C₂₆H₄₆O₄P]⁺: 453.3). (+)-ESI-MS/MS (CID, 50 eV, *m/z*): 371.2 ([M-cyclohexene]⁺), 175.1 ([M-PCy₃+2H]⁺), 147.1 ([M-3Cy-CO₂Me+H]⁺). Assignments for [**B**]Cl are supported by a combination of ¹H–¹H COSY (Figure A3), ¹H–¹³C HMQC (Figure A4) ¹H–¹³C HMBC (Figure A5), Elemental analysis of [**B**]Cl was precluded by difficulties in obtaining pure material. Attempts to separate [**B**]Cl, [**A**]Cl and related phosphonium salts were frustrated by the similar solubility properties of these species; see above.

2.5.6 Decomposition of **GII** during acrylate-anethole CM

a) A stock solution containing **GII** (17.2 mg in 450 μL C₇H₈) was prepared. Subsequently, anethole (45 μL, 0.30 mmol) and dry methyl acrylate (163 μL, 1.80 mmol) were diluted with C₇H₈ (1.10 mL) in a 20 mL Schlenk flask equipped with a magnetic stir bar. **GII** stock (200 μL, 0.009 mmol, 3 mol%) was added, and the reaction was warmed to 70 °C in a pre-heated, thermostatted oil bath (final [anethole]: 200 mM). The pink solution turned orange over ca. 30 min, and an orange precipitate appeared. After 90 min, an aliquot was removed for NMR analysis. ³¹P{¹H} NMR (C₇H₈, 121.5 MHz): δ 37.9 (s, 2%, **GII**m), 34.0 (s, 5%, MePCy₃Cl), 33.3 (s, 13%, **C**⁺), 33.2 (s, 32%, **B**⁺), 32.8 (s, 19%, **C**⁺), 32.3 (s, 27%, **A**⁺), 27.8 (s, 2%, unassigned). Assignment of **A**⁺, **B**⁺, and MePCy₃Cl was confirmed by spiking the NMR sample with material synthesized as above. The remaining reaction solution was extracted with H₂O (3 x 1 mL) in the glovebox. The aqueous phase was washed with hexanes (3 x 2 mL) in air and

stripped to dryness. ³¹P{¹H} NMR (D₂O, 121.5 MHz): δ 33.5 (minor, s), 33.3 (s, C⁺), 33.0 (s, C⁺), 32.9 (s, B⁺), 32.7 (s, A⁺) ppm; integrations of A⁺-C⁺ within 3% of values in C₇H₈. ¹H NMR (D₂O, 300.1 MHz): 3.83 (s, C⁺), 3.82 (s, C⁺), 3.81 (s, H8 of B⁺), 3.79 (s, C⁺), 3.77 (s, C⁺), 3.76 (s, H8 of A⁺), 3.73 (two overlapping s, C⁺), 3.72 (s, H12 of B⁺). (+)ESI-MS (*m/z*): 367.3 (A⁺, 30% relative intensity), 453.3 (B⁺, 40%), 511.3 (C⁺, 100%). Calculated for C₂₈H₄₈O₆P (C⁺): 511.3.

b) This experiment was repeated with 2 equiv CuI (vs. Ru). No signals for A⁺, B⁺, or C⁺ were observed. ³¹P{¹H} NMR (C₇D₈, 121.5 MHz): δ 34.0 (s, [MePCy₃]Cl; ca. 10%), 12.89 (br s, assigned to a Cu-PCy₃ adduct; ca. 90%: the breadth of this signal limits precision).

2.6 References

- (1) For recent reviews, see: (a) Prunet, J.; Grimaud, L., Cross-metathesis in Natural Products Synthesis. In *Metathesis in Natural Product Synthesis: Strategies, Substrates and Catalysts*, Cossy, J.; Arseniyadis, S.; Meyer, C., Eds. Wiley-VCH: Weinheim, 2010; pp. 287–312. (b) 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. (c) Żukowska, K.; Grela, K., Cross Metathesis. In *Olefin Metathesis-Theory and Practice*, Grela, K., Ed. Wiley: Hoboken, NJ, 2014; pp 39–84. For tandem catalysis routes to heteroaromatics, beginning with metathesis of vinyl ketones, see: (d) Donohoe, T. J.; Bower, J. F. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 3373–3376. For an analysis of the context and opportunities of these methodologies, see: (e) Krische, M. J. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 3279–3280. For a tandem intramolecular-hydroarylation sequence enabled by metathesis of α,β-unsaturated carbonyl compounds, see: (f) Chen, J.-R.; Li, C.-F.; An, X.-L.; Zhang, J.-J.; Zhu, X.-Y.; Xiao, W.-J. *Angew. Chem. Int. Ed.* **2008**, *47*, 2489–2492.
- (2) Chikkali, S.; Mecking, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 5802–5808.
- (3) Biermann, U.; Bornscheuer, U.; Meier, M. A. R.; Metzger, J. O.; Schafer, H. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 3854–3871.
- (4) Marshall, A.-L.; Alaimo, P. J. *Chem. - Eur. J.* **2010**, *16*, 4970–4980.
- (5) Lummiss, J. A. M.; Oliveira, K. C.; Pranckevicius, A.; Santos, A.; dos Santos, E. N.; Fogg, D. E. *J. Am. Chem. Soc.* **2012**, *134*, 18889–18891.
- (6) For recent applications in the synthesis of natural products of medicinal relevance, see: (a) Plummer, C. W.; Wei, C. S.; Yozwiak, C. E.; Soheili, A.; Smithback, S. O.; Leighton, J. L. *J. Am. Chem. Soc.* **2014**, *136*, 9878–9881; (b) Chatterjee, S.; Ghadigaonkar, S.; Sur, P.; Sharma, A.; Chattopadhyay, S. *J. Org. Chem.* **2014**, *79*, 8067–8076; (c) Xiao, Q.; Jackson, J. J.; Basak, A.; Bowler, J. M.; Miller, B. G.; Zakarian, A. *Nature Chem.* **2013**, *5*, 410–416; (d) Willwacher, J.; Fürstner, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 4217–4221; (e) Fuwa, H.; Saito, A.; Sasaki, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 3041–3044; (f) Brewitz, L.; Llaveria, J.; Yada, A.; Fürstner, A. *Chem. – Eur. J.* **2013**, *19*, 4532–4537.

- (7) Corma, A.; Iborra, S.; Velty, A. *Chem. Rev.* **2007**, *107*, 2411–2502.
- (8) Schulz, M. D.; Ford, R. R.; Wagener, K. B. *Polym. Chem.* **2013**, *4*, 3656–3658.
- (9) Rybak, A.; Meier, M. A. R. *Green Chem.* **2007**, *9*, 1356–1361.
- (10) Miao, X.; Fischmeister, C.; Dixneuf, P. H.; Bruneau, C.; Dubois, J. L.; Couturier, J. L. *Green Chem.* **2012**, *14*, 2179–2183.
- (11) Malacea, R.; Fischmeister, C.; Bruneau, C.; Dubois, J.-L.; Couturier, J.-L.; Dixneuf, P. H. *Green Chem.* **2009**, *11*, 152–155.
- (12) Winkler, M.; Meier, M. A. R. *Green Chem.* **2014**, *16*, 3335–3340.
- (13) The superior performance of **III** relative to **GII** for acrylate metathesis has since been confirmed in multiple reports. See, for example, refs 8, 10, and: (a) Schweitzer, D.; Snell, K. D. *Org. Process Res. Dev.* **2015**, *19*, 715–720; (b) Lafaye, K.; Nicolas, L.; Guérinot, A.; Reymond, S. b.; Cossy, J. *Org. Lett.* **2014**, *16*, 4972–4975; (c) Meng, X.; Matson, J. B.; Edgar, K. J. *Biomacromolecules* **2014**, *15*, 177–187; (d) Bilel, H.; Hamdi, N.; Zagrouba, F.; Fischmeister, C.; Bruneau, C. *Green Chem.* **2011**, *13*, 1448–1452; (e) Djigoué, G. B.; Meier, M. A. R. *Appl. Catal. A* **2009**, *368*, 158–162.
- (14) See, for example, refs 10, 13a,d-e, and: (a) Vignon, P.; Vancompernelle, T.; Couturier, J.-L.; Dubois, J.-L.; Mortreux; Gauvin, R. M. *ChemSusChem* **2015**, *8*, 1143–1146; (b) Ho, T. T.; Jacobs, T.; Meier, M. A. R. *ChemSusChem* **2009**, *2*, 749–754.
- (15) For selected noteworthy examples, see: refs 1a, 6e, and: (a) Cash, B. M.; Prevost, N.; Wagner, F. F.; Comins, D. L. *J. Org. Chem.* **2014**, *79*, 5740–5745; (b) Kinzurik, M. I.; Hristov, L. V.; Matsuda, S. P. T.; Ball, Z. T. *Org. Lett.* **2014**, *16*, 2188–2191; (c) Beemelmans, C.; Gross, S.; Reissig, H.-U. *Chem. – Eur. J.* **2013**, *19*, 17801–17808; (d) Trost, B. M.; Aponick, A.; Stanzl, B. N. *Chem. – Eur. J.* **2007**, *13*, 9547–9560; (e) Marjanovic, J.; Kozmin, S. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 8854–8857. Additional examples appear in a recent review of RCM methods for the synthesis of lactones from acrylates. See: (f) Bassetti, M. D. A., Andrea *Curr. Org. Chem.* **2013**, *17*, 2654–2677.
- (16) Early suggestions centered on the limited capacity of the electron-deficient olefin to compete with PCy₃ for binding to the metal. See: (a) Love, J. A.; Morgan, J. P.; Trnka, T. M.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2002**, *41*, 4035–4037. (b) Hoveyda, A. H.; Gillingham, D. G.; Van Veldhuizen, J. J.; Kataoka, O.; Garber, S. B.; Kingsbury, J. S.; Harrity, J. P. A. *Org. Biomol. Chem.* **2004**, *2*, 8–23. Conversely, excessively strong binding of PCy₃ to electron-deficient Ru intermediates has been proposed: see Ref. (b).
- (17) Also potentially plausible is nucleophilic attack of PCy₃ on the electron-deficient alkylidene, by analogy to the pathway established for the methyldiene complexes RuCl₂(L)(PCy₃)(=CH₂). Crystallographic evidence demonstrating attack of PCy₃ on the methyldiene ligand was recently reported. See: (a) Lummiss, J. A. M.; McClennan, W. L.; McDonald, R.; Fogg, D. E. *Organometallics* **2014**, *33*, 6738–6741. Abstraction of the methyldiene moiety from isolated **GII**m liberates [MePCy₃]Cl. See: (b) Hong, S. H.; Wenzel, A. G.; Salguero, T. T.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2007**, *129*, 7961–7968. For evidence of this pathway during catalysis, see: (c) Lummiss, J. A. M.; Ireland, B. J.; Sommers, J. M.; Fogg, D. E. *ChemCatChem* **2014**, *6*, 459–463. While nucleophilic attack of phosphine on Ru-alkylidene species is rare, Diver has demonstrated such a pathway where CO binding

rendered the alkylidene carbon more electrophilic. See: Galan, B. R.; Pitak, M.; Keister, J. B.; Diver, S. T. *Organometallics* **2008**, *27*, 3630–3632.

(18) (a) Vougioukalakis, G.C. Ruthenium-Benzylidene Olefin Metathesis Catalysts. In *Olefin Metathesis-Theory and Practice*, Grela, K., Ed. Wiley: Hoboken, NJ, 2014; pp 397–416. (b) Ginzburg, Y.; Lemcoff, N. G. Hoveyda-Type Olefin Metathesis Complexes. In *Olefin Metathesis – Theory and Practice*, Grela, K., Ed. Wiley: Hoboken, NJ, 2014; pp 437–451.

(19) (a) Weskamp, T.; Schattenmann, W. C.; Spiegler, M.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2490. (b) Herrmann, W. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 262.

(20) These experiments were carried out at 50 °C, to permit interception of low-energy organometallic pathways, rather than downstream events. At higher temperatures, attack of **A** on additional CM products is observed; see text.

(21) The cation **B**⁺ was identified by mass spectrometric and NMR analysis of material isolated by aqueous extraction. The cation is unperturbed by isolation, as confirmed by spiking a reaction aliquot with the isolated salt and assessing the ³¹P{¹H} NMR spectrum. Diagnostic for the structure of **B**⁺ is the upfield location and doublet multiplicity of the ¹³C{¹H} NMR signal for PCH₂ (C5: 17.5 ppm, d, ¹J_{PC} = 44 Hz). This signal exhibits the expected HMQC correlation to two diastereotopic methylene protons (2.84, ddd, ²J_{HH} = 16 Hz, ²J_{PH} = 12 Hz, ³J_{HH} = 10 Hz, 1H; 2.35, m, 1H). The ¹³C{¹H} NMR doublet at 38.2 for the PCH₂CH methine carbon also exhibits the expected HMBC correlations with the adjacent methylene protons (H5, H9, and H10).

(22) Fan, Y. C.; Kwon, O. *Chem. Commun.* **2013**, *49*, 11588–11619.

(23) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035–1050.

(24) Gimbert, C.; Lumbierres, M.; Marchi, C.; Moreno-Mañas, M.; Sebastián, R. M.; Vallribera, A. *Tetrahedron* **2005**, *61*, 8598–8605.

(25) Gómez-Bengoa, E.; Cuerva, J. M.; Mateo, C.; Echavarren, A. M. *J. Am. Chem. Soc.* **1996**, *118*, 8553–8565.

(26) Morita, K.-i.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Japan* **1968**, *41*, 2815–2815.

(27) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–892.

(28) The Ru center may also act as a Lewis acid, complexing the carbonyl group of **A**, and thus favouring subsequent Michael addition reactions. Such behaviour was reported for a related Ru-hydride complex. See Ref. 25.

(29) Ireland, B. J.; Dobigny, B. T.; Fogg, D. E. *ACS Catal.* **2015**, *5*, 4690–4698.

(30) The phenol inhibitors present in methyl acrylate are not significant contributors. The maximum level of 100 ppm 4-methoxyphenol cited in the supplier's specification sheet (Sigma-Aldrich; 99% purity reagent) would account for just 0.5% yield of **A**⁺.

(31) Adding a phenol (the renewable phenol guaiacol) to the reaction resulted in selective formation of [A]Cl: see experimental details (Section 2.5.5).

(32) Forman, G. S.; Tooze, R. P. *J. Organomet. Chem.* **2005**, *690*, 5863–5866.

(33) 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.

(34) Schmidt, B.; Hauke, S. *Org. Biomol. Chem.* **2013**, *11*, 4194–4206.

(35) Scavenging of phosphine offers an alternative solution. CuI has recently been employed to enhance yields in **GII**-promoted acrylate metathesis. See: (a) Nair, R. N.; Bannister, T. D. *J. Org. Chem.* **2014**, *79*, 1467–1472; (b) Voigtritter, K.; Ghorai, S.; Lipshutz, B. H. *J. Org. Chem.* **2011**, *76*, 4697–4702. As expected, adding CuI during the anethole-acrylate CM reaction completely suppressed formation of the phosphonium salts. Instead visible in the ³¹P{¹H} NMR spectrum were a sharp singlet for [MePCy₃]Cl (34.0 ppm) and a broad singlet at 12.89 ppm, likely corresponding to a copper-phosphine adduct.

(36) van Lierop, B. J.; Reckling, A. M.; Lummiss, J. A. M.; Fogg, D. E. *ChemCatChem* **2012**, *4*, 2020–2025.

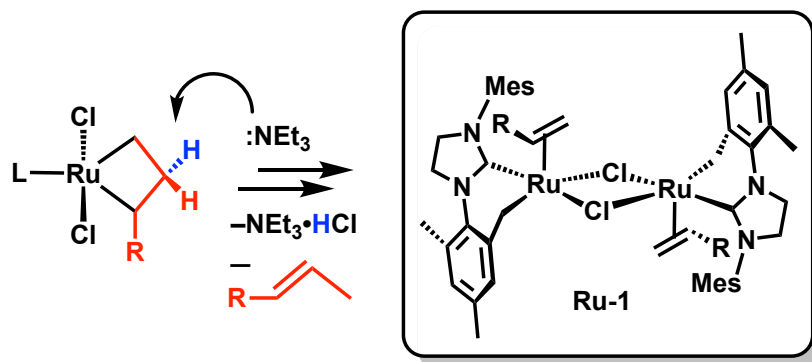
(37) Harris, R. K.; Becker, E. D.; Cabral de Menezes, S. M.; Granger, P.; Hoffman, R. E.; Zilm, K. W. *Pure Appl. Chem.* **2008**, *80*, 59–84.

(38) Blacquiere, J. M.; Jurca, T.; Weiss, J.; Fogg, D. E. *Adv. Synth. Catal.* **2008**, *350*, 2849–2855.

Chapter 3. Catalyst Decomposition by Brønsted Base: Metallacyclobutane Deprotonation as a Primary Deactivating Event

3.1 Published Contributions

Decomposition of Olefin Metathesis Catalysts by Brønsted Base: Metallacyclobutane Deprotonation as a Primary Deactivating Event. Gwendolyn A. Bailey, Justin A. M. Lummiss, Marco Foscato, Giovanni Occhipinti, Robert McDonald, Vidar R. Jensen, and Deryn E. Fogg. *J. Am. Chem. Soc.* **2017**, 16446–16449. (Communication)



Abstract: Brønsted bases of widely varying strength are shown to decompose the metathesis-active Ru intermediates formed by the second-generation Hoveyda and Grubbs catalysts. Major products, in addition to propenes, are base•HCl and olefin-bound, cyclometallated dimers **Ru-1**. These are generated in ca. 90% yield on metathesis of methyl acrylate, styrene, or ethylene in the presence of either DBU, or enolates formed by nucleophilic attack of PCy₃ on methyl acrylate. They also form, in lower proportions, on metathesis in the presence of the weaker base NEt₃. Labeling studies reveal that the initial site of catalyst deprotonation is not the H₂IMes ligand, as the cyclometallated structure of **Ru-1** might suggest, but the metallacyclobutane (MCB) ring. Computational analysis supports the unexpected acidity of the MCB protons, even for the unsubstituted ring, and by implication, its overlooked role in decomposition of Ru metathesis catalysts.

Author Contributions: This manuscript was conceived, written, edited, and revised by GAB and DEF. X-ray quality crystals of **Ru-1b** were obtained by JAML, and analyzed by RM. All other

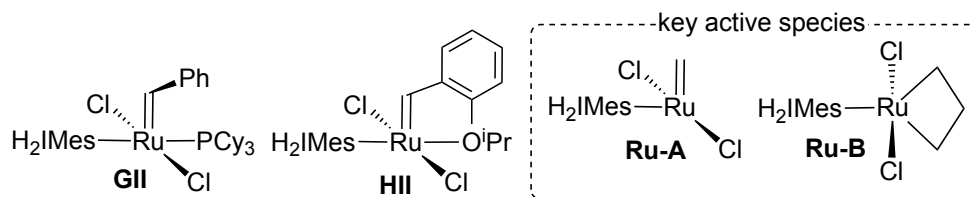
experiments were performed by GAB. DFT calculations were performed by MF and GO, in consultation with VRJ.

3.2 Introduction

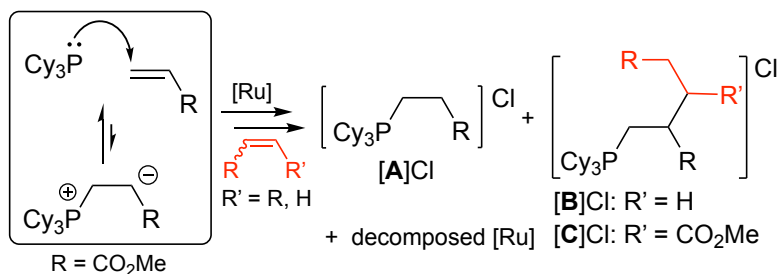
With the advent of Ru-catalyzed olefin metathesis in pharmaceutical manufacturing,¹ the need to understand the fundamental pathways governing catalyst decomposition² takes on new prominence. Decomposition limits metathesis productivity: as well, because decomposed catalyst can promote non-metathetical side-reactions, it affects selectivity and reproducibility.³ Particularly important are decomposition pathways triggered by even trace amounts of base, a recurring problem for metathesis in process chemistry in pharma.^{4,5}

Sterically accessible Lewis bases are now known to play an important role in decomposition of the leading metathesis catalysts of Chart 3.1.⁶⁻⁸ Small nucleophiles (e.g., NH_2^tBu) abstract the benzyldiene moiety from **GII**^{1d} and **III**,^{9a} or the methylidene ligand from **Ru-A**.^{6c} For PCy_3 -stabilized catalysts, associative binding of sterically accessible Lewis donors accelerates loss of PCy_3 , and hence loss of the methylidene ligand from **Ru-A**.^{6,7}

Chart 3.1. Metathesis Catalysts and Key Active Species



Less is yet understood about the pathways operative for Brønsted bases, but multiple studies attest to their negative impact.^{4,5,9} Nitrogen bases of widely varying strength (DBU, pK_a 24; NEt_3 , pK_a 18) were shown to decompose **GII** and **III** during macrocyclization^{6d} or styrene metathesis,^{9a} via pathways hitherto conjectural.¹⁰ Likewise, yields in acrylate metathesis catalyzed by **GII** are severely reduced relative to those attainable with the phosphine-free Hoveyda catalyst **III**.^{9c} The latter problem was traced to highly basic¹¹ enolates formed by reaction of acrylate with liberated PCy_3 (Scheme 3.1).^{9b}

Scheme 3.1. Enolates and phosphonium salts generated during acrylate metathesis when PCy₃ is present

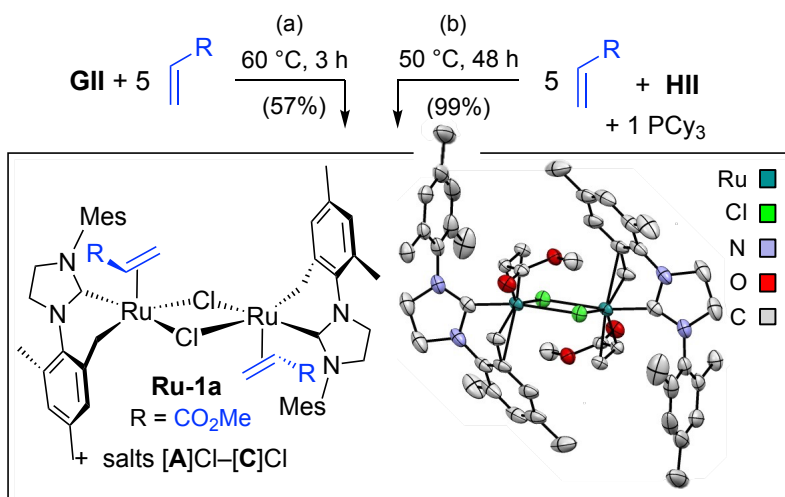
Here we demonstrate that the negative impact of Brønsted bases on **GII** and **III** in metathesis is due to metallacyclobutane (MCB) deprotonation, which triggers elimination of the ring hydrocarbons as propene(s). Computational analysis substantiates the implied acidity of the MCB protons, even for unsubstituted **Ru-B** (Chart 3.1). These findings highlight the significance of the MCB moiety in decomposition by base, and of MCB protection in catalyst redesign.

3.3 Results and Discussion

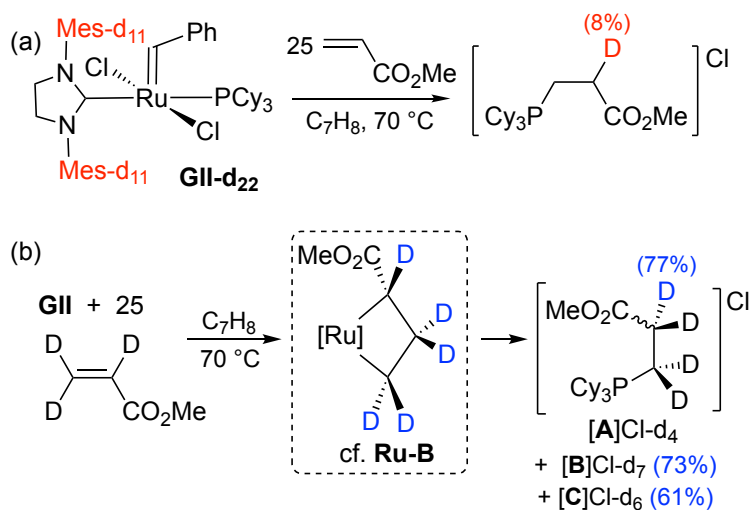
We began by isolating the Ru decomposition products formed in reactions with enolate. On treating **GII** with methyl acrylate (Scheme 3.2a), cyclometallated dimer **Ru-1a** deposited in ca. 60% yield, accompanied by phosphonium salts **[A]Cl**–**[C]Cl**. This reaction was cleaner when PCy₃ and methyl acrylate were added to the faster-initiating^{12,13} catalyst **III** (Scheme 3.2b). Dimeric **Ru-1a** then precipitated quantitatively. NMR and X-ray analysis support the acrylate-bound structure depicted. Strong back-donation onto acrylate is indicated by the elongated C=C distance (1.426(3) Å, vs 1.337(7) Å for free methyl acrylate).^{14–16}

The cyclometallated structure of **Ru-1a** suggests that decomposition by enolate commences with abstraction of an *o*-methyl proton from the H₂IMes ligand.¹⁷ To probe this point, we reacted methyl acrylate with **GII-d₂₂**, in which the mesityl rings are perdeuterated,¹⁸ and deprotonation should thus generate **[A]Cl**–**[C]Cl-d₁**.^{9b} However, limited deuteration was observed by quantitative MALDI-MS analysis (e.g., <10% into **[A]Cl**, which presents fewest sites for scrambling; Scheme 3.3a). In contrast, reaction of non-labeled **GII** with deuterated methyl acrylate-d₃ gave 77% deuterium uptake into **[A]Cl-d₄** (Scheme 3.3b).¹⁹ We infer that the primary initial site of deprotonation is the MCB ring, not the H₂IMes ligand. Computational analysis (see below) ruled out an alternative possibility, deprotonation of the methylenide in **Ru-A**.²⁰ We will return below to the pathway by which **Ru-1** subsequently forms.

Scheme 3.2. Formation of Ru-1a from GII and HII



^a ORTEP plot shown with Gaussian ellipsoids at 50% probability level; hydrogen atoms omitted.

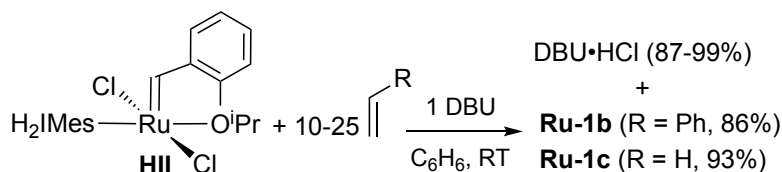
Scheme 3.3. Labeling study showing deprotonation of the MCB ring, rather than the H₂IMes ligand ^a

^a Numbers in brackets indicate D incorporation at the designated positions. For mass spectra, see Figures A39 and A40 in the Appendix.

Attack of enolate on the acrylate-derived MCB could arguably be a special case enabled by the high acidity conferred by the ester group. However, fortuitous isolation of **Ru-1b** (R = Ph) led us to suspect that MCB deprotonation might be more general. X-ray quality crystals of **Ru-1b** deposited from a macrocyclization reaction promoted by **GII** in the presence of DBU (Figures 3.2, A38).^{6d} The styrene ligand presumably originates in the first cycle of metathesis.

Deliberate reaction of **III** with styrene and DBU at RT (Scheme 3.4) enabled isolation of **Ru-1b** in 86% yield. In situ NMR analysis indicated near-quantitative co-formation of DBU•HCl. Experiments with D₂C=CDPh (not shown) revealed 80% deuterium incorporation into DBU•DCl, confirming that this proton originates in the MCB ring.¹⁹ Remarkably, even protons on the unsubstituted ring are sufficiently acidic to participate. Thus, ca. 90% DBU•HCl was also observed in the corresponding reaction with ethylene, and known^{7b} ethylene adduct **Ru-1c** was isolated in 93% yield. On replacing DBU with NEt₃, yields of both **Ru-1c** and base•HCl drop to ca. 50%, consistent with the lower basicity of NEt₃ (and, potentially, competing decomposition of **Ru-A**; see Chapter 4 below).

Scheme 3.4. Isolation of dimers **Ru-1b** and **Ru-1c**



To validate the acidity of the protons in the unsubstituted MCB ring, and to exclude the alternative possibility of methyldene deprotonation,²¹ we undertook computational analysis. Ground-state structures for **Ru-A**, **Ru-B**, and their deprotonated derivatives appear in Figure 3.1. Density functional theory (DFT) calculations indicate preferential deprotonation of **Ru-B** at C_β (i.e., the β-carbon of the MCB), rather than C_α. Computed relative pK_a values confirm the lower acidity of H_α vs H_β, as expected from the greater stability of the allyl anion vs 1-propenyl anion. The susceptibility of C_β to deprotonation is consistent with recent studies in which this site is predicted to carry a positive charge.²²

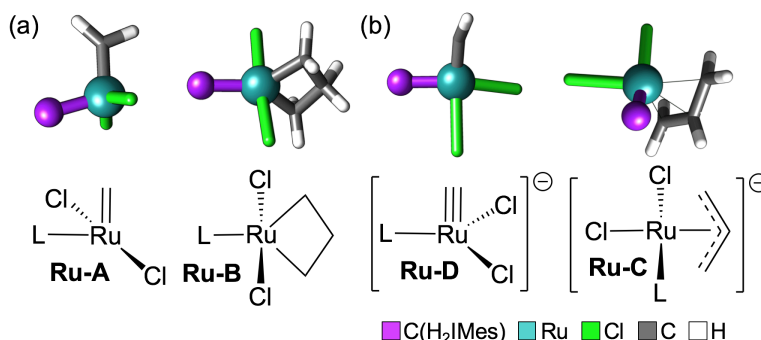
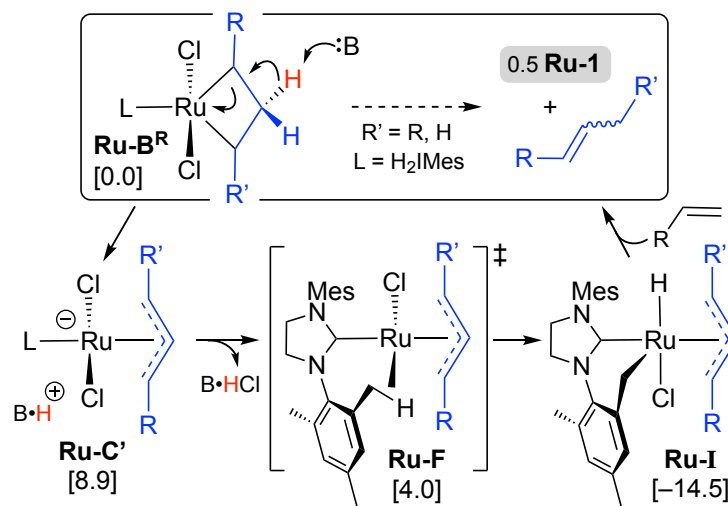


Figure 3.1. Computed (DFT) structures for (a) **Ru-A** and **Ru-B**, and (b) their deprotonated congeners. For visual clarity, the H₂IMes ligand L is truncated to the carbene carbon (purple).

Deprotonation at C $_{\beta}$ converts the MCB ring into an Ru-allyl species. Shown in Figure 3.1 is anionic **Ru-C** (the dichloro complex that precedes loss of Cl $^{-}$), as the most stable η^3 -allyl, cis-Cl $_2$ isomer.²³ The methyldiyne species **Ru-D** formed by deprotonation of methyldiene **Ru-A** is strongly disfavored relative to **Ru-C**, as judged from the proton exchange reaction **Ru-B** + **Ru-D** $\rightleftharpoons$ **Ru-A** + **Ru-C**.²⁴ The reaction free energy of ca. -25 kcal/mol (see Computational Details below) indicates that the β -MCB protons are more acidic than the methyldiene protons by ca. 20 pKa units, confirming the MCB ring as the most plausible site of deprotonation.²⁰

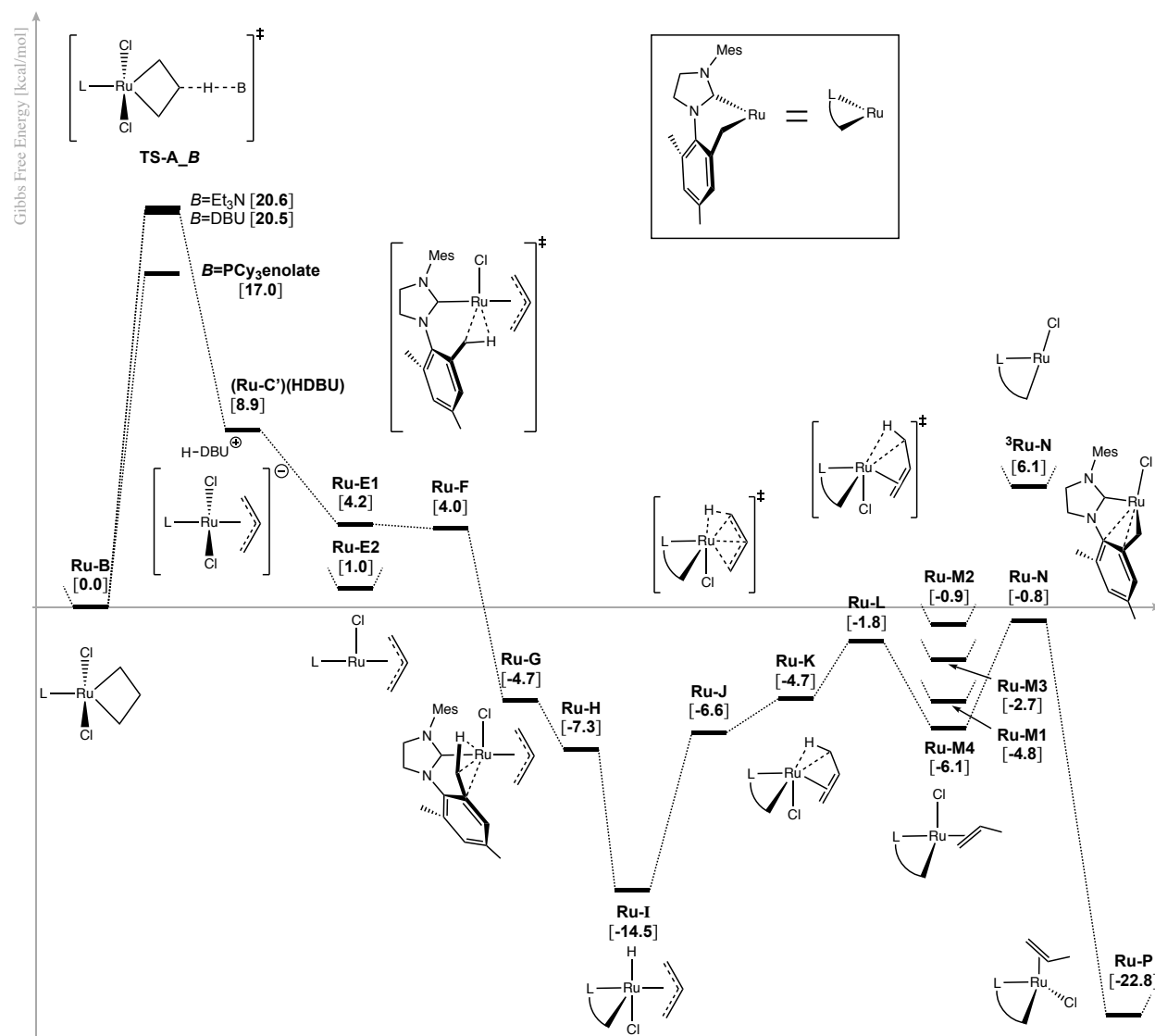
Formation of dimeric **Ru-1** necessitates loss of the allyl group and a chloride ligand. This most probably occurs via **Ru-C'**, the kinetic product of deprotonation,²³ shown in Scheme 3.5. DFT calculations predict that this process is facile: all barriers are lower than that for deprotonation of **Ru-B^R** by DBU (i.e., transition state **TS-A**; 20.5 kcal mol $^{-1}$, Scheme 3.6). Loss of base•HCl from **Ru-C'** leads to intermediate **Ru-F**, which is stabilized by an agostic interaction with a mesityl *o*-methyl group. Oxidative addition of the C–H bond generates cyclometallated allyl hydride **Ru-I**. Reductive elimination of propene,^{9a} accompanied by olefin capture and dimerization, would yield the observed dimers of type **Ru-1**.

Scheme 3.5. Computed pathway depicting key intermediates in the Brønsted base-induced elimination of the metallacyclobutane ring^a



^a Gibbs free energies vs **Ru-B** (R = R' = H; kcal mol $^{-1}$) in square brackets. For the full pathway, see Scheme 3.6.

Scheme 3.6. Computed Gibbs free energy profile (kcal/mol) for the proposed reaction path connecting metallacyclobutane Ru-B with Ru-P, the “monomeric”, propene-bound analogue of Ru-1, where *B* = base (*L* = H₂IMes).



Consistent with this pathway, >80% propenyl products (chiefly 1,3-diphenylpropene, as well as β -methylstyrene) are observed on metathesis of styrene in the presence of DBU or NEt_3 .^{9a} Loss of propene has also been reported in Ru-catalyzed metathesis in the absence of base,²⁵ and in metathesis via d^0 catalysts.²⁶ The accepted pathway involves proton migration from the β -position of the MCB, and subsequent elimination (with, in the d^0 systems, an intervening C_2H_4 insertion step).²⁷ The tendency of Brønsted base to promote this pathway is plausibly due to a reduced energy barrier for transformation of the MCB into a π -allyl species when β -deprotonation is involved, rather than β -H migration.

3.4 Conclusions

The foregoing demonstrates that the MCB ring is the primary site of attack in decomposition of metathesis-active intermediates by Brønsted base. Cyclometalation of the N-heterocyclic carbene ligand is not a primary deactivating event, as hitherto believed, but an ensuing, opportunistic step. Importantly, the susceptibility to deprotonation by base is not limited to MCBs formed by metathesis of electron-deficient olefins. MCB deprotonation proves an unexpectedly general feature, most notably for the unsubstituted MCB **Ru-B**. We conclude that protection of the MCB ring is an important, overlooked priority in improving the lifetime and productivity of ruthenium metathesis catalysts.

3.5 Experimental and Computational Details

3.5.1 General Procedures

Reactions were carried out under N₂ using a glovebox or Schlenk line. Solvents were dried and degassed as described below, then stored under N₂ over 4 Å molecular sieves for at least 6 h prior to use. C₆H₆, C₇H₈, CH₂Cl₂ (Fisher; HPLC grade): purified with a Glass Contour solvent purification system (water content prior to further drying, as measured by Karl Fischer titration: C₆H₆, 4 ppm; C₇H₈, 4 ppm; CH₂Cl₂, 5 ppm). Pentane (Fisher; HPLC grade): distilled over MgSO₄, then P₂O₅. C₆D₆, CDCl₃ (Cambridge Isotopes): 5 × freeze-pump-thaw degassing cycles. Methyl acrylate (Aldrich, 99%), styrene (Aldrich, 99%), DBU (1,8-diazabicyclo[5.4.0]undec-7-ene; Acros, 98%), NEt₃ (Aldrich, 99%), H₂O (distilled): 5 × freeze/pump/thaw cycles, then stored under N₂ at –35 °C in the dark. Dimethyl terephthalate (DMT; Aldrich, 99%), trimethoxybenzene (TMB; Aldrich, 99%), C₂H₄ gas (Linde, BOC Ultra-High-Purity grade 3.0, 99.9%): used as received. Methyl acrylate-d₃ (Cambridge Isotopes, 98%; 98% isotopic enrichment; BHT-stabilized), styrene-d₃ (CDN Isotopes, 98%; 97% isotopic enrichment; hydroquinone-stabilized); both sealed ampoules: used as received, and stored under N₂ at –35 °C in the dark. Literature methods were used to prepare the second-generation Grubbs catalysts (**GII**),²⁸ the second-generation Hoveyda catalyst (**III**),²⁸ and the diene hex-5-enylundec-10-enoate (**6**).²⁹ **GII**-d₂₂, in which the mesityl groups are fully deuterated, was prepared by minor modification of the method reported for non-labelled **GII**,²⁸ using free H₂IMes-d₂₂.^{30,31}

For deuterium labelling studies, all glassware was silanized by soaking overnight in neat TMSCl (Alfa Aesar, 98%). The silanized glassware was rinsed with copious CH₂Cl₂ and allowed to dry in the glovebox prior to use.

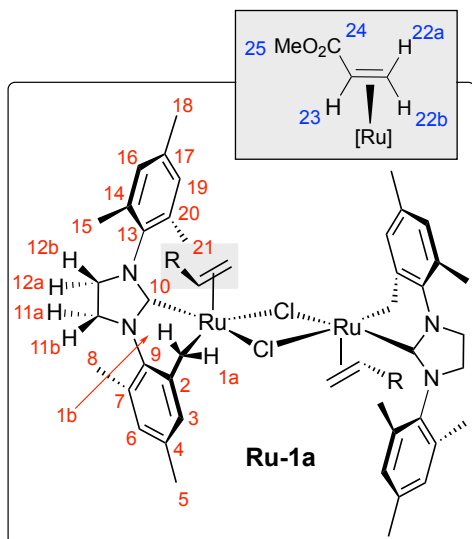
NMR spectra were recorded on Avance 300 or Avance II 300 NMR spectrometers at 23 ± 2 °C, unless otherwise indicated. Chemical shifts are reported in ppm, and referenced to the residual proton or carbon signals of the solvent (¹H, ¹³C), or to an external sample of CDCl₃ in chloroform (²H), 85% H₃PO₄ (³¹P), or free PPh₃ (³¹P capillary: 72 mM in C₆D₆; -5.06 ppm relative to 85% H₃PO₄ at 0 ppm). Infrared (IR) spectra were recorded on a Thermo Scientific Nicolet 6700 Fourier Transform IR spectrometer equipped with a Smart iTR Attenuated Total Reflectance (ATR) sampling accessory.

Anaerobic MALDI mass spectra were collected on a Bruker UltrafleXtreme MALDI-TOF/TOF mass spectrometer interfaced to a glovebox. Samples were prepared by the dried-droplet protocol,^{32,33} using the charge-transfer matrix pyrene³³ (Aldrich, 98%) and C₆H₆ or CH₂Cl₂ as solvent, unless otherwise noted. TOF spectra were collected in positive reflectron mode, with the accelerating voltage held at 20 kV. To minimize fragmentation, the laser energy was maintained at the threshold level required to observe a signal within 1,000 shots. Raster scanning (using the “random walk” setting) was employed to limit sample consumption in any one raster location. To maintain the fidelity and reproducibility of isotope ratios, each spectrum was summed from 5,000–10,000 shots collected in 1,000-shot increments. Samples were analyzed within ca. 20 min of target insertion, to minimize matrix evaporation in the source (in-source pressure: ca. 10⁻⁷ mbar). Before each use, the mass spectrometer was calibrated externally using **III** (pyrene matrix; calculated *m/z*: [M]⁺ 626.141, [M-Cl]⁺ 592.179, [H₂IMes•H]⁺ 307.217, pyrene 202.078), or internally using the peaks for pyrene, [H₂IMes•H]⁺, and/or [MePCy₃]Cl (calculated *m/z* 295.256).

3.5.2 Synthesis and Characterization of Ru-1, [RuCl(κ²-H₂IMes-H)(η²-H₂C=CHR)]₂

(a) Ru-1a; R = CO₂Me. A solution of **III** (50 mg, 0.080 mmol), PCy₃ (26.9 mg, 0.95 mmol, 1.2 equiv), and methyl acrylate (36 μL, 0.40 mmol, 5 equiv) in C₆H₆ (3 mL) was heated at 50 °C for 48 h. The solution was permitted to cool to RT. The Ru product crystallized as a dark red-orange mass over 24 h. Filtering, washing with pentane (4 x 0.5 mL), and drying (200 mTorr, 48 h) gave 45 mg (99%) of **Ru-1a**•0.9C₆H₆. The C₆H₆ solvate was detected by ¹H and ¹³C NMR

spectroscopy, and X-ray crystallography. Further drying for several days at 1 mTorr reduced the proportion of C₆H₆ to ca. 15% vs. **Ru-1a**. Also present was residual pentane (ca. 5%), the proportion of which did not decrease on further drying. X-ray quality crystals (Scheme 3.2, Figure A37) deposited from a reaction performed as above, but on 10 mg scale.



¹H NMR (300 MHz, CDCl₃; Figure A6): δ 7.60 (s, 1H, *H*3), 7.30 (s, 1H, *H*6), 6.84 (s, 2H, *H*16 and *H*19), 4.34 (d, ²*J*_{HH} = 6.0 Hz, 1H, *H*1b), 3.86 (m, 1H, *H*11a), 3.77 (d, ²*J*_{HH} = 6.0 Hz, 1H, *H*1a), 3.56 (m, 1H, *H*12b), 3.44 (s, 3H, *H*25), 3.37 (m, 1H, *H*12a), 3.36 (m, 1H, *H*11b), 2.46 (dd, ³*J*_{HH} = 7.7 Hz, ³*J*_{HH} = 10.0 Hz, 1H, *H*23), 2.37 (s, 3H, *H*5), 2.31 (s, 3H, *H*15), 2.29 (s, 3H, *H*21), 2.24 (s, 3H, *H*8), 2.03 (s, 3H, *H*18), 2.01 (d, 1H, *H*22b; overlaps with *H*18), 1.96 (d, ³*J*_{HH} = 10.3 Hz, 1H, *H*22a). ¹³C{¹H} NMR (77.5 MHz, CDCl₃; Figure A7): δ 209.4 (s, C10), 179.5 (s, C24), 138.5 (s, Mes Ar-C), 137.7 (s, Mes Ar-C), 137.6 (s, Mes Ar-C), 136.7 (s, C3), 135.4 (s, Mes Ar-C), 135.3 (2 s, Mes Ar-C), 133.8 (s, Mes Ar-C), 133.2 (s, C6), 129.1 (s, C19), 128.9 (s, C16), 124.0 (s, C2), 53.6 (s, C12), 50.3 (s, C11), 49.8 (s, C25), 41.9 (s, C1), 41.6 (s, C22), 33.7 (s, C23), 21.0 (s, C21), 20.9 (s, C5), 18.5 (s, C8), 18.3 (s, C18), 18.0 (s, C15). Assignment of the RuCH₂ carbon (C1) is supported by DEPT-135 (Figure A8), and by correlations in the ¹H–¹³C HMQC spectrum to both *H*1b and *H*1a at δ_H 4.34 and 3.77 (Figure A9). Assignment of *H*1a is supported by a ¹H–¹H NOESY correlation to *H*3 (Figure A11). Assignment of the acrylate olefinic carbons (C22 and C23) is supported by DEPT-135, and by correlations in the ¹H–¹³C HMQC spectrum to the corresponding ¹H signals: δ_C 41.6 (C22) and δ_H 2.01 / 1.96 (*H*22b / *H*22a), as well as δ_C 33.7 (C23) and δ_H 2.46 (*H*23). Assignment of the NCH₂ carbons (C11 and C12) is supported by DEPT-135, and by correlations in the ¹H–¹³C HMQC spectrum to four distinct multiplets: δ_C 53.6 (C12) and δ_H 3.56 / 3.37 (*H*12b / *H*12a); δ_C 50.3 (C11) and δ_H 3.86 / 3.36 (*H*11a / *H*11b). All other assignments are supported by a combination of ¹H–¹³C HMQC, ¹H–¹³C HMBC (Figure A10), ¹H–¹H NOESY, and ¹H–¹H COSY (Figure A12). MALDI-TOF MS (pyrene matrix), *m/z*: [**Ru-1a**–2H₂C=CHCO₂Me]⁺⁺ 884.09

(simulated: 884.15). IR (ATR; cm^{-1}): $\nu(\text{C}=\text{O}; \text{MA})$ 1678; $\nu(\text{C}=\text{C}; \text{MA})$ 1599, cf. 1723 and 1634 cm^{-1} for the free acrylate.

From **GII.** As above, without added PCy_3 ; 30 mg **GII** (0.035 mmol, heated at 60 °C for 3 h). Yield of **Ru-1a**: 10.6 mg, 57%.

(b) **Ru-1b; R = Ph. Serendipitous Crystallization.** Complex **Ru-1b** was originally identified by X-ray analysis of crystals that deposited in a RCM macrocyclization reaction (Figure 3.2). In this experiment, a solution of **GII** (10.7 mg, 0.0126 mmol) and TMB (ca. 1 mg, NMR internal standard) in C_6D_6 (630 μL) was prepared in a screw-cap NMR tube, and DBU (2.1 μL , 0.0136 mmol, 1.1 equiv) was added. The solution was heated at 60 °C for 0.5 h, after which diene hex-5-enylundec-10-enoate (**1**: 33.6 mg, 0.126 mmol, 10 equiv) was injected via syringe. The puncture was immediately sealed with tape, and heating was resumed. After 0.5 h, colourless needles ($\text{DBU}\cdot\text{HCl}$; identified from the match between their ^1H NMR chemical shifts and reported³⁴ values) were observed, and were removed by filtration. The filtrate was diluted with pentane and stored at -35 °C for several days, over which time X-ray quality red crystals of **Ru-1b** deposited (Figure A38).

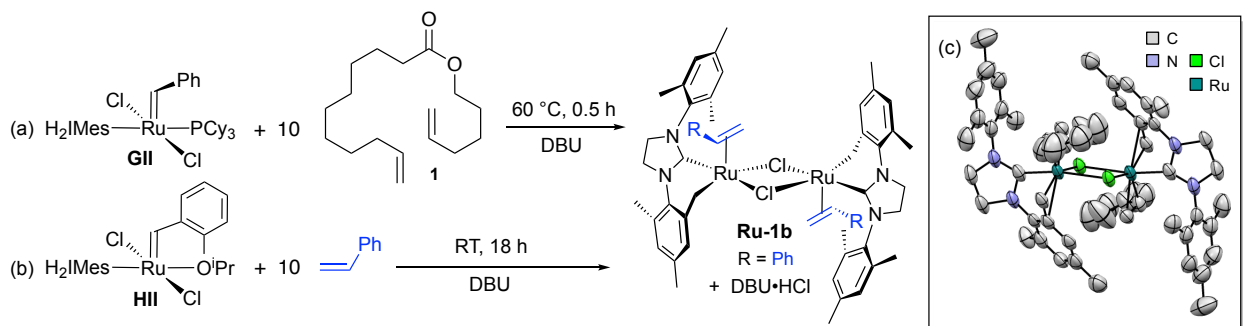
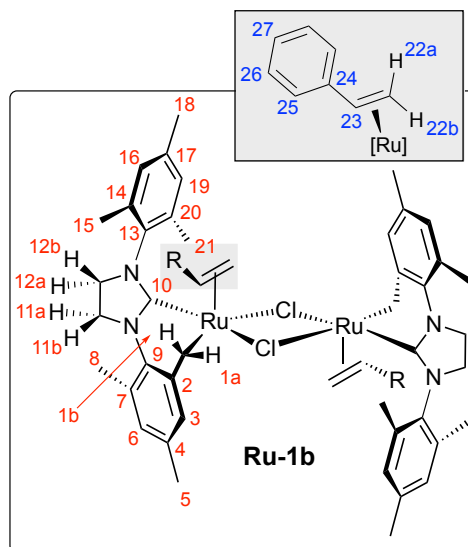


Figure 3.2. (a) Formation of **Ru-1b** from reactions in which macrocyclization of **1** was catalyzed by **GII** in the presence of DBU base. (b) Deliberate synthesis of **Ru-1b** via styrene metathesis by **HII** in the presence of DBU. (c) ORTEP plot of **Ru-1b**, shown with Gaussian ellipsoids at 50% probability level; hydrogen atoms omitted for clarity. For reaction (a), the bound styrene ligand originates in the benzyldiene ligand of **GII**.

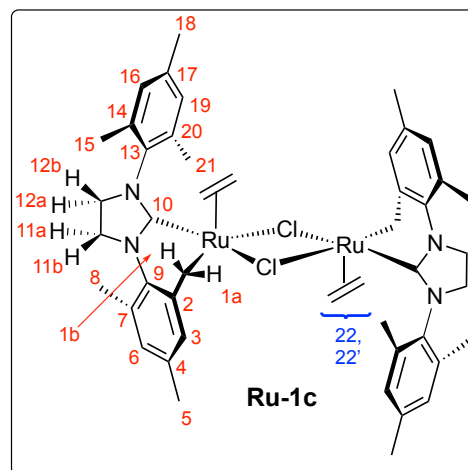
Ru-1b. Deliberate Synthesis. To a solution of **HII** (50 mg, 0.080 mmol) in 800 μL C_6H_6 in a 4 mL vial equipped with a magnetic stir bar was added styrene (91 μL , 0.80 mmol, 10 equiv) and DBU (13 μL , 0.088 mmol, 1.1 equiv). The reaction was stirred at RT for 18 h, over which time the solution changed colour from green to orange, and orange crystals deposited. Filtering,



washing with pentane (5 x 0.5 mL) and water (3 x 0.5 mL, to remove DBU•HCl), and drying in vacuo (1 mTorr) for 72 h afforded 38 mg (86%) of **Ru-1b**•0.2C₆H₆.

¹H NMR (300 MHz, CDCl₃; Figure A13): δ 7.45 (s, 1H, *H*3), 7.21 (s, 1H, *H*6), 7.08-6.96 (m, 3H, *PhH*), 6.90 (d, ³*J*_{HH} = 7.6 Hz, 2H, *PhH*), 6.80 (s, 2H, *H*16 and *H*19), 3.96 (d, 1H, ²*J*_{HH} = 5.4 Hz, *H*1b), 3.86 (m, 1H, *H*11a), 3.63 (m, 1H, *H*12b), 3.51-3.33 (overlapping m, 3H, *H*11b, *H*12a, *H*23), 2.94 (d, 1H ²*J*_{HH} = 5.4 Hz, *H*1a), 2.45 (s, 3H, *H*15), 2.37 (s, 3H, *H*8), 2.29 (s, 3H, *H*5), 2.24 (s, 3H, *H*21), 2.03 (s, 3H, *H*18), 2.00 (d, 1H, ³*J*_{HH} = 7.7 Hz, *H*22b), 1.78 (d, 1H, ³*J*_{HH} = 10.7 Hz, *H*22a). ¹³C{¹H} NMR (77.5 MHz, CDCl₃; Figure A14): δ 211.4 (s, C10), 147.2 (s, C24), 138.6 (s, Mes Ar-C), 138.1 (s, Mes Ar-C), 137.6 (s, Mes Ar-C), 136.9 (s, C3), 135.9 (s, Mes Ar-C), 135.1 (s, Mes Ar-C), 134.0 (s, Mes Ar-C), 133.5 (s, Mes Ar-C), 132.4 (s, C6), 129.2 and 129.0 (both s, C16 and C19), 128.0 (s, Ph-C), 126.6 (s, Ph-C), 125.2 (s, C2), 123.5 (s, Ph-C), 53.9 (s, C12), 50.6 (s, C11), 44.0 (s, C23), 42.6 (s, C1), 39.4 (s, C22), 21.1 (s, C21), 21.0 (s, C5), 18.8 (s, C8), 18.7 (s, C18), 18.2 (s, C15). Assignments for **Ru-1b** are supported by a combination of ¹H–¹³C HMQC, ¹H–¹³C HMBC, ¹H–¹H NOESY, and ¹H–¹H COSY, as for **Ru-1a** above. MALDI-TOF MS (pyrene matrix), *m/z*: [**Ru-1a**–2H₂C=CHPh]⁺⁺ 884.08 (simulated: 884.15). IR (ATR): 1596 (C=C stretch for H₂C=CHPh), cf. 1629 cm^{–1} for free styrene.

(c) Ru-1c; R = H. The complex was originally identified by X-ray analysis of crystals that deposited on reacting **GII-PPh₃** RuCl₂(H₂IMes)(PPh₃)(=CHPh) with 1 atm C₂H₄ over 5 d (C₇H₈, RT; not isolated in bulk).³⁵ Provided here is a faster, high-yield route. A green solution of **III** (50 mg, 0.080 mmol) and DBU (13 μL, 0.088 mmol, 1.1 equiv) in C₆H₆ (800 μL) in a J. Young NMR tube was freeze/pump/thaw degassed (3x), thawed, and opened to an atmosphere of ethylene (replenished at 1 h). After 2.5 h at RT, the product was filtered off, washed with pentane (5 x 0.5



mL) and water (3 x 0.5 mL; to remove DBU•HCl), and dried in vacuo (1 mTorr) for 48 h, to afford 35 mg (93%) of orange **Ru-1c**•0.1C₆H₆•0.1C₅H₁₁. Further attempts at removing residual solvent reduced the proportion of benzene, but the pentane solvate remained.

¹H NMR (300 MHz, CDCl₃; Figure A15): δ 7.47 (s, 1H, *H*3), 7.17 (s, 1H, *H*6), 6.88 and 6.85 (both s, 2H, *H*16 and *H*19), 3.76 (m, 1H, *H*11a), 3.64 and 3.61 (ABq, ²*J*_{HH} = 5.5 Hz, 2H, *H*1a and *H*1b), 3.53 (m, 1H, *H*12b), 3.37 (m, 2H, *H*11b and *H*12a), 2.32 (s, 3H, *H*5), 2.30 (s, 6H, *H*21), 2.27 (s, 3H, *H*15), 2.18 (s, 3H, *H*8), 2.07 (s, 3H, *H*18), 1.96–0.98 (br s, 4H, *H*22 and *H*22'). ¹³C{¹H} NMR (300 MHz, CDCl₃; Figure A16): δ 212.3 (s, C10), 138.4 (s, Mes Ar-C), 138.3 (s, Mes Ar-C), 137.6 (s, Mes Ar-C), 136.5 (s, C3), 135.9 (s, Mes Ar-C), 135.4 (s, Mes Ar-C), 134.0 (s, Mes Ar-C), 133.9 (s, Mes Ar-C), 131.9 (s, C6), 129.0 (2 s, C16 and C19), 121.2 (s, C2), 53.6 (s, C12), 50.5 (s, C11), 36.9 (s, C1), 21.2 (s, C21), 21.0 (s, C5), 18.6 (s, C18), 18.4 (s, C8), 18.1 (s, C15). Assignments for **Ru-1c** are supported by a combination of ¹H–¹³C HMQC, ¹H–¹³C HMBC, ¹H–¹H NOESY, and ¹H–¹H COSY, as for **Ru-1a** and **Ru-1b** above. At –20 °C, the broad ethylene singlet at δ_H 1.96–0.98 ppm resolved into four distinct triplets. ¹H NMR (300 MHz, CDCl₃, –20 °C; ethylene signals only): δ 1.82 (t, ³*J*_{HH} = 8.8 Hz, 1H, *H*22'), 1.58 (t, ³*J*_{HH} = 9.2 Hz, 1H, *H*22), 1.29 (t, ³*J*_{HH} = 9.6 Hz, 1H, *H*22'), 0.93 (t, ³*J*_{HH} = 10.2 Hz, 1H, *H*22). Location of the corresponding ethylene carbons was accomplished by ¹H–¹³C HSQC (CDCl₃, 300 MHz, –20 °C; ethylene signals only): δ 42.5 (s, C22) and 33.3 (s, C22').

3.5.3 In Situ Quantification of Base•HCl

In a representative procedure, stock solutions of catalyst and base were prepared by (respectively) dissolving **III** (15.4 mg, 0.0246 mmol) and DMT (ca. 1 mg) in C₆D₆ (2.34 mL), or diluting DBU (10 μL, 0.0066 mmol, 1.1 equiv) to 100 μL in C₆D₆. Aliquots of the catalyst (570 μL, 0.006 mmol **III**) and DBU (10 μL, 0.0066 mmol, 1.1 equiv) solutions were transferred to a J. Young NMR tube. A ¹H NMR spectrum was recorded to establish the initial integration ratio of **III** relative to DMT. Styrene (17 μL, 0.15 mmol, 25 equiv) was then added. After 24 h at RT, the benzene was lyophilized (–35 °C) and the residue was redissolved in CDCl₃ (after confirming that DBU is not itself protonated by this solvent). ¹H NMR (CDCl₃, 300 MHz; diagnostic signals only): δ 11.81 (br s, NH⁺ of DBU•HCl; 99%), 8.11 (s, 4H, ArCH of DMT).

In ethenolysis experiments: as above, but using solutions saturated in ethylene.

3.5.4 Labelling Studies

GII and methyl acrylate; complementary labelling experiments. In these experiments, the proportion of deuterium incorporated into the phosphonium salts [A]Cl–[C]Cl (Scheme 3.1) was assessed by quantitative MALDI-MS. Specifically, the % deuterium uptake in each was quantified from the ratio of labelled vs. non-labelled H/D isotopologues. These were identified from their unique m/z ratio, and assigned to deprotonation at non-labelled or labelled sites according to the number of ^2H atoms incorporated. The proportion of each isotopologue was assessed from the relative peak heights, after correcting for the known ^{13}C isotopic abundances for each species (calculated using the ChemCalc isotopic modeling software³⁶).

Pyrene was not used as MALDI matrix, as it appears to promote scrambling (as inferred from the consistently higher proportions of H/D exchange observed relative to sulfur matrix).³⁷ Elemental sulfur (Acros: $\geq 99.99\%$) was therefore used. A ca. 1 μL aliquot of S-saturated C_6H_6 was evaporated on the target plate, and a ca. 1 μL aliquot of the reaction solution (diluted 10-fold in C_6H_6 or CH_2Cl_2) was applied on top.

Labelled GII-d₂₂. Methyl acrylate (25 μL , 0.275 mmol, 25 equiv) was added to a solution of **GII-d₂₂** (9.6 mg, 0.011 mmol) in toluene (1.1 mL) in a 4 mL vial with a magnetic stir bar. The vial was capped, and the reaction was heated to 70 °C (thermostatted oil bath) in the glovebox for 1 h, over which time the solution changed colour from pink to bright orange. MALDI-MS analysis (Table 3.1; Figure A39) indicates minimal deuterium uptake into phosphonium cations $\text{A}^+ - \text{C}^+$, i.e. limited deprotonation at Mes-d₂₂ sites: A^+ : 8%, B^+ : 14%, C^+ : 23%.

Table 3.1. Assessment of deuterium uptake into $\text{A}^+ - \text{C}^+$ by MALDI-TOF MS, following reaction of GII-d₂₂ with methyl acrylate.

Site of Deprotonation ^a	Isotopologues of A^+			Isotopologues of B^+			Isotopologues of C^+		
		m/z	%		m/z	%		m/z	%
non-labelled	A^+	367.3	92%	B^+	453.4	86%	C^+	511.4	76%
labelled	$\text{A}^+ - \text{d}_1$	368.3	6%	$\text{B}^+ - \text{d}_1$	454.4	11%	$\text{C}^+ - \text{d}_1$	512.4	22%
labelled ^b	$\text{A}^+ - \text{d}_2$	369.3	1%	$\text{B}^+ - \text{d}_2$	455.4	3%	$\text{C}^+ - \text{d}_2$	513.4	1%
labelled ^b	$\text{A}^+ - \text{d}_3$	370.3	1%	$\text{B}^+ - \text{d}_3$	456.4	0%	$\text{C}^+ - \text{d}_3$	514.4	0%

^a Deprotonation at labelled (metallacyclobutane, MCB) or non-labelled (*o*-Mes) sites. ^b More than one ^2H atom has been incorporated, possibly by H/D exchange.

Labelled methyl acrylate-d₃. As above, but with methyl acrylate-d₃ (25 μ L, 0.275 mmol, 25 equiv) and non-labelled **GII** (9.4 mg, 0.011 mmol). MALDI-MS analysis (Table 3.2; Figure A40) indicates extensive deuterium uptake into phosphonium cations A^+-C^+ , i.e. extensive deprotonation at metallacyclobutane (MCB) sites: A^+ : 77%, B^+ : 73%, C^+ : 61%.

Table 3.2. Assessment of deuterium uptake into A^+-C^+ by MALDI-TOF MS, following reaction of **GII with methyl acrylate-d₃.**

Site of Deprotonation ^a	Isotopologues of A^+			Isotopologues of B^+			Isotopologues of C^+		
		<i>m/z</i>	%		<i>m/z</i>	%		<i>m/z</i>	%
non-labelled ^b	A^+-d_1	367.3	0%	B^+-d_4	457.4	1%	C^+-d_3	514.4	0%
non-labelled ^b	A^+-d_2	369.3	2%	B^+-d_5	458.4	3%	C^+-d_4	515.4	5%
non-labelled	A^+-d_3	370.3	19%	B^+-d_6	459.4	23%	C^+-d_5	516.4	34%
labelled	A^+-d_4	371.3	77%	B^+-d_7	460.4	73%	C^+-d_6	517.4	61%

^a Deprotonation at labelled (MCB) or non-labelled (*o*-Mes) sites. ^b One or more ²H atoms have been lost, possibly by H/D exchange.

III, DBU, and labelled styrene. Reaction as in section 3.5.3 above, but using styrene-d₃ (17 μ L, 0.15 mmol, 25 equiv). After 18 h, the precipitated solids were filtered off and rinsed with pentane (5 x 1 mL). A 1:2 mixture of **Ru-1b-d₆** and DBU•DCl was present (¹H NMR analysis), with ca. 80% ²H incorporation into DBU•DCl (¹H and ²H NMR analysis). Specifically, the reduced integration of the HCl singlet relative to those for DBU CH₂ protons reports on any DCl salt, and hence the HCl / DCl ratio. ²H NMR was used to confirm the presence of the DCl salt.

DBU•DCl. ¹H NMR (CDCl₃, 300 MHz): δ 11.83 (br s, 0.2H, NH⁺), 3.56–3.39 (m, 6H, NCH₂; overlaps with NCH₂ of **Ru-1b-d₆**), 3.05 (br m, 2H, CH₂), 2.03 (quint, 2H, CH₂; overlaps with Mes CH₃ of **Ru-1b-d₆**), 1.88–1.63 (m, 6H, CH₂). ²H NMR (CHCl₃, 46.1 MHz): 11.65 (br s, ND⁺).

Ru-1b-d₆. ¹H NMR (300 MHz, CDCl₃): δ 7.45 (s, 1H, H₃), 7.21 (s, 1H, H₆), 7.08–6.96 (m, 3H, PhH), 6.90 (m, 2H, PhH), 6.80 (s, 2H, H₁₆ and H₁₉), 3.96 (d, 1H, ²J_{HH} = 5.4 Hz, H_{1b}), 3.86 (m, 1H, H_{11a}), 3.62 (m, 1H, H_{12b}), 3.51–3.33 (overlapping m, 3H, H_{11b}, H_{12a}; overlaps with CH₂ of DBU•DCl), 2.94 (d, 1H, ²J_{HH} = 5.4 Hz, H_{1a}), 2.44 (s, 3H, H₁₅), 2.37 (s, 3H, H₈), 2.28 (s, 3H, H₅), 2.23 (s, 3H, H₂₁), 2.03 (s, 3H, H₁₈). The olefinic styrene deuterons were not observed in the ²H NMR spectrum, likely because of the relatively low concentration of **Ru-1b-d₆** present, as well as ²H–²H splitting.

3.5.5 Computational Details

(a) Acidity of ruthenacyclobutane and Ru-methylidene

Computational Methods. DFT calculations were performed with Gaussian 09, revision D01.³⁸ Initial geometries for optimization of the organometallic anions **Ru-C**, **Ru-D**, and their isomers were constructed by removing the relevant proton from **Ru-B** / **Ru-A**. All geometries were optimized in the gas phase using the M06-2X³⁹ functional with ultrafine numerical integration grid and a basis set of valence double- ζ quality. The Stuttgart/Cologne 28-electron relativistic effective core potentials (ECP28MDF)⁴⁰ were used for Ru atoms, and coupled with the corresponding correlation-consistent valence double- ζ plus polarization basis set augmented by diffuse functions (aug-cc-pVDZ-PP),⁴⁰ as obtained from the Stuttgart/Cologne basis set repository.⁴¹ Correlation-consistent, valence double- ζ plus polarization basis sets (cc-pVDZ⁴² from the EMSL basis set exchange website)⁴³ were used on all atoms of the H₂IMes ligand, except the carbene carbon. The latter, and all other non-H₂IMes atoms, were described by the same correlation-consistent, augmented basis sets (i.e., aug-cc-pVDZ^{42,44} from the EMSL basis set exchange website).⁴³ Geometries were optimized using tight convergence criteria (max. force $1.5 \cdot 10^{-5}$ a.u., RMS force $1.0 \cdot 10^{-5}$ a.u., max. force $6.0 \cdot 10^{-5}$ a.u., RMS force $4.0 \cdot 10^{-5}$ a.u.), without symmetry constraints, using default convergence criteria for the self-consistent field (SCF) optimization procedure (RMS change in density matrix $< 1.0 \cdot 10^{-8}$, max. change in density matrix $= 1.0 \cdot 10^{-6}$). All stationary points were confirmed to be minima by analytical calculation of the eigenvalues of the Hessian matrix. The only exception was model **Ru-C_isom-11**, where calculations using the above settings returned a fictitious imaginary frequency that most likely resulted from the limited accuracy of the integration grid.⁴⁵ First, all of the energies obtained in single-point calculations along the intrinsic reaction coordinate corresponding to the imaginary mode were higher than that of the stationary point, indicating that the latter is a local minimum. Next, further geometry optimization with a finer grid (the “superfine” grid) introduced only negligible changes and analytical calculation of the eigenvalues of the Hessian matrix confirmed that the stationary point is indeed a minimum (i.e., no fictitious imaginary frequency). Textbook procedures were used to calculate the translational, rotational, and vibrational components of the thermal corrections to enthalpies and Gibbs free energies within the ideal-gas, rigid-rotor, and harmonic oscillator approximations, except that all frequencies below 100 cm^{-1} were shifted to 100 cm^{-1} when calculating the vibrational component of entropy (i.e. the quasi-harmonic

oscillator approximation).^{46,47} This approach is aimed at preventing breakdown (i.e., the asymptote corresponding to infinite entropy) of the harmonic approximation for low-frequency modes.⁴⁸

Single-point energy calculations were performed on gas-phase geometries using the M06,³⁹ B3LYP,^{49,50} and PBE⁵¹ functionals with the SMD⁵² polarizable continuum solvent model to account for solvation effects using default parameters for benzene as solvent. As well, all B3LYP and PBE calculations included Grimme's empirical D3 dispersion corrections,^{53,54} with revised Becke–Johnson damping parameters (labelled D3M(BJ) for brevity).^{53,54} In all single-point calculations, the basis set structure above was extended to the valence quadruple- ζ level. Specifically, Ru was described by combining the 28-electron relativistic effective core potential (ECP28MDF)⁴⁰ with the corresponding correlation-consistent valence quadruple- ζ plus polarization basis set augmented by diffuse functions (aug-cc-pVQZ-PP)⁴⁰ from the Stuttgart/Cologne basis set repository.⁴¹ The H₂IMes atoms were described by correlation-consistent, valence quadruple- ζ plus polarization basis sets (cc-pVQZ⁴² from the EMSL),⁴³ with the exception of the carbene carbon, which (along with the remaining non-H₂IMes atoms), was described by correlation-consistent, valence quadruple- ζ basis sets augmented by diffuse functions (i.e., aug-cc-pVQZ^{42,44} from the EMSL).⁴³ The convergence criteria for the SCF procedure were relaxed in single-point calculations (to RMS change in density matrix $< 1.0 \cdot 10^{-5}$, max. change in density matrix $< 1.0 \cdot 10^{-3}$).

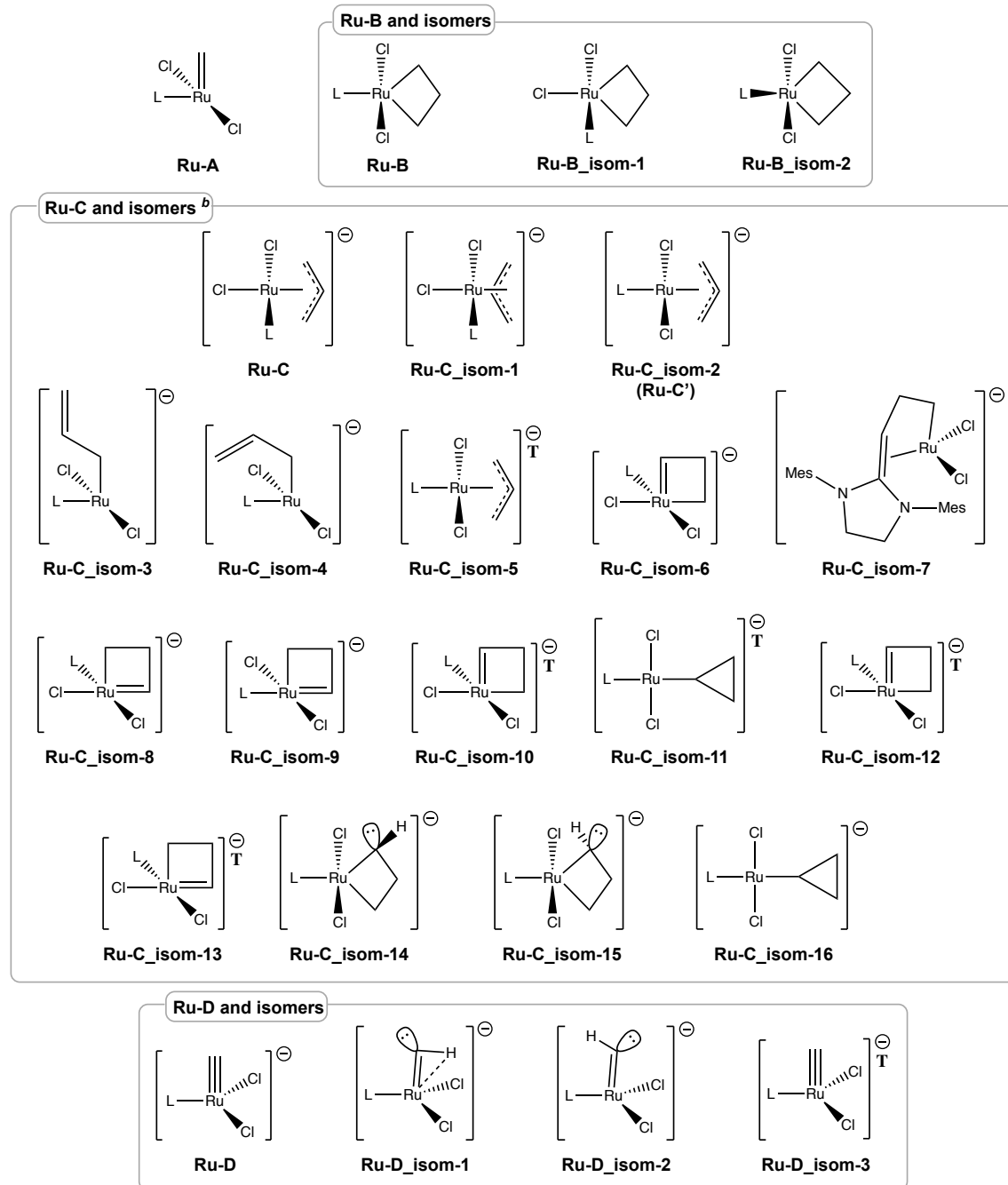
Finally, prior to all geometry optimizations and single-point calculations, the wavefunction was tested for instability and, if necessary, re-optimized to a real, spin-restricted solution (for singlet spin states) or (for higher spin states) an unrestricted solution. Free energies in benzene solution were calculated by adding the quasi-harmonic thermal corrections obtained from the gas-phase frequency calculations of the optimized geometries to the single-point potential energies, including solvent effects.

Models for Conjugate Bases. We considered a number of potential alternatives for the anions generated by deprotonating Ru-methylidene **Ru-A**, or ruthenacyclobutanes **Ru-B**, **Ru-B_isom-1**, and **Ru-B_isom-2** (Chart 3.2). In each case, we chose as the conjugate base the most stable of the anions generated by deprotonating at a given site.

Deprotonation of the C_β site of the ruthenacyclobutanes led to the η^3 -allyl species **Ru-C**, **Ru-C_isom-1**, and **Ru-C_isom-2**. In addition, we tested the Ru-alkyl isomers **Ru-C_isom-3** and **Ru-C_isom-4**. The latter four structures, as well as the spin-triplet **Ru-C_isom-5**, are thermodynamically less stable than **Ru-C** (Table 3.3). We therefore chose **Ru-C** as the conjugate base for the C_β site.

The most stable anion generated by deprotonating at C_α is ruthenacyclobutene **Ru-C_isom-6**, which is therefore chosen as the conjugate base for the C_α site. This anion is 12.5 kcal/mol less stable than **Ru-C** (see Table 3.3). Next, in addition to the carbanions (**Ru-C_isom-14** and **Ru-C_isom-15** are different conformations), we evaluated two alternative rearrangements. One leads to Ru-cyclopropane (**Ru-C_isom-11** and **Ru-C_isom-16**); the other involves attack on the NHC ligand to give **Ru-C_isom-7**. The latter is the second most stable isomer generated by deprotonation at C_α. Nevertheless, none of these anions competes with the stability of **Ru-C**. The calculations thus predict that the C_α site is less acidic than the C_β site.

Deprotonation of Ru-methyldiene sites was considered next. Three conjugate anions (**Ru-D**, **Ru-D_isom-1**, **Ru-D_isom-2**) were evaluated, in addition to the spin-triplet **Ru-D_isom-3**. The lowest energy was obtained for **Ru-D**, which is accordingly the conjugate base of **Ru-A**. This species has a distorted tetrahedral geometry with a wide Ru-C-H angle (152°), suggestive of a metal-alkylidyne bond with the charge chiefly on the metal. In contrast, the other two models (**Ru-D_isom-1**, **Ru-D_isom-2**) resemble the initial Ru=CH₂ fragment, apart from the loss of one methyldiene proton. In addition, the strong α -C-H agostic interaction in **Ru-D_isom-1** imposes a sharp Ru-C-H angle (84°).

Chart 3.2. Conjugate acid-base pairs considered in this study ($L = H_2IMes$).^a

^a Relative energies are reported in Table 3.3. Spin-triplet states are indicated by a superscript **T**. ^b In this section (3.5.5a), we underscore the commonality of the isomers of **Ru-C** by designating the most stable, cis-Cl₂ isomer as simply **Ru-C**, with all others being denoted as **Ru-C_isom-#**. In the Chart above, we therefore depict the trans-Cl₂ isomer (which is central to the mechanistic study), with a dual designation: both **Ru-C_isom-2**, and **Ru-C'**. The latter, a simplified naming convention suitable for use in the main text, is used both there and in the mechanistic section (3.5.5b).

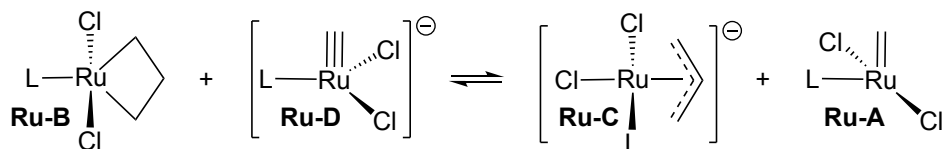
Table 3.3. Gibbs free energies and their components for the conjugate acid-base pairs.^a

Model ID	M06-2X		M06 SMD(benzene)			B3LYP-D3M(BJ) SMD(benzene)			PBEPBE-D3M(BJ) SMD(benzene)		
	Double- ζ^b		Quadruple- ζ^b			Quadruple- ζ^b			Quadruple- ζ^b		
	E _{gas}	G _{gas,corr}	E _{solv}	G _{solv}		E _{solv}	G _{solv}		E _{solv}	G _{solv}	
	a.u.	a.u.	a.u.	a.u.	kcal/mol ^c	a.u.	a.u.	kcal/mol ^c	a.u.	a.u.	kcal/mol ^c
Ru-A	-1979.323025	0.395426	-1979.493030	-1979.097604	-	-1980.516714	-1980.121288	-	-1978.789418	-1978.393992	-
Ru-B	-2057.922130	0.451376	-2058.095580	-2057.644204	0.0	-2059.186504	-2058.735128	0.0	-2057.343815	-2056.892439	0.0
Ru-B_{isom-1}	-2057.903694	0.454231	-2058.080353	-2057.626122	11.3	-2059.169979	-2058.715748	12.2	-2057.329939	-2056.875708	10.5
Ru-B_{isom-2}	-2057.895570	0.453159	-2058.067029	-2057.613870	19.0	-2059.167994	-2058.714835	12.7	-2057.325366	-2056.872207	12.7
Ru-C	-2057.402337	0.440004	-2057.604891	-2057.164887	0.0	-2058.690675	-2058.250671	0.0	-2056.852295	-2056.412291	0.0
Ru-C_{isom-1}	-2057.400821	0.439706	-2057.601288	-2057.161582	2.1	-2058.686049	-2058.246343	2.7	-2056.847553	-2056.407847	2.8
Ru-C_{isom-2}	-2057.403232	0.438209	-2057.602541	-2057.164332	0.3	-2058.688655	-2058.250446	0.1	-2056.844382	-2056.406173	3.8
Ru-C_{isom-3}	-2057.387342	0.435997	-2057.578610	-2057.142613	14.0	-2058.678856	-2058.242859	4.9	-2056.827505	-2056.391508	13.0
Ru-C_{isom-4}	-2057.385574	0.436402	-2057.577180	-2057.140778	15.1	-2058.678072	-2058.241670	5.6	-2056.826603	-2056.390201	13.9
Ru-C_{isom-5}	-2057.392712	0.435041	-2057.590407	-2057.155366	6.0	-2058.668336	-2058.233295	10.9	-2056.817578	-2056.382537	18.7
Ru-C_{isom-6}	-2057.364129	0.437315	-2057.571040	-2057.133725	19.6	-2058.666232	-2058.228917	13.7	-2056.829666	-2056.392351	12.5
Ru-C_{isom-7}	-2057.387968	0.441465	-2057.574379	-2057.132914	20.1	-2058.661840	-2058.220375	19.0	-2056.824700	-2056.383235	18.2
Ru-C_{isom-8}	-2057.347072	0.436305	-2057.555873	-2057.119568	28.4	-2058.650997	-2058.214692	22.6	-2056.813426	-2056.377121	22.1
Ru-C_{isom-9}	-2057.336871	0.434124	-2057.539169	-2057.105045	37.6	-2058.628403	-2058.194279	35.4	-2056.785621	-2056.351497	38.1
Ru-C_{isom-10}	-2057.326225	0.434353	-2057.525597	-2057.091244	46.2	-2058.623928	-2058.189575	38.3	-2056.784817	-2056.350464	38.8
Ru-C_{isom-11}	-2057.363707	0.434567	-2057.560739	-2057.126172	24.3	-2058.638673	-2058.204106	29.2	-2056.780533	-2056.345966	41.6
Ru-C_{isom-12}	-2057.324029	0.434465	-2057.522742	-2057.088277	48.1	-2058.620879	-2058.186414	40.3	-2056.780119	-2056.345654	41.8
Ru-C_{isom-13}	-2057.321889	0.434149	-2057.520878	-2057.086729	49.0	-2058.619014	-2058.184865	41.3	-2056.776416	-2056.342267	43.9
Ru-C_{isom-14}	-2057.309651	0.436183	-2057.517674	-2057.081491	52.3	-2058.599758	-2058.163575	54.7	-2056.767601	-2056.331418	50.7
Ru-C_{isom-15}	-2057.305132	0.435896	-2057.514669	-2057.078773	54.0	-2058.595952	-2058.160056	56.9	-2056.762136	-2056.326240	54.0
Ru-C_{isom-16}	-2057.320911	0.436617	-2057.512298	-2057.075681	56.0	-2058.600418	-2058.163801	54.5	-2056.747027	-2056.310410	63.9
Ru-D	-1978.748495	0.381297	-1978.963211	-1978.581914	0.0	-1979.971316	-1979.590019	0.0	-1978.251997	-1977.870700	0.0
Ru-D_{isom-1}	-1978.744915	0.380978	-1978.949163	-1978.568185	8.6	-1979.957719	-1979.576741	8.3	-1978.237274	-1977.856296	9.0
Ru-D_{isom-2}	-1978.740361	0.381264	-1978.946957	-1978.565693	10.2	-1979.956990	-1979.575726	9.0	-1978.235506	-1977.854242	10.3
Ru-D_{isom-3}	-1978.736518	0.377965	-1978.937085	-1978.559120	14.3	-1979.950940	-1979.572975	10.7	-1978.226969	-1977.849004	13.6

^a See Chart 3.2 for compound labels. ^b See Computational Methods for basis sets. ^c Relative free energies are calculated using the most stable isomer as reference. For example, the values reported for **Ru-B_{isom-1}** and **Ru-B_{isom-2}** are calculated with respect to **Ru-B**.

pK_a Calculations. We next turned to calculating pK_a values for **Ru-A** and **Ru-B**. Assessing such values with high accuracy is challenging, however, because these organometallic structures are very different from the molecules for which strategies for accurate pK_a prediction have been developed.⁵⁵ Thus, no closely related compounds with experimentally known or estimated pK_a values are available to “anchor” the computational predictions, and to estimate the accuracy of predicted pK_a values.⁵⁶⁻⁵⁸ For the present purpose of identifying the most acidic moieties in the key metathesis intermediates, we therefore focused on calculating *relative* pK_a values, rather than quantitative values. Accordingly, we estimate ΔpK_a values to arrive at a qualitative measure of the relative acidity of these intermediates. Specifically, we evaluate the acid-base equilibrium between **Ru-A** and **Ru-B** (see Scheme 3.7 and Figure 3.1 above). Associated benefits arise from error cancellation, owing to the structural similarities between the acid and base in each of the two pairs.

Scheme 3.7. Proton exchange reaction used to calculate ΔpK_a between Ru-A and Ru-B.



The reaction Gibbs free energy of this proton exchange reaction in benzene (Δ_rG) is ca. –25 kcal/mol, which corresponds to ca. 20 pK_a units (Table 3.3, Table 3.4). Clearly, the C_β methylene protons in **Ru-B** are more acidic than the methylidene moiety in **Ru-A**. This acidity is due chiefly to the stability of the η³-coordination in π-allyl species **Ru-C**, which significantly outweighs the stabilization arising from the α,β-(C–C) agostic interactions present in the MCB.

In contrast, the proton exchange involving the C_α sites of **Ru-B** (i.e., considering **Ru-C_isom-6** as the conjugate base of **Ru-B**) is associated with a reaction Gibbs free energy that is less negative than that for C_β (specifically, between –3.3 and –15.7 kcal/mol). The C_α sites remain more acidic by 2-12 pK_a units than the methylidene ones. Different computational models disagree to some extent in their assessment of the acidity of the C_α vs. the C_β sites. The M06 functional, in particular, predicts lower stability for **Ru-C_isom-6** than the other functionals. Nevertheless, the trend is consistent among all three computational methods: the C_β sites of the

metallacyclobutane are more acidic than the corresponding C_α sites, and the latter are more acidic than those of methyldiene.

Table 3.4. Reaction Gibbs free energies (kcal/mol) and ΔpK_a for proton exchange reactions.

	M06 SMD(benzene)		B3LYP D3M(BJ) SMD(benzene)		PBEPBE D3M(BJ) SMD(benzene)	
	$\Delta_r G$	ΔpK_a	$\Delta_r G$	ΔpK_a	$\Delta_r G$	ΔpK_a
Ru-B + Ru-D $\rightleftharpoons$ Ru-C + Ru-A	-22.8	-17	-29.4	-22	-27.1	-20
Ru-B + Ru-D $\rightleftharpoons$ Ru-C_isom-6 + Ru-A	-3.3	-2	-15.7	-12	-14.6	-11
Ru-B + Ru-C $\rightleftharpoons$ Ru-C_isom-6 + Ru-B	19.6	14	13.7	10	12.5	9

(b) Mechanism of ruthenacyclobutane decomposition

Computational Methods. Geometry optimizations were performed in the gas phase using Head-Gordon's long-range and dispersion-corrected hybrid density functional ω B97XD⁵⁹⁻⁶¹ as implemented in Gaussian 09 revision D01.³⁸ This functional reproduces the geometries of ruthenium olefin metathesis catalysts and other homogeneous catalysts with high accuracy.⁶² The Stuttgart 28-electron relativistic effective core potential (ECP28MDF),⁴⁰ in combination with the correlation-consistent valence double- ζ plus polarization basis set (EML: cc-pVDZ-PP),⁴⁰ was used for ruthenium atoms, as retrieved from the EML basis set exchange database.⁴³ The other elements were described using Dunning's correlation-consistent valence double- ζ plus polarization basis sets (EML: cc-pVDZ)⁴² from the EML database.⁴³ Numerical integrations were performed using the "ultrafine" grid of Gaussian 09. The default convergence criteria (RMS change in density matrix $< 1.0 \cdot 10^{-8}$, maximum change in density matrix $1.0 \cdot 10^{-6}$) were used for the SCF procedure. The wavefunction was tested for instability prior to geometry optimization. Unstable solutions were re-optimized to real, spin-restricted or spin-unrestricted solutions for spin-singlet or spin-triplet states, respectively. Geometries were optimized using tight convergence criteria (max. force $1.5 \cdot 10^{-5}$ a.u., RMS force $1.0 \cdot 10^{-5}$ a.u., max. force $6.0 \cdot 10^{-5}$ a.u., RMS force $4.0 \cdot 10^{-5}$ a.u.), without symmetry constraints. All stationary points were characterized by the eigenvalues of their analytically calculated Hessian matrices. All minima were confirmed to have real frequencies only. Similarly, transition states were confirmed to have a single

imaginary frequency with a mode corresponding to the reaction coordinate. With the methods described above, one of the transition states, **TS-A_DBU**, was initially characterized as a second-order saddle point. However, whereas one of the two modes corresponding to imaginary frequencies describe the expected proton transfer, the second imaginary frequency is an artifact resulting from the reduced-quality integration grid used, by default in Gaussian 09, in the analytical calculation of second derivatives (i.e., “SG1” rather than the “ultrafine” integration grid used for energy and gradient calculations).⁴⁵ The second imaginary frequency disappeared on explicitly using the “ultrafine” grid when calculating the second derivatives, confirming that this stationary point is also a transition state.

Single-point (SP) calculations were performed on optimized geometries using the generalized gradient approximation (GGA) functional of Perdew, Burke and Ernzerhof (PBE) in combination with Grimme's empirical dispersion with Becke-Johnson damping D3M(BJ).^{53,63} The PBE-D3M(BJ) functional was chosen for its excellent performance in reproducing experimental gas-phase relative energies of ruthenium-mediated olefin metathesis.⁶⁴ Ruthenium was described by the ECP28MDF⁴⁰ relativistic effective core potential in conjunction with the correlation-consistent valence quadruple- ζ plus polarization basis set of cc-pVQZ-PP quality (primitive [14s11p10d3f2g1h], contracted [6s6p5d3f2g1h]).⁴⁰ Carbon and hydrogen atoms were described by valence quadruple- ζ plus polarization (EMSL: cc-pVQZ)^{43,65} basis sets.⁴² The other atoms were treated with valence quadruple- ζ plus polarization basis sets augmented with diffuse functions^{42,66} (EMSL: aug-cc-pVQZ).^{43,65} Electrostatic and non-electrostatic solvation effects were evaluated using the polarizable continuum model (PCM) in combination with the “Dis”, “Rep”, and “Cav” keywords and the built-in program values (dielectric constant, number density, etc.) for tetrahydrofuran (THF).⁶⁷⁻⁷² The united atom topological model with atomic radii optimized for Hartree–Fock (termed “UAHF”) was used for the solute cavity.^{70,73-75} Numerical integrations used the “ultrafine” grid. The SCF convergence criterion was set to 10^{-5} (i.e., RMS change in density matrix $< 1.0 \cdot 10^{-5}$, max. change in density matrix $= 1.0 \cdot 10^{-3}$).

Gibbs free energies were obtained using a standard state corresponding to 1M infinitely diluted solution (ideal-gas-like behavior), and calculated for a temperature of 298.15 K. Accordingly, a standard-state correction $\Delta G_{1\text{atm} \rightarrow 1\text{M}}^{T=298.15\text{K}} = 1.89 \text{ kcal mol}^{-1}$ ($= RT \cdot \ln(24.46)$) was added to the calculated free energy of each molecule to account for the change in standard state from 1 atm to

1 M.⁶⁴ Thermal corrections were calculated using the quasi-harmonic oscillator approximation. All frequencies below 100 cm⁻¹ were shifted to 100 cm⁻¹ when calculating the vibrational contribution to the entropy.^{46,47} In total, the following expression was used for the calculation of Gibbs free energies:

$$G_{\text{PBE-D3M(BJ)}}^{\text{THF}} = E_{\text{PBE-D3M(BJ)}}^{\text{THF}} + \Delta G_{\text{wB97XD;qa}}^{T=298.15\text{K}} + \Delta G_{1\text{atm} \rightarrow 1\text{M}}^{T=298.15\text{K}}$$

where $E_{\text{PBE-D3M(BJ)}}^{\text{THF}}$ is the potential energy resulting from SP calculation with PBE-D3BJ functional, including the contributions from the implicit solvation model, $\Delta G_{\text{wB97XD;qa}}^{T=298.15\text{K}}$ is the thermal correction to the Gibbs free energy calculated at the geometry optimization level with the quasi-harmonic oscillator approximation, and $\Delta G_{1\text{atm} \rightarrow 1\text{M}}^{T=298.15\text{K}}$ is the standard-state correction.

Mechanistic study. Deprotonation at the C_β site in metallacyclobutane **Ru-B** proceeds with relatively low activation barriers: 20.5 kcal/mol for DBU, 20.6 kcal/mol for NEt₃, and 17.0 kcal/mol for the enolate generated via attack by PCy₃ on the methyl acrylate (Table 3.5). The fate of the resulting anion is depicted in Scheme 3.6. While the *cis* isomer (**Ru-C**) of the anion is the most stable (see Table 3.3), the *trans* isomer (**Ru-C'**) is the kinetic product of deprotonation. Barriers to *cis-trans* isomerization in ruthenium dichloride metathesis catalysts are known to be substantial,⁷⁶ and loss of chloride from the anion can therefore be assumed to be faster. Loss of DBU•HCl from the ion pair **Ru-C'**(HDBU) leads to the more stable, neutral mono-chloride species **Ru-E1** and **Ru-E2**. Despite the stability of the latter, an *o*-methyl group in **Ru-E1** is relatively close to the Ru atom (Ru-H_{methyl} = 2.89 Å). **Ru-E1** is geometrically similar to the subsequent intermediate (**Ru-F**), leading, without a barrier,⁷⁷ to the agostic structure **Ru-G**. Further activation of the C–H bond and oxidative addition (**Ru-H**) is also barrierless,⁷⁷ and leads to the relatively stable hydride complex **Ru-I**.

Multiple agostic and non-agostic isomers and conformers (**Ru-K** and **Ru-M**) exist for the Ru-propene complex formed by reductive elimination. These isomers differ from **Ru-P**, the “monomeric”, propene-bound analogue of **Ru-1**. Several pathways can be envisaged for isomerization of **Ru-M** to **Ru-P**, including associative olefin exchange starting from **Ru-M4**. The latter has not been explored here, but even the completely dissociated state (**Ru-N** and propene) has a lower free energy than **Ru-B**, and generates **Ru-P** upon olefin binding. This

suggests that the structural changes by which **Ru-P** generated are facile compared to the initial deprotonation step.

Table 3.5. Calculated Gibbs free energies (kcal/mol) of the mechanistic study.

Mol. ID	$E_{\omega B97XD}$ [a.u.]	$G_{\omega B97XD}^{T=298.15K}$ [a.u.]	$\Delta G_{\omega B97XD;qa}^{T=298.15K}$ [a.u.]	$E_{PBE-D3BJ}^{THF}$ [a.u.]	$G_{PBE-D3BJ}^{THF}$ [a.u.]	$\Delta G_{PBE-D3BJ}^{THF}$ w.r.t. Ru-B	
						[a.u.]	[kcal/mol]
Ru-B	-2058.195575	-2057.753637	0.452809	-2057.297572	-2056.841744	0.000000	0.0
DBU	-461.985308	-461.773150	0.212899	-461.726912	-461.510994	-	-
Et₃N	-292.337748	-292.164864	0.173230	-292.147737	-291.971488	-	-
PCy₃ enolate	-1353.396885	-1352.868607	0.532471	-1352.663810	-1352.128320	-	-
TS-A_DBU	-2520.180678	-2519.503168	0.688191	-2519.011289	-2518.320079	0.032660	20.5
TS-A_NEt₃	-2350.526000	-2349.890739	0.648877	-2349.432374	-2348.780478	0.032754	20.6
TS-A_enolate	-3411.617096	-3410.624060	1.010610	-3409.956595	-3408.942967	0.027098	17.0
Ru-C'(HDBU)	-2520.210764	-2519.526301	0.694997	-2519.036627	-2518.338611	0.014128	8.9
Ru-E1	-1597.327697	-1596.896227	0.440291	-1596.595269	-1596.151959	0.006685	4.2
Ru-E2	-1597.334445	-1596.904605	0.439112	-1596.599136	-1596.157005	0.001639	1.0
DBU•HCl	-922.827697	-922.607088	0.222449	-922.419562	-922.194095	-	-
Ru-F	-1597.327017	-1596.894563	0.440206	-1596.595487	-1596.152262	0.006382	4.0
Ru-G	-1597.334125	-1596.899771	0.441429	-1596.610634	-1596.166186	-0.007542	-4.7
Ru-H	-1597.332177	-1596.899123	0.439961	-1596.613220	-1596.170240	-0.011596	-7.3
Ru-I	-1597.342102	-1596.906344	0.441929	-1596.626628	-1596.181680	-0.023036	-14.5
Ru-J	-1597.329565	-1596.894635	0.440069	-1596.612176	-1596.169088	-0.010444	-6.6
Ru-K	-1597.340112	-1596.902490	0.442696	-1596.611783	-1596.166068	-0.007424	-4.7
Ru-L	-1597.335512	-1596.897925	0.442660	-1596.607204	-1596.161525	-0.002881	-1.8
Ru-M1	-1597.332708	-1596.895388	0.443198	-1596.612486	-1596.166269	-0.007625	-4.8
Ru-M2	-1597.327212	-1596.890049	0.443756	-1596.606816	-1596.160042	-0.001397	-0.9
Ru-M3	-1597.331078	-1596.897741	0.441460	-1596.607396	-1596.162917	-0.004273	-2.7
Ru-M4	-1597.339138	-1596.903795	0.441821	-1596.613281	-1596.168441	-0.009797	-6.1
propene	-117.870107	-117.815267	0.054839	-117.791385	-117.733527	-	-
Ru-N	-1479.433826	-1479.077154	0.362767	-1478.792230	-1478.426445	-0.001327	-0.8
³Ru-N (spin triplet)	-1479.429412	-1479.077224	0.360549	-1478.778887	-1478.415319	0.009798	6.1
Ru-P	-1597.364527	-1596.928230	0.443291	-1596.641236	-1596.194926	-0.036282	-22.8

3.6 References

- (1) (a) Weskamp, T.; Schattenmann, W. C.; Spiegler, M.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2490. (b) Herrmann, W. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 262.
- (2) (a) Schrodi, Y., Mechanisms of Olefin Metathesis Catalyst Decomposition and Methods of Catalyst Reactivation. In *Handbook of Metathesis*, Grubbs, R. H.; Wenzel, A. G., Eds. Wiley-VCH: Weinheim, 2015; pp 323–342. (b) Crabtree, R. H. *Chem. Rev.* **2015**, *115*, 127–150. (c) 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.
- (3) For a review of non-metathetical side-reactions originating in the Ru catalysts or their decomposition products, see: (a) Alcaide, B.; Almendros, P.; Luna, A. *Chem. Rev.* **2009**, *109*, 3817–3858. For unintended double-bond isomerization, see ref 1d. Candidate isomerization catalysts include Ru nanoparticles (see: (b) Higman, C. S.; Lanterna, A. E.; Marin, M. L.; Scaiano, J. C.; Fogg, D. E. *ChemCatChem* **2016**, *8*, 2446–2449) and four-coordinate RuHCl(CO)(H₂IMes) (see: (c) Nelson, D. J.; Percy, J. M., *Dalton Trans.* **2014**, *43*, 4674–4679), but not the PCy₃ adduct of the latter; see: (d) Higman, C. S.; Plais, L.; Fogg, D. E. *ChemCatChem* **2013**, *5*, 3548–3551.
- (4) (a) Higman, C. S.; Lummiss, J. A. M.; Fogg, D. E. *Angew. Chem., Int. Ed.* **2016**, *55*, 3552–3565. (b) Farina, V.; Horváth, A., Ring-Closing Metathesis in the Large-Scale Synthesis of Pharmaceuticals. In *Handbook of Metathesis*, Grubbs, R. H.; Wenzel, A. G., Eds. Wiley-VCH: Weinheim, 2015; Vol. 2, pp 633–658. (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*, Grela, K., Ed. Wiley: Hoboken, 2014; pp 349–366. (d) 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) Reports from process chemistry in pharma: (a) Nicola, T.; Brenner, M.; Donsbach, K.; Kreye, P. *Org. Process Res. Dev.* **2005**, *9*, 513–515. (b) Wang, H.; Goodman, S. N.; Dai, Q.; Stockdale, G. W.; Clark, W. M. *Org. Process Res. Dev.* **2008**, *12*, 226–234. (c) 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) (a) McClennan, W. L.; Rufh, S.; Lummiss, J. A. M.; Fogg, D. E. *J. Am. Chem. Soc.* **2016**, *138*, 14668–14677. (b) Lummiss, J. A. M.; McClennan, W. L.; McDonald, R.; Fogg, D. E. *Organometallics* **2014**, *33*, 6738–6741. (c) Lummiss, J. A. M.; Botti, A. G. G.; Fogg, D. E. *Catal. Sci. Technol.* **2014**, *4*, 4210–4218. (d) Lummiss, J. A. M.; Ireland, B. J.; Sommers, J. M.; Fogg, D. E. *ChemCatChem* **2014**, *6*, 459–463.
- (7) For abstraction of methylidene by PCy₃ in the absence of donors or olefin, see: (a) Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2004**, *126*, 7414–7415. (b) Hong, S. H.; Wenzel, A. G.; Salguero, T. T.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2007**, *129*, 7961–7968. (c) Lummiss, J. A. M.; Higman, C. S.; Fyson, D. L.; McDonald, R.; Fogg, D. E. *Chem. Sci.* **2015**, *6*, 6739–6746. .

- (8) Strategies designed to counter the deleterious impact of sterically accessible amines on metathesis productivity focus on *N*-protection and/or limiting the basicity of the nitrogen site. See, for example: (a) Lafaye, K.; Nicolas, L.; Guérinot, A.; Reymond, S. b.; Cossy, J. *Org. Lett.* **2014**, *16*, 4972–4975. (b) Woodward, C. P.; Spiccia, N. D.; Jackson, W. R.; Robinson, A. J. *Chem. Commun.* **2011**, *47*, 779–781. For a superb early overview and recent update, see: (c) Compain, P. *Adv. Synth. Catal.* **2007**, *349*, 1829–1846. (d) Compain, P.; Hazelard, D. *Top. Heterocyclic Chem.* **2015**, 1–43.
- (9) See ref 5d and: (a) Ireland, B. J.; Dobigny, B. T.; Fogg, D. E. *ACS Catal.* **2015**, *5*, 4690–4698. (b) Bailey, G. A.; Fogg, D. E. *J. Am. Chem. Soc.* **2015**, *137*, 7318–7321. (c) Santos, A. G.; Bailey, G. A.; dos Santos, E. N.; Fogg, D. E. *ACS Catal.* **2017**, *7*, 3181–3189.
- (10) We originally proposed **Ru-B** or other MCB species as the primary targets of deprotonation, based on analysis of decomposition byproducts (refs 8a, 8b). Interception of cyclometallated Ru products in the present work initially called this inference into question.
- (11) While the pK_a values of the phosphonium enolates are unknown, a lower limit of 17.4–22.0 is estimated from values measured for $R_3NCH_2CH_2CO_2Me$ ($NR_3 = NMe_3$ or DABCO) in water or methanol, respectively. See: (a) Rios, A.; Amyes, T. L.; Richard, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 9373–9385. (b) Plata, R. E.; Singleton, D. A. *J. Am. Chem. Soc.* **2015**, *137*, 3811–3826. The enolates are presumed to be more basic, given poorer stabilization of the negative charge by a nearby positive charge on phosphorus, vs. nitrogen.
- (12) Bates, J. M.; Lummiss, J. A. M.; Bailey, G. A.; Fogg, D. E. *ACS Catal.* **2014**, *4*, 2387–2394.
- (13) Griffiths, J. R.; Keister, J. B.; Diver, S. T. *J. Am. Chem. Soc.* **2016**, *138*, 5380–5391.
- (14) Brown, A.; Gillbro, T.; Nilsson, B. *J. Polym. Sci., Polym. Phys. Ed.* **1971**, *9*, 1509–1515.
- (15) Short Ru-C_{ipso} bond distances (2.45 ± 0.01 Å; cf. 2.19 Å as the sum of covalent radii) for the activated H₂IMes ligand in **Ru-1** are attributed to the coordinative unsaturation of the Ru center, and the flexibility and lack of encumbrance at Ru and C_{ipso}. For RuCl(κ^2 -IMes-H)(PPh₃)₂, in which two relatively bulky PPh₃ ligands are present, the corresponding value is 2.613 Å. See: Abdur-Rashid, K.; Fedorkiw, T.; Lough, A. J.; Morris, R. H. *Organometallics* **2004**, *23*, 86–94.
- (16) Comparable C=C bond elongation is observed for the styrene-bound analogue **Ru-1b** discussed below ($1.416(10)$ Å, vs. a value of $1.3175(16)$ Å reported for free styrene in: Bond, A. D.; Davies, J. E. *Acta Cryst.* **2001**, *E57*, o1191–o1193).
- (17) Precedents for cyclometallation of H₂IMes and IMes in Ru systems appear in the work cited in ref 14 and: (a) Trnka, T. M.; Morgan, J. P.; Sanford, M. S.; Wilhelm, T. E.; Scholl, M.; Choi, T.-L.; Ding, S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 2546–2558. (b) Endo, K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2011**, *133*, 8525–8527. (c) Endo, K.; Herbert, M. B.; Grubbs, R. H. *Organometallics* **2013**, *32*, 5128–5135. (d) Huang, J.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2000**, *19*, 1194. (e) Jazzar, R. F. R.; Macgregor, S. A.; Mahon, M. F.; Richards, S. P.; Whittlesey, M. K. *J. Am. Chem. Soc.* **2002**, *124*, 4944–4945. (f) Phillips, N.; Tang, C. Y.; Tirfoin, R.; Kelly, M. J.; Thompson, A. L.; Gutmann, M. J.; Aldridge, S. *Dalton Trans.* **2014**, *43*, 12288–12298. (g) Chilvers, M. J.; Jazzar, R. F. R.; Mahon, M. F.; Whittlesey, M. K. *Adv. Synth. Catal.* **2003**, *345*, 1111–1114.

- (18) For the synthesis of H₂IMes-d₂₂, see: Leita, E. M.; Dubberley, S. R.; Piers, W. E.; Wu, Q.; McDonald, R. *Chem. – Eur. J.* **2008**, *14*, 11565–11572.
- (19) Much smaller proportions (20%) of the non-labelled base•HCl salts were observed. We suspect that these arise from H/D exchange pathways, though the possibility of direct mesityl deprotonation cannot be completely ruled out.
- (20) The corresponding benzylidene complex does not undergo deprotonation by DBU, instead forming the stable adduct RuCl₂(H₂IMes)(DBU)(=CHPh). See ref 5d.
- (21) Deprotonation of Ru benzylidene species can occur, where steric pressure drives intramolecular α -elimination. See: (a) Conrad, J. C.; Amoroso, D.; Czechura, P.; Yap, G. P. A.; Fogg, D. E. *Organometallics* **2003**, *22*, 3634–3636. (b) Coalter, J. N.; Bollinger, J. C.; Eisenstein, O.; Caulton, K. G. *New J. Chem.* **2000**, *24*, 925–927.
- (22) Gordon, C. P.; Yamamoto, K.; Liao, W.-C.; Allouche, F.; Andersen, R. A.; Copéret, C.; Raynaud, C.; Eisenstein, O. *ACS Cent. Sci.* **2017**, *3*, 759–768.
- (23) Because acidity is a thermodynamic property, defined via the equilibrium constant, we calculate pK_a values from the most stable acid-base pairs. For **Ru-C**, this means using the cis-Cl₂ isomer. The mechanistic investigation instead focuses on the trans-Cl₂ isomer, as the kinetic product of deprotonation. The two are denoted **Ru-C** and **Ru-C'**, respectively.
- (24) The structural similarity of these acid-base pairs aids in evaluating the relative pK_as of **Ru-B** and **Ru-A**. For details, including deprotonation energies, see the Computational Details.
- (25) (a) Romero, P. E.; Piers, W. E. *J. Am. Chem. Soc.* **2007**, *129*, 1698–1704. (b) Nizovtsev, A. V.; Afanasiev, V. V.; Shutko, E. V.; Bessalova, N. B. *NATO Sci. Ser. II* **2007**, *243*, 125–135. (c) van Rensburg, W. J.; Steynberg, P. J.; Meyer, W. H.; Kirk, M. M.; Forman, G. S. *J. Am. Chem. Soc.* **2004**, *126*, 14332–14333.
- (26) See ref 2a and: (a) Schrock, R. R.; Copéret, C. *Organometallics* **2017**, *36*, 1884–1892. (b) Solans-Monfort, X.; Copéret, C.; Eisenstein, O. *J. Am. Chem. Soc.* **2010**, *132*, 7750–7757.
- (27) A related pathway in alkyne metathesis involves β -H transfer from the MCB, and reductive elimination of an anionic ligand X as HX. See: (a) Heppekausen, J.; Stade, R.; Kondoh, A.; Seidel, G.; Goddard, R.; Fürstner, A. *Chem. – Eur. J.* **2012**, *18*, 10281–10299. (b) McCullough, L. G.; Listemann, M. L.; Schrock, R. R.; Churchill, M. R.; Ziller, J. W. *J. Am. Chem. Soc.* **1983**, *105*, 6729–6730.
- (28) van Lierop, B. J.; Reckling, A. M.; Lummiss, J. A. M.; Fogg, D. E. *ChemCatChem* **2012**, *4*, 2020–2025.
- (29) Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792–803.
- (30) Leita, E. M.; Dubberley, S. R.; Piers, W. E.; Wu, Q.; McDonald, R. *Chem. – Eur. J.* **2008**, *14*, 11565–11572.
- (31) Arduengo, A. J.; Krafczyk, R.; Schmutzler, R.; Craig, H. A.; Goerlich, J. R.; Marshall, W. J.; Unverzagt, M. *Tetrahedron* **1999**, *55*, 14523–14534.
- (32) Bailey, G. A.; Fogg, D. E. *ACS Catal.* **2016**, *6*, 4962–4971.
- (33) Eelman, M. D.; Blacquiere, J. M.; Moriarty, M. M.; Fogg, D. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 303–306.

- (34) Coady, D. J.; Fukushima, K.; Horn, H. W.; Rice, J. E.; Hedrick, J. L. *Chem. Commun.* **2011**, 47, 3105–3107.
- (35) Hong, S. H.; Wenzel, A. G.; Salguero, T. T.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2007**, 129, 7961–7968.
- (36) Patiny, L.; Borel, A. *J. Chem. Inf. Model.* **2013**, 53, 1223–1228.
- (37) Zhu, W.; Wang, H.-Y.; Guo, Y.-L. *J. Mass Spectrom.* **2012**, 47, 352–354.
- (38) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J., Gaussian 09, Revision D.01, Gaussian, Inc., Wallingford CT. 2013.
- (39) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, 120, 215–241.
- (40) Peterson, K. A.; Figgen, D.; Dolg, M.; Stoll, H. *J. Chem. Phys.* **2007**, 126, 124101.
- (41) , Energy-consistent Pseudopotentials of the Stuttgart/Cologne Group, <http://www.tc.uni-koeln.de/PP/clickpse.en.html>.
- (42) Dunning, T. H. *J. Chem. Phys.* **1989**, 90, 1007–1023.
- (43) Schuchardt, K. L.; Didier, B. T.; Elsethagen, T.; Sun, L.; Gurumoorthi, V.; Chase, J.; Li, J.; Windus, T. L. *J. Chem. Inf. Model.* **2007**, 47, 1045–1052.
- (44) Woon, D. E.; Dunning, T. H. *J. Chem. Phys.* **1993**, 98, 1358–1371.
- (45) Martin, J. M. L.; Bauschlicher, C. W.; Ricca, A. *Comput. Phys. Commun.* **2001**, 133, 189–201.
- (46) Zhao, Y.; Truhlar, D. G. *Phys. Chem. Chem. Phys.* **2008**, 10, 2813–2818.
- (47) Ribeiro, R. F.; Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2011**, 115, 14556–14562.
- (48) Grimme, S. *Chem. – Eur. J.* **2012**, 18, 9955–9964.
- (49) Becke, A. D. *J. Chem. Phys.* **1993**, 98, 5648–5652.
- (50) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, 98, 11623–11627.
- (51) Perdew, J. P.; Burke, K.; Ernzerhof, M. *Phys. Rev. Lett.* **1996**, 77, 3865–3868.
- (52) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2009**, 113, 6378–6396.
- (53) Grimme, S.; Ehrlich, S.; Goerigk, L. *J. Comput. Chem.* **2011**, 32, 1456–1465.

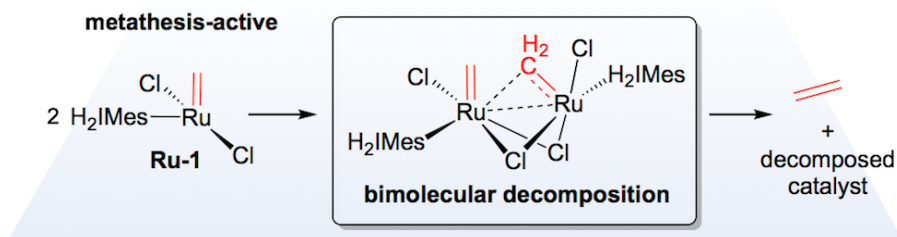
- (54) Smith, D. G. A.; Burns, L. A.; Patkowski, K.; Sherrill, C. D. *J. Phys. Chem. Lett.* **2016**, *7*, 2197–2203.
- (55) Ho, J.; Coote, M. L. *Theor. Chem. Acc.* **2010**, *125*, 3–21.
- (56) Rezende, M. C. *Tetrahedron* **2001**, *57*, 5923–5930.
- (57) Casasnovas, R.; Ortega-Castro, J.; Frau, J.; Donoso, J.; Muñoz, F. *Int. J. Quantum Chem.* **2014**, *114*, 1350–1363.
- (58) Casasnovas, R.; Fernández, D.; Ortega-Castro, J.; Frau, J.; Donoso, J.; Muñoz, F. *Theor. Chem. Acc.* **2011**, *130*, 1–13.
- (59) Becke, A. D. *J. Chem. Phys.* **1997**, *107*, 8554–8560.
- (60) Wu, Q.; Yang, W. *J. Chem. Phys.* **2002**, *116*, 515–524.
- (61) Chai, J.-D.; Head-Gordon, M. *Phys. Chem. Chem. Phys.* **2008**, *10*, 6615–6620.
- (62) Minenkov, Y.; Singstad, Å.; Occhipinti, G.; Jensen, V. R. *Dalton Trans.* **2012**, *41*, 5526–5541.
- (63) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. *J. Chem. Phys.* **2010**, *132*, 154104.
- (64) Minenkov, Y.; Occhipinti, G.; Jensen, V. R. *Organometallics* **2013**, *32*, 2099–2111.
- (65) Feller, D. *J. Comput. Chem.* **1996**, *17*, 1571–1586.
- (66) Kendall, R. A.; Dunning, T. H.; Harrison, R. J. *J. Chem. Phys.* **1992**, *96*, 6796–6806.
- (67) Cossi, M.; Scalmani, G.; Rega, N.; Barone, V. *J. Chem. Phys.* **2002**, *117*, 43–54.
- (68) Scalmani, G.; Frisch, M. J. *J. Chem. Phys.* **2010**, *132*, 114110.
- (69) Tomasi, J.; Mennucci, B.; Cammi, R. *Chem. Rev.* **2005**, *105*, 2999–3093.
- (70) Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027–2094.
- (71) While the experiments were performed in benzene, THF was used in the implicit-solvent calculations to retain consistency with a large body of in-house computational data on ruthenium olefin metathesis, catalyst decomposition, and catalyst regeneration (including recently-published work; see ref 45). Replacing THF by benzene in these calculations is expected to affect relative energies by at most up to a few kilocalories per mole, and to have no effect on the conclusions regarding the computed reaction mechanism. We have found that barriers of ruthenium olefin metathesis and catalyst decomposition calculated using the polarizable continuum model (PCM) are only marginally affected by solvent polarity. For example, the barrier to allylbenzene self-metathesis using the second-generation Hoveyda catalyst **III** is 23.5 kcal/mol in THF, 23.3 kcal/mol in heptane, and 22.6 kcal/mol in toluene, using the same computational model as that employed the present work. See ref 45.
- (72) Engel, J.; Smit, W.; Foscatto, M.; Occhipinti, G.; Törnroos, K. W.; Jensen, V. R. *J. Am. Chem. Soc.* **2017**, *139*, 16609–16619.
- (73) Tomasi, J. *Theor. Chem. Acc.* **2004**, *112*, 184–203.
- (74) Cramer, C. J.; Truhlar, D. G. *Acc. Chem. Res.* **2009**, *42*, 493–497.

- (75) Klamt, A.; Mennucci, B.; Tomasi, J.; Barone, V.; Curutchet, C.; Orozco, M.; Luque, F. J. *Acc. Chem. Res.* **2009**, *42*, 489–492.
- (76) Poater, A.; Ragone, F.; Correa, A.; Szadkowska, A.; Barbasiewicz, M.; Grela, K.; Cavallo, L. *Chem. Eur. J.* **2010**, *16*, 14354–14364.
- (77) At the geometry optimization level, a transition state exists on the PES. With larger basis sets and thermo-chemical and solvent corrections, the final free energy surface is barrierless.

Chapter 4. Bimolecular Coupling as a Vector for Catalyst Decomposition

4.1 Published Contributions

Bimolecular Coupling as a Vector for Decomposition of Fast-Initiating Olefin Metathesis Catalysts. Gwendolyn A. Bailey, Marco Foscato, Carolyn S. Higman, Craig S. Day, Vidar R. Jensen, and Deryn E. Fogg. *J. Am. Chem. Soc.* **2018**, Accepted. (Article)



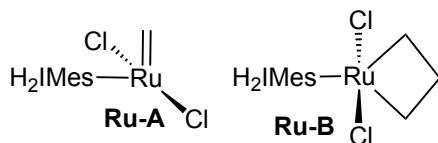
Abstract: The correlation between rapid initiation and rapid decomposition in olefin metathesis is probed for a series of fast-initiating Ru catalysts: the Hoveyda catalyst **III**, $\text{RuCl}_2(\text{L})(=\text{CHC}_6\text{H}_4\text{-}o\text{-O}^i\text{Pr})$; the Grela catalyst **nG** (a derivative of **III** with a nitro group *para* to O^iPr); the Piers catalyst **PII**, $[\text{RuCl}_2(\text{L})(=\text{CHPCy}_3)]\text{OTf}$; the third-generation Grubbs catalyst **GIII**, $\text{RuCl}_2(\text{L})(\text{py})_2(=\text{CHPh})$; and dianiline catalyst **DA**, $\text{RuCl}_2(\text{L})(o\text{-dianiline})(=\text{CHPh})$ ($\text{L} = \text{H}_2\text{IMes} = N,N'$ -bis (mesityl)-imidazolin-2-ylidene). Prior studies of ethylene metathesis established that various Ru metathesis catalysts can decompose by β -elimination of propene from metallacyclobutane $\text{RuCl}_2(\text{H}_2\text{IMes})(\kappa^2\text{-C}_3\text{H}_6)$ **Ru-B**. The present work demonstrates that in metathesis of terminal olefins, β -elimination yields only ca. 25–40% propenes for **III**, **nG**, **PII** or **DA**, and *none* for **GIII**. The discrepancy is attributed to competing decomposition via bimolecular coupling of methyldiene intermediate $\text{RuCl}_2(\text{H}_2\text{IMes})(=\text{CH}_2)$ **Ru-A**. Direct evidence for methyldiene coupling is presented, via the controlled decomposition of transiently-stabilized adducts of **Ru-A**, $\text{RuCl}_2(\text{H}_2\text{IMes})\text{L}_n(=\text{CH}_2)$ ($\text{L}_n = \text{py}_n$, where $n = 1, 2$; or *o*-dianiline). These adducts were synthesized by treating in situ-generated metallacyclobutane **Ru-B** with pyridine or *o*-dianiline, and isolated at low temperature (-116°C or -78°C , respectively). On warming, both undergo methyldiene coupling, liberating ethylene and forming $\text{RuCl}_2(\text{H}_2\text{IMes})\text{L}_n$. A mechanism is proposed based on kinetic studies and molecular-level computational analysis. Bimolecular coupling emerges as an important contributor to the instability of **Ru-A**, and a potentially major pathway for decomposition of fast-initiating, phosphine-free metathesis catalysts.

Author Contributions: This manuscript was conceived, written, edited, and revised by GAB and DEF. MF performed the molecular-level computational analysis, with input from VRJ. CSH discovered the susceptibility of **GIII** to bimolecular coupling, and participated in drafting an early version of the paper. The styrene metathesis studies and characterization of pyridine-stabilized products **Ru-2** and **Ru-2'** were conducted by GAB and CSD, with input from CSH. The protocol for isolation of **Ru-3** was refined by GAB and CSD. All other experiments were designed and conducted by GAB.

4.2 Introduction

Olefin metathesis represents an exceptionally powerful, general methodology for the catalytic assembly of carbon-carbon bonds.¹ Ru-catalyzed olefin metathesis, long embraced in academia, is now beginning to see industrial uptake.² Reports from pharmaceutical manufacturing, however, highlight catalyst productivity as a challenge in process chemistry.² Improved understanding of catalyst decomposition, particularly the pathways operative for the most vulnerable active species (Chart 4.1), is critical to guide process implementation and catalyst redesign.

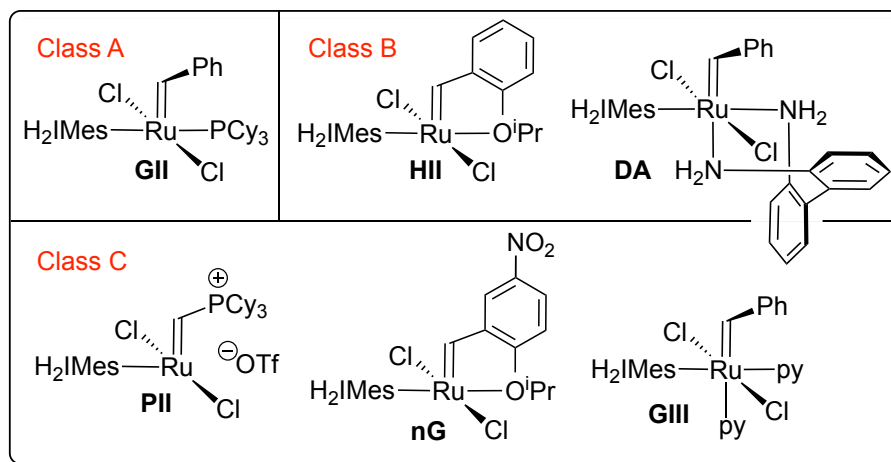
Chart 4.1. Key Active Species in Olefin Metathesis.



The ease with which catalysts enter and exit the active cycle is fundamental to their productivity and stability. To aid in systematic analysis, the classification scheme in Chart 4.2 is proposed. Class A metathesis catalysts, exemplified by the second-generation Grubbs catalyst **GII**, initiate slowly, but the ligand dissociated from the precatalyst is slow to recapture the active species **Ru-A**.³ Class B catalysts (e.g. **III** or the recently-reported⁴ dianiline catalyst **DA**) initiate readily, but recapture of the active species is facile, resulting in rapid shuttling into and out of the catalytic cycle.^{3,5} Class C catalysts (e.g. the third-generation Grubbs catalyst **GIII**, the Grela

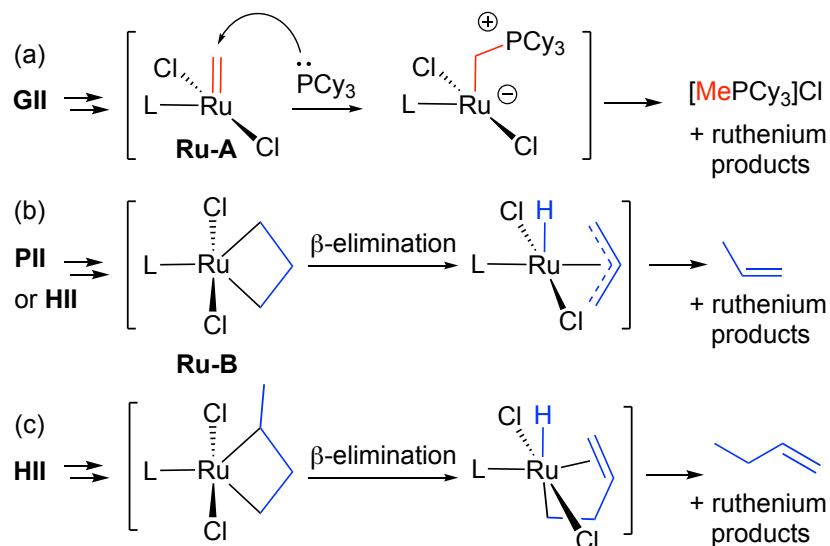
catalyst **nG**, or the Piers catalyst **PII**) also initiate rapidly, and recapture of **Ru-A** by the released ligand is minimal.^{3,6} The trade-off between activity and stability evident from recent prominent reviews⁷ underscores the importance of understanding the decomposition pathways for fast-initiating Class B/C metathesis catalysts, in particular.

Chart 4.2. Classification of Metathesis Catalysts



4.2.1 Intrinsic Decomposition Pathways Established for the Dominant Ru Metathesis Catalysts

The decomposition chemistry intrinsic to the PCy₃-stabilized catalysts of Class A has been extensively studied. **GII**, for example, although robust as the precatalyst, readily decomposes once converted into the metathesis-active methylidene intermediate **Ru-A**. Methylidene abstraction from **Ru-A** by free PCy₃ (Scheme 4.1a) is widely documented,^{8,9} although nucleophilic primary amines such as NH₂ⁿBu can compete to abstract this key ligand.^{9d} For phosphine-free Class B/C catalysts such as **HIII** and **PII**, the sole *intrinsic* decomposition pathway for which experimental evidence has been reported to date is depicted in Scheme 4.1b. β-Hydride elimination from the metallacyclobutane intermediate **Ru-B** generates an allyl hydride, from which propene is liberated by reductive elimination. Evidence for this pathway was established by the Piers group, via synthesis of an isotopologue of **Ru-B** bearing a ¹³C-labelled metallacyclobutane ring. Decomposition of the labelled complex afforded ¹³C₃H₆, unequivocally confirming the origin of the propene byproduct in the metallacyclobutane ring.¹⁰ Of note, Eisenstein and co-workers reported that β-H transfer within the metallacyclobutane intermediate is also the key initial step in decomposition of d⁰ ML₄ olefin metathesis catalysts.¹¹

Scheme 4.1. Intrinsic decomposition pathways for catalysts of classes A–C (where L = H₂IMes).^a

^aThe proton required to eliminate the σ -alkyl ligand in path (a) is supplied by cyclometallation of the H₂IMes ligand.^{9a}

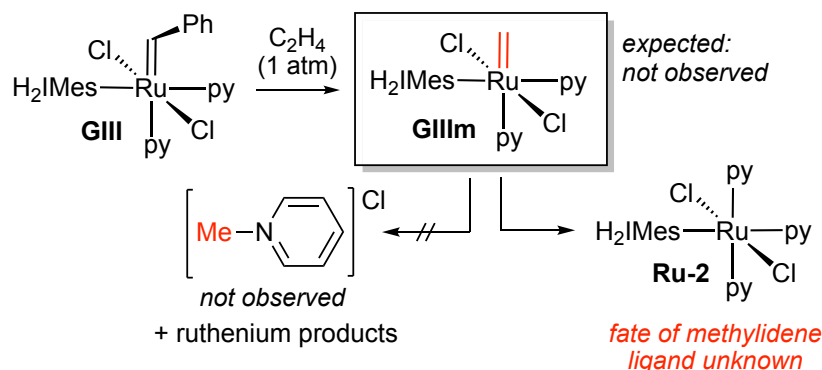
Bespalova and co-workers likewise invoked β -elimination / reductive elimination from **Ru-B** to account for formation of propene upon heating **III** in the presence of ethylene.^{12,13} Propene is thus a key marker for the β -elimination pathway in these experiments. (Caution must be exercised, however, to ensure that no Brønsted base is present that can generate propenes via an alternative process, which commences with metallacyclobutane deprotonation).^{14,15}

A related pathway was proposed based on density functional theory (DFT) calculations, for terminal olefins bearing a suitable aliphatic substituent.¹⁶ For substrates in which an exocyclic β -H is present, expansion of the metallacyclobutane ring was predicted, with ultimate loss of this ligand as an olefin (Scheme 4.1c).

In comparison, the decomposition of pyridine-stabilized catalysts such as **GIII** is poorly understood. Sponsler and coworkers reported that **GIII**^{Br} (in which the pyridine ligands are 3-bromopyridine) decomposed within seconds on exposure to ethylene.¹⁷ Hong and Grubbs^{8a} undertook the corresponding reaction of **GIII** with ethylene, with the intention of synthesizing methylidene species **GIII^m** (Scheme 4.2). The latter complex, a pyridine analogue of **GII^m** $\text{RuCl}_2(\text{H}_2\text{IMes})(\text{PCy}_3)(=\text{CH}_2)$ (the resting state species formed in metathesis by **GII**), was too unstable even to observe in situ at RT. Instead, the sole product identified was the tris-pyridine

derivative **Ru-2**. (**Ru-2** was also formed, and crystallographically characterized, on decomposition of **GIII** in the presence of pyridine).^{8a} The absence of [Me-py]Cl in these reactions was explicitly noted, indicating that pyridine – unlike PCy₃ or primary amines – is insufficiently nucleophilic¹⁸ (or insufficiently basic) to attack the methyldiene ligand. The fate of the methyldiene ligand was not determined.

Scheme 4.2. Reported decomposition behavior of **GIII**.^a



^aLoss of [Me-py]⁺ via deprotonation (cyclometallation) of H₂IMes was postulated: cf. footnote a in Scheme 4.1a.

4.2.2 Proposed Role for Bimolecular Coupling

We speculated that bimolecular coupling of the 14-electron intermediate **Ru-A**, with elimination of the methyldiene ligands as ethylene, might contribute to decomposition for *all* of the fast-initiating Ru metathesis catalysts. This pathway would go unrecognized during the “ethenolysis” experiments described above, because ethylene (the marker for methyldiene coupling) is masked by the reagent gas. By the same token, any methyldiene coupling during metathesis of 1-olefins – the majority of substrates – would be masked by ethylene formed as the coproduct of metathesis.

Bimolecular coupling has been extensively documented for d⁰ metathesis catalysts, and is indeed well established across group 3-7 chemistry.^{7,19} The rate of decomposition is, unsurprisingly, sensitive to the bulk of R in the [M]=CHR species: accordingly, it is generally rapid for methyldiene species, and much slower for complexes containing bulky alkylidenes. In some cases, the ethylene liberated by coupling of methyldiene complexes afforded isolable ethylene adducts, an important aid in confirming the operation of bimolecular coupling.^{7,19} Although bimolecular coupling is also widely accepted for “first-generation” Ru catalysts,⁷ it is regarded as

considerably less likely for the important Ru-NHC catalysts, owing in part to the steric impediment to approach of two $\text{RuCl}_2(\text{NHC})(=\text{CH}_2)$ molecules.²⁰ It is undoubtedly inhibited for **GII** and its resting-state species **GII_m**, for which slow loss of PCy_3 limits the concentration of **Ru-A** present at any given time. Rapid olefin binding to **Ru-A** (a distinct feature of the NHC catalysts, which led Chen to term them “high commitment”,²¹ and Piers “olefinophilic”^{10b}) further limits the concentration of **Ru-A**. Finally, the kinetically dominant decomposition pathway for **GII** during metathesis is typically abstraction of the methylidene ligand by free PCy_3 , as shown in Scheme 1a above.^{8,9}

For phosphine-free **III**, bimolecular coupling is thought to be limited by facile “boomerang” recapture of **Ru-A** by free isopropoxystyrene.⁵ This proposition is difficult to examine, however. **III** itself is sterically protected against such coupling, while the active methylidene intermediate **Ru-A** is spectroscopically unobservable. Important alternative opportunities for insight are offered by the *o*-dianiline catalyst **DA** and pyridine catalyst **GIII**. We considered that the labile *N*-donor ligands in these precatalysts could offer potential access to transiently-stabilized methylidene species (that is, adducts of **Ru-A**), if suitable synthetic routes could be envisaged. Here we report the successful low-temperature synthesis of such adducts, and the first direct evidence that bimolecular coupling, with loss of the methylidene ligand as ethylene, represents a major pathway for decomposition of Class B/C metathesis catalysts. Further, we demonstrate that the contribution of this pathway to decomposition of **III**, the dominant Class B catalyst in current use, has almost undoubtedly been underestimated.

4.3 Results and Discussion

4.3.1 Quantifying Decomposition via β -Elimination

Prior studies of the decomposition of phosphine-free ruthenium metathesis catalysts, as noted above, focused on the behavior of **PII** and **III** under ethylene. The observation of propene in these experiments provided important qualitative evidence for β -elimination from the metallacyclobutane **Ru-B** (Scheme 4.1b). However, the yield of propene based on Ru, and hence the extent of this pathway, was not determined.

We therefore began by seeking to quantify the propene byproducts generated during styrene metathesis. Here propene and β -methylstyrene (Figure 4.1) serve as markers for catalyst decomposition via β -elimination from **Ru-B** or a Ph-substituted metallacyclobutane,

respectively. This experiment serves two purposes. First, it reports on the importance of this decomposition route. Secondly, it shifts the focus to 1-olefins, a family of metathesis substrates of very broad relevance. Styrene is chosen because, unlike most 1-olefins, it cannot isomerize. This is critical to prevent formation of “false” propenyl markers: that is, propenes formed by isomerization-metathesis (see Experimental, section 4.5.3), rather than β -elimination.

Accordingly, metathesis of styrene was undertaken with **HII**, **nG**, **GIII**, **PII**, and **DA** (1 mol%; Figure 4.1). These experiments were carried out in NMR tubes completely filled with solvent,²² to minimize loss of volatile propene to the headspace. This results in co-retention of ethylene, which was expected to maximize formation of metallacyclobutane **Ru-B**, and consequently propene elimination. Notably, however, *no* propenes were observed for **GIII**, and <40% propenes for **HII**, **nG**, **PII**, and **DA**. Clearly, some additional decomposition pathway is operative. If bimolecular coupling indeed accounts for the balance, it is a much more significant contributor to decomposition of Class B/C catalysts than has been considered to date.

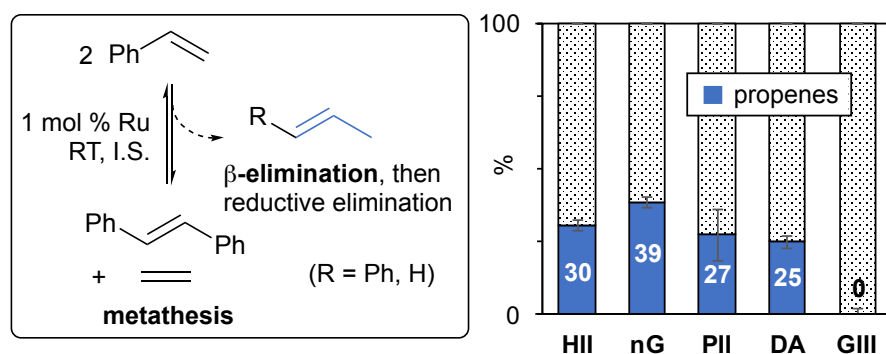


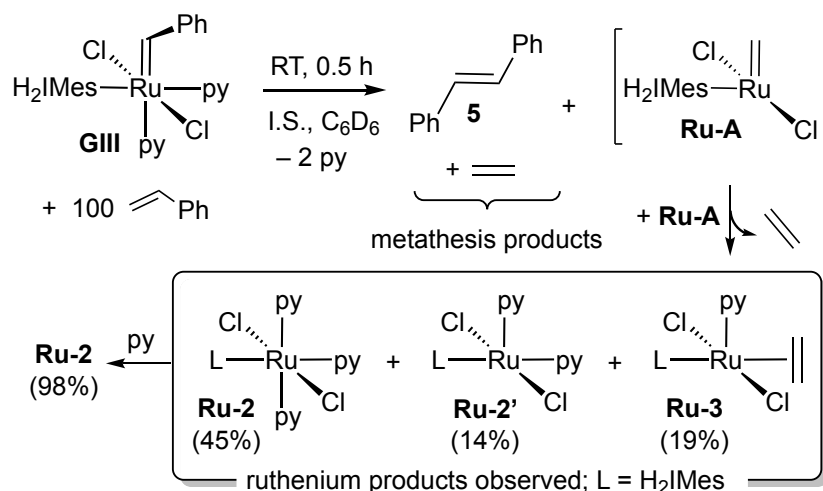
Figure 4.1. Quantifying the β -elimination pathway in decomposition of fast-initiating metathesis catalysts: propene yields at full catalyst decomposition. (Yields based on Ru precatalysts; reactions in C₆D₆ except for **PII**, for which solubility required use of CD₂Cl₂). I.S. = internal standard. See also Scheme 4.1b.

4.3.2 Examining Alternative Decomposition Pathways: Insight from the Nature of the Ruthenium Products

The py ligands in **GIII** offer opportunities to trap the Ru products of decomposition. Of particular interest is the fate of the H₂IMes ligand in these products, as NHC activation and/or cyclometalation are common features in numerous potential pathways, including Buchner expansion (see below).⁷ We therefore sought to identify the methyldiene-free Ru species formed

on reaction of **GIII** with styrene. Scheme 4.3 depicts the major products observed under conditions corresponding to those of Figure 4.1: that is, the known tris-pyridine complex **Ru-2** (a known thermodynamic sink in this chemistry; see above),^{8a} its bis-pyridine analog **Ru-2'**, and a new species assigned as ethylene adduct **Ru-3**.

Scheme 4.3. Bimolecular decomposition of GIII during olefin metathesis in a sealed system.^a



^a Ethylene is generated by both metathesis of styrene, and methyldene coupling.

These sealed-tube reactions generate **Ru-2/2'** in ca. 60% yield, and **Ru-3** in ca. 20% yield based on ruthenium (Figure 4.2a; inverted spectrum). The presence of an ethylene ligand in **Ru-3** is supported by the observed transformation of this complex into **Ru-2'** when the solution is degassed to remove ethylene, and its reappearance when ethylene is reintroduced (Figure A19). Labile coordination of C₂H₄ is common in electron-rich Ru complexes.^{8a,14,23} As further evidence for a weakly-bound ethylene ligand in **Ru-3**, the latter complex undergoes conversion to tris-pyridine complex **Ru-2** when pyridine is added (as does bis-pyridine complex **Ru-2'**). As shown in the upper NMR trace of Figure 4.2a, **Ru-2** is then the sole observable Ru species, being present in 98% yield based on starting **GIII**. As an indicator of generality, it should be noted that **Ru-2** is likewise observed for **HII** on successive treatment with styrene and pyridine, and (as discussed below) on decomposition of the methyldene and ethylidene complexes **GIII_m** and **GIII_e**.

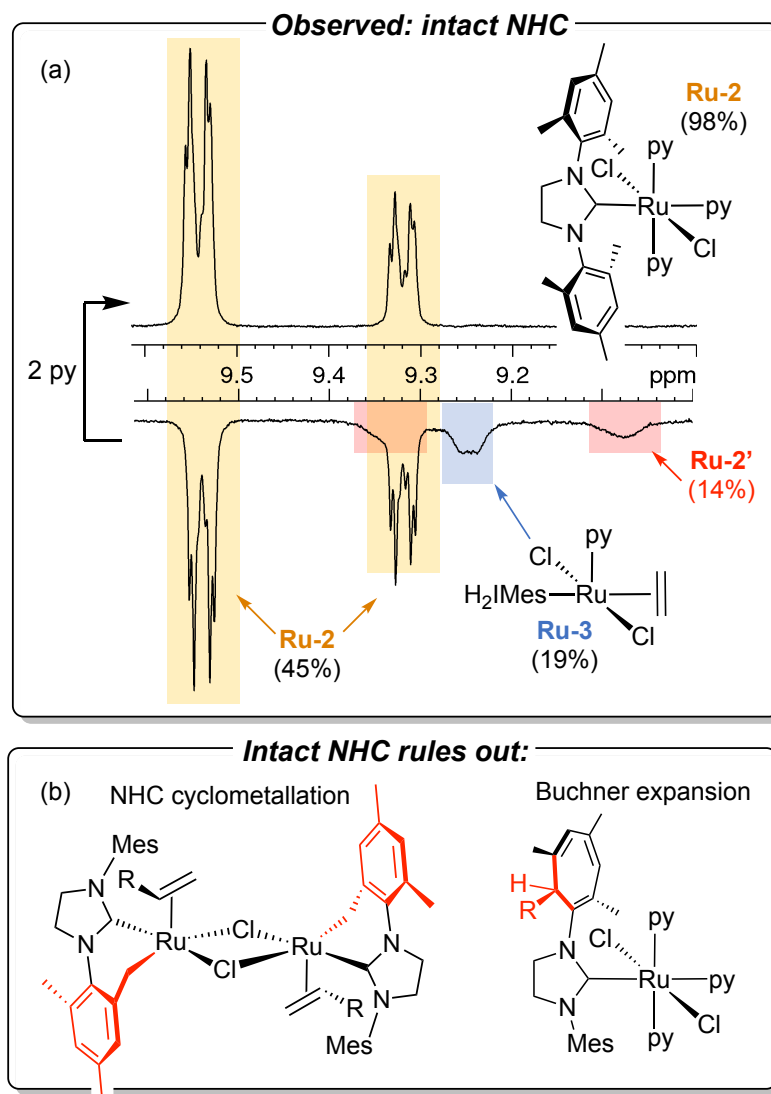


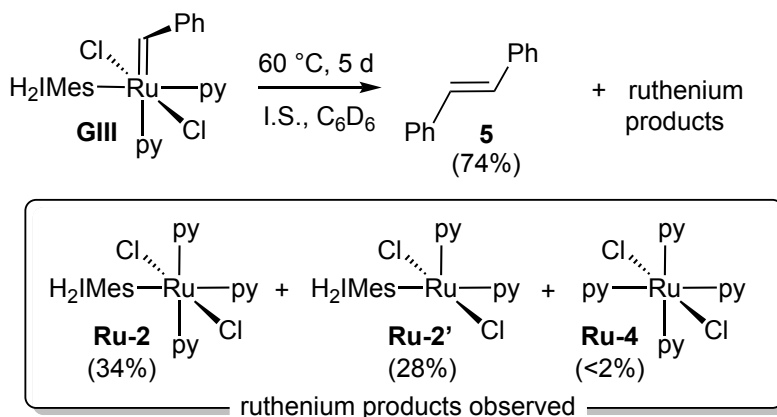
Figure 4.2. Ruthenium decomposition products: identification and mechanistic implications. (a) ^1H NMR spectra corresponding to Scheme 4.3: diagnostic py *o*-CH region (C_6D_6 , 300 MHz). Upper trace: **Ru-2**, formed by adding pyridine to (inverted trace) sample at full decomposition. For full spectra, see Figure A18. (b) Decomposition pathways ruled out by quantitative formation of **Ru-2**.

A key structural feature in **Ru-2** is the intact H_2IMes ligand, which rules out decomposition processes that involve activation of H_2IMes . This precludes, for example, base-induced deprotonation of the metallacyclobutane, which would generate a Ru dimer containing a cyclometallated H_2IMes ligand¹⁴ (Figure 4.2b, left) as well as “false” propenyl markers, as discussed above. The poor Brønsted basicity of pyridine²⁴ is a key parameter in inhibiting this pathway.

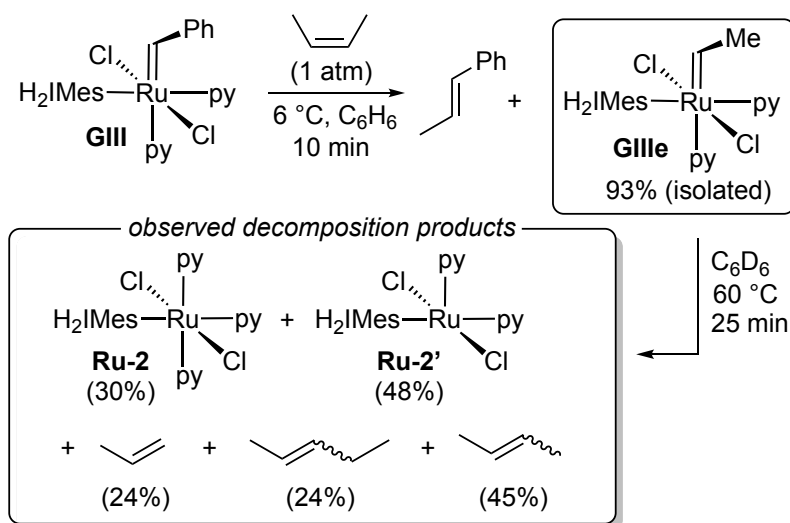
Also ruled out is pyridine-induced attack of the [Ru]=CHR carbon on a mesityl ring, which would give a cycloheptatriene product following Buchner expansion (Figure 4.2b, right).^{25,26} Such transformations of **GII**, **III**, and other Ru-H₂IMes catalysts were deliberately induced by Diver and co-workers, via reactions with CO or isonitriles.²⁵ Coordination of these π -acids heightens the electrophilicity of the Ru=CHR carbon, promoting cyclopropanation of a mesityl ring and ensuing ring expansion.^{25,26a} Computational analysis by the Cavallo group suggested that pyridines are insufficiently π -acidic to cause Buchner expansion of benzylidene complexes,²⁶ and the present studies bear out this prediction.²⁷

4.3.3 Evidence for Bimolecular Coupling of [Ru]=CHR (R = Ph, Me)

The foregoing demonstrates that several decomposition pathways known from other contexts are either inoperative, or less important than hitherto presumed. We next turned to establishing whether bimolecular coupling is operative. Unambiguous evidence for such coupling is seen for the benzylidene complex **GIII**. This precatalyst (in fact, typically a mixture of **GIII** and its mono-pyridine derivative **GIII'**; see below) eliminates stilbene **5** in up to 75% yield on prolonged heating at 60 °C (Scheme 4.4). The major Ru products are again **Ru-2** and its bis-pyridine analog **Ru-2'**, formed in up to 70% yield. Batch-to-batch variations in the proportions of these products (e.g., 1.5:1 to the reverse ratio) are not unexpected, given the known variability in the number of pyridine ligands present in the precatalyst^{28,29} (a **GIII**–**GIII'** mixture, although exchange averaging results in observation of a single benzylidene peak by ¹H NMR analysis). Also observed, albeit as a minor product (invariably <5%), is RuCl₂(py)₄ **Ru-4**. Formation of the latter NHC-free complex indicates H₂IMes loss via a minor additional process as yet undetermined.³⁰

Scheme 4.4. Representative product speciation on thermal decomposition of **GIII**.

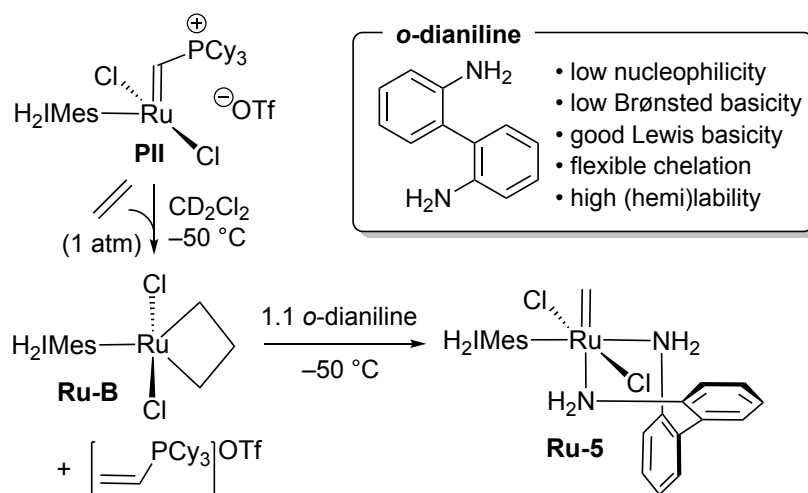
Ethylidene complex **GIIIe** (Scheme 4.5) decomposes dramatically faster than **GIII**. We were able to isolate **GIIIe** by stirring **GIII** under 1 atm cis-2-butene at the minimum accessible solution temperature in benzene, then lyophilizing the solvent to prevent premature decomposition upon concentrating. Heating a C₆D₆ solution of **GIIIe** and an internal standard at 60 °C causes loss of the alkylidene signal over 25 min, with evolution of up to 45% 2-butene. Also observed are propene and 2-pentene (24% each), indicating isomerization–metathesis of 2-butene. On adding pyridine, the Ru products again convert into **Ru-2** (85% yield, based on starting **GIIIe**).

Scheme 4.5. Synthesis and bimolecular decomposition of **GIIIe**.

4.3.4 Evidence for Bimolecular Coupling of $[\text{Ru}]=\text{CH}_2$

While the observation of alkylidene coupling products in up to 75% yield for the benzyldiene and ethylidene complexes is suggestive, the sterically unprotected methylidene ligand could be subject to additional reaction pathways. To clarify the decomposition behavior of methylidene intermediate **Ru-A**, we sought a weakly stabilized adduct that would permit direct study. No such complex is described in the literature. The sole isolable, metathesis-active Ru methylidene complexes reported to date are the “Grubbs methylidenes”, i.e. **GIIIm**^{8,31} and its first-generation analog $\text{RuCl}_2(\text{PCy}_3)_2(=\text{CH}_2)$, **GIm**.^{32a} Use of these complexes to probe bimolecular coupling is precluded by the low lability of the PCy_3 ligand³³ (which limits the concentration of **Ru-A** present at any given time), and by facile abstraction of the methylidene ligand as $[\text{MePCy}_3]\text{Cl}$,^{8,9} as cited in the Introduction. As noted above, Hong and Grubbs attempted to synthesize the corresponding pyridine-stabilized species **GIIm** via reaction of **GIII** with ethylene, but were unable to observe **GIIm** even in situ.^{8a} Few other Ru methylidene complexes are known, and these rare examples are not metathesis-active.³²

Nevertheless, we envisaged that **Ru-A** might be successfully trapped by synthesizing the metallacyclobutane complex **Ru-B** in situ,¹⁰ and introducing a stabilizing ancillary ligand to trigger retro-addition. While pyridine is an obvious candidate ligand, the literature reports emphasize its limited stabilizing ability.^{8a,17} *o*-Dianiline (Scheme 4.6) offers an attractive alternative. This ancillary ligand, originally chosen to maximize catalyst productivity in ring-closing macrocyclization,⁴ is similarly well-suited to stabilization of **Ru-A**. Design criteria common to both of these objectives include low nucleophilicity and low Brønsted basicity (essential to prevent ligand-mediated methylidene or proton abstraction, respectively).⁹ Also critical is a balance between the coordinating properties required to *isolate* an adduct of **Ru-A**, vs. the lability required to readily *release* **Ru-A**. These conflicting demands are reconciled via a combination of good ligand donor ability (achieved, for *o*-dianiline, via a combination of donicity, steric accessibility at the nitrogen sites, and flexible chelation),³⁴ and high (hemi)lability.

Scheme 4.6. Synthesis of *o*-dianiline adduct **Ru-5**.^a

^a Isolated by precipitating with pentane at -78°C .

Synthesis of Transiently-Stabilized Methylidene Adducts of Ru-A. In initial NMR-tube experiments (Scheme 4.6), a solution of **PII** in CD_2Cl_2 was freeze-thaw degassed, thawed at -50°C , and exposed to ethylene. A color change from brown to dark pink occurred within 5 min, with clean conversion to **Ru-B** (Figure 4.3, top trace). Slow injection of *o*-dianiline in CD_2Cl_2 caused a further color change to green over the next 0.5 h, with loss of the diagnostic upfield signal for the metallacycle (H_β ; -2.6 ppm), and emergence of the methylidene singlet for **Ru-5** (19.3 ppm; Figure 4.3, inverted trace). The diagnostic, formally diastereotopic NH_2 signals for bound *o*-dianiline appear as two broad, unresolved signals at ca. 3.6 and 4.3 ppm. Their assignment was confirmed by injecting D_2O into the cooled solution, and briefly agitating to dissolve the ice. In situ yields of **Ru-5** were quantitative. To isolate **Ru-5** free of reagent ethylene, the reaction was repeated on 75 mg scale, and **Ru-5** was isolated as a pale green solid in 75% yield by precipitating with a trickle of cold pentane at -78°C .

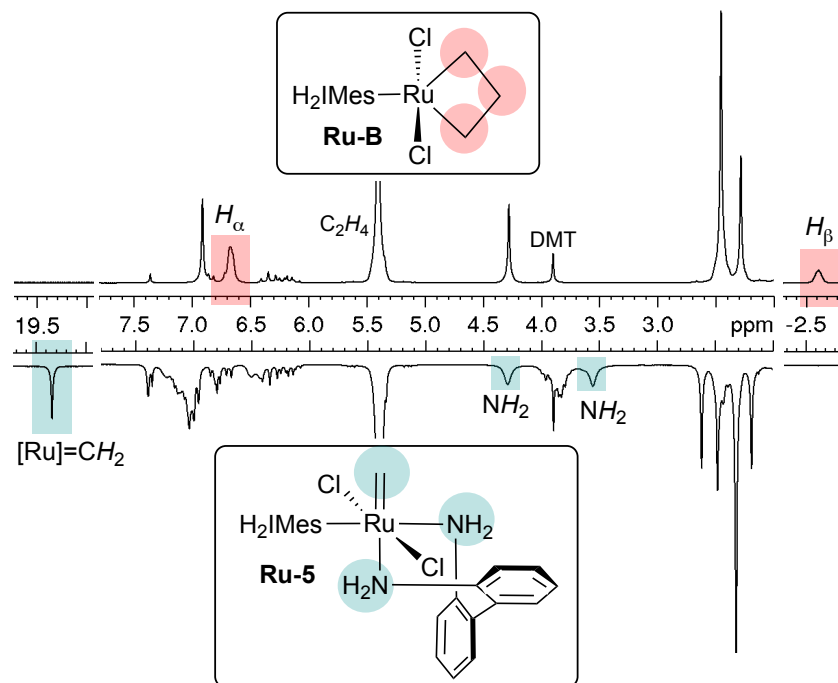
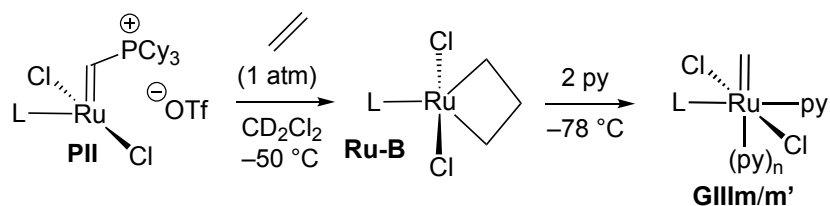


Figure 4.3. ¹H NMR spectra showing (top) **Ru-B**, and (inverted) its *o*-dianiline-stabilized derivative **Ru-5** (300 MHz, CD₂Cl₂, -50 °C). Diagnostic NMR signals for **Ru-B** and **Ru-5** are highlighted with bars that approximate the colours of the complexes.

The corresponding experiments with **GIIIm**, synthesized by adding 2 equiv py (Scheme 4.7), afforded a mixture of **GIIIm** and its mono-pyridine derivative **GIIIm'**. These species were generated in a 30:70 ratio, as determined by integration of the two distinct methyldene signals (19.35 and 18.63 ppm, respectively) at -50 °C. The higher lability of the monodentate pyridine ligand renders these complexes much more unstable than **Ru-5**, and considerably more challenging to isolate. However, they were successfully obtained by carrying out pyridine addition at -78 °C to form **GIIIm/m'**, and precipitating the product mixture by cannula addition of cold pentane at ca. -120 °C. Even under these conditions, competing decomposition (loss of ethylene) was evident. Nonetheless, the methyldene products were isolated as a yellow solid, in ca. 60% yield based on starting **PII**, by decanting the pentane and drying in vacuo. Their stability was insufficient to withstand washing, even in the solid state.

Scheme 4.7. Synthesis of pyridine-stabilized **GIII**m/m'.^a

^a **GIII**m: $n = 1$; **GIII**m': $n = 0$; L = H₂IMes. The 30:70 mixture was precipitated with pentane at -116 °C. The vinylphosphonium coproduct in step 1 is omitted for clarity.

Evidence for Bimolecular Coupling of Transiently-Stabilized Methylidene Species. To measure the proportion of ethylene released by coupling of dianiline adduct **Ru-5**, this complex was dissolved in cold CD₂Cl₂ and added to the internal standard in a pre-chilled J. Young tube. The temperature was maintained at -20 °C during sample preparation by use of a sand-bath chilled in the glovebox freezer. Warming to RT resulted in 95% decomposition over 75 min (Figure 4.4), and formation of methylidene-free **Ru-6** in up to 90% yield. Only 30% yield of ethylene was detected, however, owing to volatilization into the headspace. The proportion of ethylene detected increased to ca. 65% when **Ru-5** was permitted to decompose in NMR tubes filled to 80% capacity. This constitutes the minimum headspace volume deemed safe to prevent explosion on warming (for calculations, see Appendix F).

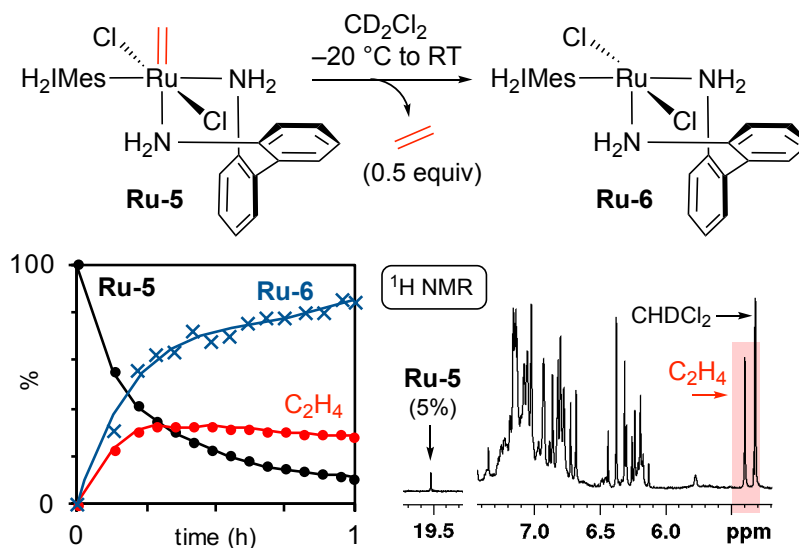


Figure 4.4. Bimolecular coupling of **Ru-5**: rate curve and ¹H NMR spectrum (300 MHz, CD₂Cl₂, RT) at 95% decomposition.

In these filled-tube experiments, the yield of the Ru decomposition product **Ru-6** dropped to ca. 65%, probably owing to the improved stability of Ru-C₂H₄ adducts (cf. **Ru-3**) at higher solution concentrations of ethylene. New ¹H NMR signals were indeed observed in the region characteristic of the Ru-bound C₂H₄ ligand (3.5–0.9 ppm),^{14,23} as well as the NH region (5.0–3.4) for Ru-dianiline complexes, although the lability of bound ethylene in these complexes precludes isolation.

The corresponding experiments with the pyridine adducts **GIII_m/m'** resulted in complete decomposition within 20 min, consistent with the high lability of the pyridine ligands noted. Higher proportions of ethylene were detected (76% in CDCl₃; 70% in CD₂Cl₂), probably because mass transfer restrictions in the NMR tube retard partitioning of ethylene into the gas phase over this short reaction time. Bimolecular coupling is thus observed for both of these exemplary class B/C catalysts, although the weaker donor ligands characteristic of Class C accelerate decomposition

4.3.5 Dependence of the Rate of Bimolecular Coupling on Alkylidene Substituent.

The data above support bimolecular decomposition of all [Ru]=CHR complexes examined, at rates that are qualitatively found to increase as the bulk of the substituent R decreases. This behaviour, which parallels trends observed in the early-metal systems, is shown more explicitly in Figure 4.5. Thus, after 30 min at 60 °C in C₆D₆, benzyldiene complex **GIII** remains intact, while its ethylidene or methylidene analogues (**GIIIe** and **GIII_m**, respectively) are completely decomposed. A striking difference between **GIIIe** and **GIII_m** is evident at room temperature, however. After 30 min in CD₂Cl₂, 99% **GIIIe** remains, while **GIII_m/m'** is completely decomposed. The greater resistance to coupling of the ethylidene complex **GIIIe** helps account for the widely-reported³⁵⁻³⁷ observation of improved metathesis performance for 2-methyl olefins, vs 1-olefins.³⁸

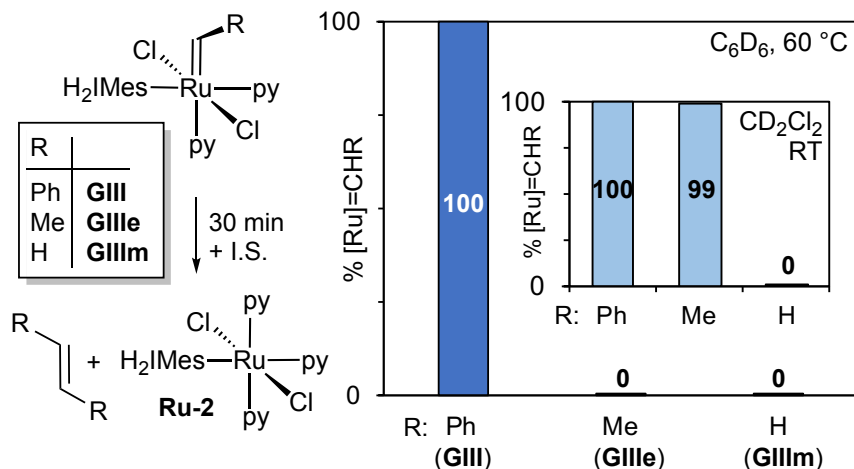


Figure 4.5. Bimolecular coupling of $[\text{Ru}]=\text{CHR}$: impact of R on rate of decomposition. Chart shows % alkylidene remaining after 30 min at 60 °C, or (inset) at RT, for **GIII**, **GIIIe**, and **GIIIIm**. All complexes shown as bis-py species for simplicity: in practice, a mixture of mono- and bis-py complexes is present (of which the latter predominates for all but **GIIIIm/m'**).

4.3.6 Mechanism of Bimolecular Coupling

To gain further insight into the mechanism of bimolecular coupling, we undertook kinetic and computational analysis.

Kinetics studies. Rate experiments focused on dianiline adduct **Ru-5**, given its greater ease of handling relative to **GIIIIm**. At 20 mM **Ru-5**, decomposition was second-order in Ru, consistent with rate-limiting bimolecular coupling of five-coordinate $\kappa^1\text{-Ru-5}$ (Figure 4.6a). At 1 mM **Ru-5**, decomposition is *first* order in Ru, but the evolution of ethylene confirms that bimolecular coupling remains operative. Indeed, the observed yield of C_2H_4 reached ca. 40% based on starting **Ru-5**, despite use of a standard NMR-tube headspace to maintain conditions that more closely approximate bench operations. Volatilization of ethylene is limited by the small amounts involved (maximum theoretical yield 0.5 mM, well below its reported solubility limit of 54 ± 3 mM in CD_2Cl_2 at 296 ± 1.5 K).^{9d}

Decomposition at 1 mM is also found to be retarded by exogenous dianiline. This, and the change in the order of reaction with respect to **[Ru-5]**, point toward a change in mechanism when the ruthenium concentration is decreased. The rate of coupling of five-coordinate $\kappa^1\text{-Ru-5}$ (path a) is expected to be highly sensitive to concentration, given its squared dependence on **[Ru-5]**. We propose that at 1 mM **Ru-5**, loss of dianiline from $\kappa^1\text{-Ru-5}$ (path b) is faster than

coupling of κ^1 -**Ru-5**. Once four-coordinate **Ru-A** is generated, its greatly reduced steric protection relative to κ^1 -**Ru-5** is expected to result in a significantly faster rate in the bimolecular coupling step (that is, $k_4 \gg k_2$).

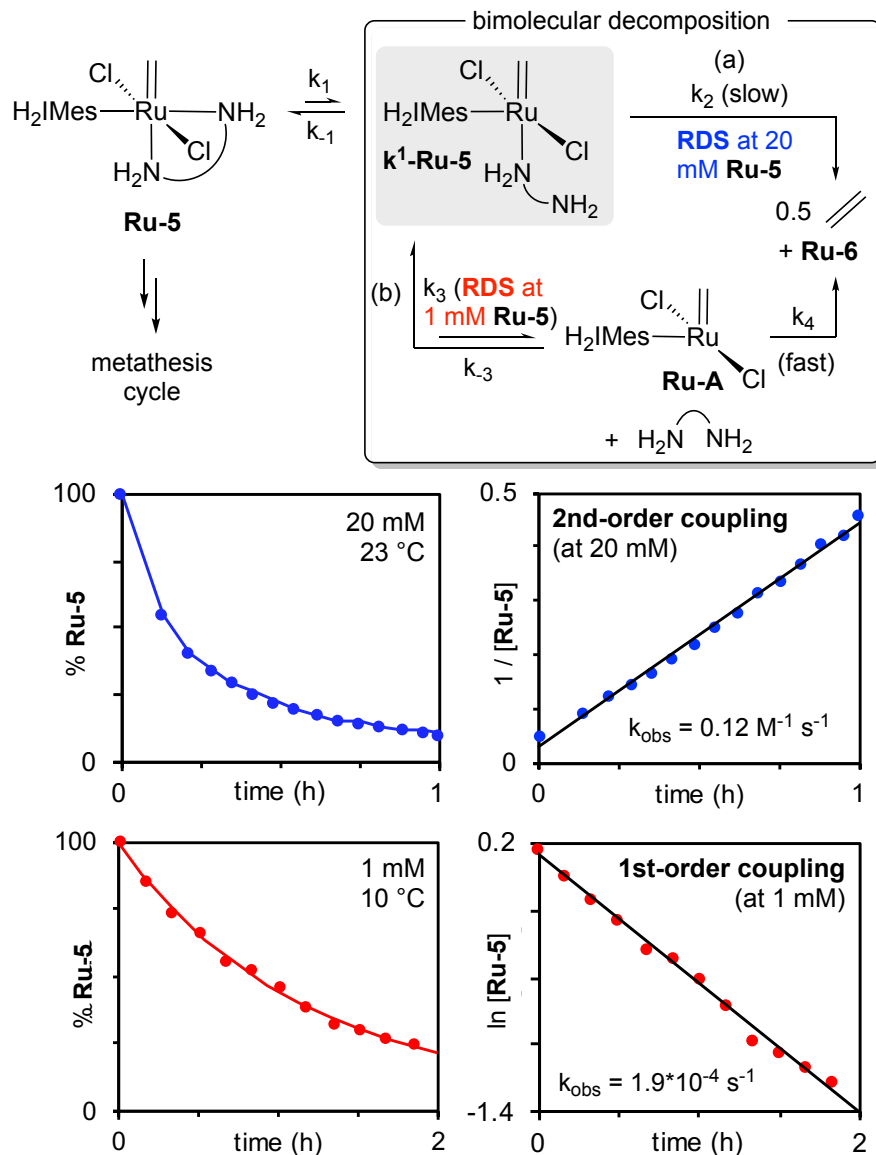


Figure 4.6. Top: Proposed mechanism for bimolecular coupling at (a) 20 mM **Ru-5**; (b) 1 mM **Ru-5**. (Reactions in CD_2Cl_2 ; $\text{H}_2\text{N-NH}_2 = o$ -dianiline). Bottom: Establishing the order of reaction with respect to Ru. To retard reaction and collect sufficient scans for good signal-to-noise ratios, the 1 mM reaction was conducted at 10 °C.

Molecular-Level Computational Studies. DFT analysis focused on coupling of **Ru-A**. This species was chosen for study in light of the kinetics findings above, which point toward **Ru-A** as

the key intermediate in decomposition at catalytically relevant concentrations of **Ru-5**. In addition, **Ru-A** is common to all of the Class B/C catalysts studied in this work, including those which (subsequent to initiation) lack a ligand that can stabilize the methyldene intermediate.

Accordingly, the mechanism by which two molecules of **Ru-A** couple to generate ethylene was examined. The dimeric structures shown at the left in Figure 4.7 were prioritized in light of prior experimental and computational work suggesting their potential importance.^{6,16,39,40} The energies shown for these structures are normalized to that of **Ru-5**. Dimer **Ru-Q** has multiple precedents in crystal structures of diruthenium species containing transoid alkylidene ligands.⁴¹ **Ru-Q** is the lowest-energy of the intermediates predicted to form on reaction of two **Ru-A** molecules. However, the long $\text{H}_2\text{C}\cdots\text{CH}_2$ distance (5.77 Å), and the substantial rearrangement needed for the two methyldene units to react, imply that this intermediate cannot generate ethylene in a single elementary step.

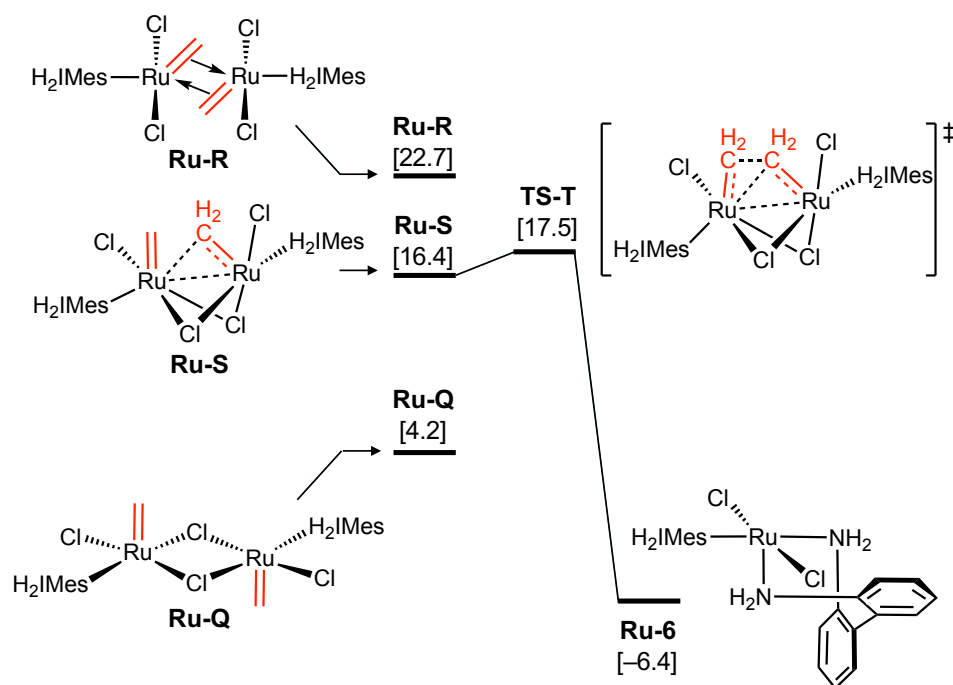


Figure 4.7. Computed Gibbs free energy profile (kcal/mol) along the reaction path involving loss of methyldene from **Ru-A**. Energies normalized to *o*-dianiline adduct **Ru-5**.

Considerably higher in energy than **Ru-Q** is **Ru-R**, precedent for which exists in a crystallographically characterized tungsten methyldene complex that exhibits reciprocal methyldene-to-tungsten donor interactions.^{19c} Shown in the structure of **Ru-R** is the

corresponding reciprocal $\text{Ru}=\text{CH}_2 \rightarrow \text{Ru}$ donation. Although the two methyldene units are closer in **Ru-R** than they are in **Ru-Q**, they are geometrically constrained and cannot easily interact. Attempts to enforce coupling by shortening the C–C distance to form an ethylene ligand between the two Ru centers required unacceptably high energies, >35 kcal/mol higher than **Ru-5**, and a transition state was therefore not located.

Much more persuasive as an intermediate on the methyldene-coupling pathway is **Ru-S**, which is higher in energy than **Ru-Q**, but lower than **Ru-R**. In structure **Ru-S**, the two $\text{Ru}=\text{CH}_2$ units form a cisoid dimer in which the methyldene carbons are sufficiently close and unconstrained to interact (2.90 Å; for 3D structure, see Figure 4.13). Also notable is a striking dissymmetry in the methyldene bonding interactions. While the calculated $\text{Ru}=\text{CH}_2$ bond distances are essentially identical, at 1.82 or 1.83 Å, one methyldene ligand interacts with both metal centers, while the other does not ($\text{Ru}_\text{A}-\text{C}_\text{B} = 2.64$ Å; $\text{Ru}_\text{B}-\text{C}_\text{A} = 3.67$ Å; for atom labeling, see Figure 4.8). Most importantly, the orientation of the methyldene groups of **Ru-S** is optimal for C–C bond formation. Less than 2 kcal/mol is needed to reach transition state **TS-T** (the 3D structure of which is shown in Figure 4.14), and these two stationary points have been connected in intrinsic reaction coordinate (IRC) calculations. A related $\text{Ru}_2(\mu\text{-Cl})_2$ transition state was identified in a recent DFT study focusing on the formation of alkylidenes $\text{RuCl}_2(\text{H}_2\text{IMes})(=\text{CRR}')$ in the reaction of $\text{RuCl}_2(\text{H}_2\text{IMes})$ with olefin.¹⁶ The relatively low energy required to reach transition state **TS-T** (<20 kcal/mol above **Ru-5**) underscores the ease of bimolecular coupling. Ensuing loss of ethylene and trapping by free dianiline affords the methyldene-free product **Ru-6**.

To clarify the orbital interactions that lead to coupling of two molecules of **Ru-A**, we undertook natural bond orbital (NBO) analysis⁴² of intermediate **Ru-S** (Figure 4.8). This analysis suggests that coupling is enabled by two principal orbital interactions. First, electron density is donated from the filled π orbital on $\text{Ru}_\text{B}=\text{C}_\text{B}$ into an empty orbital on Ru_A (Figure 4.8a). This interaction establishes a small, shared electron population between Ru_A and C_B , and between the two Ru atoms (Wiberg index⁴³ 0.14 in each case; Table 4.5). Secondly, as shown in Figure 4.8b, back-donation of electron density from the filled π orbital on $\text{Ru}_\text{A}=\text{C}_\text{A}$ into the π^* orbital on $\text{Ru}_\text{B}=\text{C}_\text{B}$ causes buildup of electron density between C_A and C_B . This interaction is strengthened by polarization of the $\text{Ru}_\text{B}=\text{C}_\text{B}$ π bond towards Ru_B , which results in polarization of the corresponding π^* orbital in the opposite direction. $\text{C} \rightarrow \text{Ru}$ polarization of the alkylidene bond is

consistent with the experimentally-observed electrophilicity of the $[\text{Ru}]=\text{CHR}$ carbon.^{8,9} Previous computational studies,⁴⁴ as well as the present work (Tables 4.6 and 4.7), indicate that this polarization is essentially limited to the π -component of the bond.

NBO analysis of the ensuing transition state **TS-T** reveals the expected enhancement of the two orbital interactions discussed for **Ru-S**. Nevertheless, the shared electron density between the C_A and C_B is low even in **TS-T** (Wiberg index⁴³ of 0.27), indicating that most of the C–C bond is formed subsequent to this transition state.

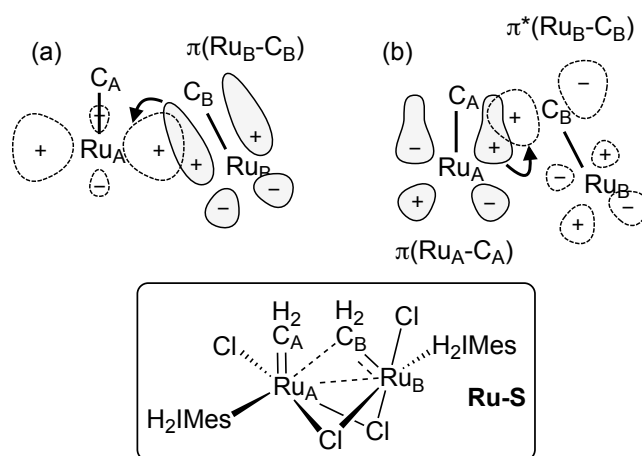


Figure 4.8. Key orbital interactions for Ru-methylidene coupling and C–C bond formation. Dashed lines signify unoccupied orbitals. Charge flow (donation) is indicated by arrows. Atom labeling in intermediate **Ru-S** shown in box.

4.4 Conclusions

Fast initiation has long been connected to fast decomposition in Ru-catalyzed olefin metathesis. Prior studies of highly active, fast-initiating Ru-NHC catalysts identified elimination of propene from the unsubstituted metallacyclobutane as central to decomposition. Bimolecular coupling, in contrast, has been viewed as largely irrelevant for the highly active Ru-NHC catalysts. The foregoing corrects this perspective. Bimolecular coupling can now be recognized as an important contributor to decomposition of fast-initiating ruthenium metathesis catalysts. Improved activity – in particular, higher initiation efficiency – has long been a major focus of catalyst design efforts in Ru-catalyzed metathesis. The present work suggests that such efforts may be undermined by accelerated decomposition. Further, it highlights the importance of inhibiting

bimolecular elimination of the methyldiene ligand in designing new metathesis catalysts or reaction protocols.

4.5 Experimental Details

4.5.1 General Procedures

Reactions were carried out under N₂ in a glovebox or on a Schlenk line. Dichloromethane, benzene, and hexanes were dried and degassed using a Glass Contour solvent purification system. Pentane was distilled over MgSO₄, then P₂O₅. C₆D₆ and CDCl₃ (Cambridge Isotopes) were degassed by five consecutive freeze/pump/thaw cycles. CD₂Cl₂ (Cambridge Isotopes) was received in sealed ampoules packed under N₂. All solvents were stored under N₂ over 4 Å molecular sieves for at least 16 h prior to use. Styrene (Aldrich, 99%), methyl 10-undecenoate (Aldrich, 96%), and D₂O (Cambridge Isotopes) were degassed by five consecutive freeze/pump/thaw cycles, and stored under N₂ at –35 °C. Dimethyl terephthalate (DMT: Aldrich, 99%), trimethoxybenzene (TMB: Aldrich, 99%), anthracene (Aldrich, 97%), pyridine (anhydrous; Aldrich, 99.8%), ethylene (BOC Ultra-High Purity grade 3.0, 99.9%; Linde), and cis-2-butene (Lab Network Inc, 99%) were used as received. *o*-Dianiline ([1,1'-biphenyl]-2,2'-diamine)⁴⁵ RuCl₂(py)₄,⁴⁶ **GIII**,²⁸ **HII**,⁴⁷ **DA**,⁴ and **PII** (as the trifluoromethanesulfonate salt)⁴⁸ were prepared via literature procedures.

NMR spectra were recorded on an Avance 300, Avance II 300, or Avance III 600 cryoprobe NMR spectrometer, at 23 ±2 °C except where otherwise indicated. Chemical shifts are reported in ppm, and referenced against the residual proton or carbon signals of the deuterated solvents (¹H, ¹³C). Overlapping ¹H NMR integrations were deconvoluted using the “deconvolve and display” function in Topspin (NMR processing software; v3.5 pl 5). Oxygen and moisture were excluded from air-sensitive samples using either screw-capped NMR tubes (equipped with PTFE septa, where *o*-dianiline solutions were to be injected) or 3 mm valved J. Young NMR tubes (Figure A47). Infrared (IR) spectra were recorded on a Thermo Scientific Nicolet 6700 Fourier Transform IR spectrometer equipped with a Smart iTR Attenuated Total Reflectance (ATR) sampling accessory. GC-MS analysis was performed using an Agilent 5975B inert XL EI/CI instrument equipped with a polysiloxane column. Anaerobic MALDI mass spectra were collected on a Bruker UltrafleXtreme MALDI-TOF/TOF mass spectrometer interfaced to a

glovebox. Samples were calibrated internally using the peaks for pyrene (m/z 202.0783) and $[\text{H}_2\text{IMes}\cdot\text{H}]^+$ (m/z 307.2174).

The metathesis experiments with methyl 10-undecenoate described below were analyzed by gas chromatography (GC) using an Agilent 7683B series gas chromatograph equipped with an auto-sampler, a flame ionization detector (FID), and an Agilent HP-5 polysiloxane column (30 m length, 320 μm diameter). The inlet temperature was maintained at 250 $^\circ\text{C}$, with a split ratio of 10:1, and He (UHP grade) as the carrier gas. The FID was heated to 275 $^\circ\text{C}$.

4.5.2 Quantification of propenyl species formed during styrene metathesis

To maximize retention of propene, these experiments were conducted in filled J. Young NMR tubes. A small headspace (0.15 mL; ca. 5% of the tube volume) was provided to accommodate any unintended thermal expansion of the solvent in these nominally isothermal (23 $^\circ\text{C}$) experiments.

In a representative reaction, a capillary tube was inserted into a J. Young NMR tube as a mechanical aid to mixing. A solution of **III** (24 mg, 0.038 mmol) and anthracene (ca. 3 mg; internal standard) in 1.46 mL C_6D_6 was added, and a ^1H NMR spectrum was measured to establish the starting ratio of **III** vs anthracene. Styrene (440 μL , 3.8 mmol, 100 equiv) was then added, and the tube was inverted several times to mix the solution. Subsequent controlled mixing was accomplished by attaching the tube to a rotary evaporator, and setting it to rotate at ca. 15 rpm (Figure 4.9). Falling of the internal capillary with every inversion of the tube effects equilibration, and enables accurate, reproducible quantitation. A color change from green to brown occurred, followed by precipitation of a dark green solid over 1 h. Complete loss of **III** was evident at this point. ^1H NMR (C_6D_6 , 300 MHz; diagnostic signals only; Figure A17): δ 16.72 (s, 1H, $[\text{Ru}]=\text{CHAr}$ of **III**; none remaining), 8.19 (s, 2H, Ar CH of anthracene), 7.00 (s, 2H, $=\text{CH}$ of stilbene), 6.58 (dd, $^3J_{\text{HH}} = 18$ Hz, $^3J_{\text{HH}} = 11$ Hz, $=\text{CHPh}$ of styrene), 6.19 (dt, $^3J_{\text{HH}} = 16$ Hz, $^3J_{\text{HH}} = 7$ Hz, 1H, $=\text{CHCH}_2\text{Ph}$ of 1,3-diphenylpropene;¹⁵ not observed), 6.03 (dq, $^3J_{\text{HH}} = 15.9$ Hz, $^3J_{\text{HH}} = 6.8$ Hz, 1H, $=\text{CHCH}_3$ of β -methylstyrene;¹⁵ 12%), 5.27 (s, C_2H_4), 5.01–4.92 (m, three-quarters of the propene $=\text{CH}_2$ pattern;⁴⁹ the remaining multiplet is partially obscured by signal for excess styrene; 18%). The corresponding propenes arising from elimination of the isopropoxyphenyl-substituted metallacyclobutane¹⁵ were not observed, perhaps reflecting the large excess of styrene present in solution. Adding 4 equiv pyridine to the reaction results in

slow dissolution of the green solid, and a colour change to from green to orange. After 24 h: ^1H NMR (C_6D_6 , 300 MHz; diagnostic signals only): δ 9.62 (dt, $^3J_{\text{HH}} = 5.2$ Hz, $^4J_{\text{HH}} = 1.5$ Hz, 4H, py *o*-CH of **Ru-2**, 78%).



Figure 4.9. Time-lapse images showing setup for controlled mixing of filled NMR-tube reactions, using a J. Young NMR tube attached to the rotary evaporator with electrical tape. Efficient, controlled mixing is achieved by rotating at 15 rpm, a rate that enables an internal capillary tube to traverse the entire length of the NMR tube at every inversion.

Quantification of propenyl species formed during styrene metathesis by nG, PII, GIII, and DA. Experiments carried out as in the Representative Procedure above. The yield of propenes was assessed at complete loss of $[\text{Ru}]=\text{CHR}$ (1 h for **HII**, **nG**, **PII**, and **GIII**, and 4 h for **DA**; Table 4.1).

Table 4.1. Yield of propenes by catalyst decomposition during metathesis of styrene (100 equiv).^a

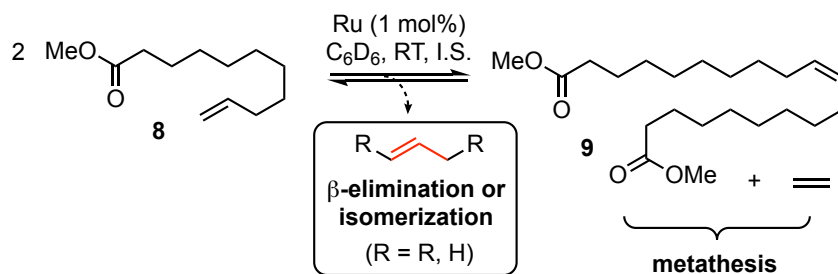
	$\delta_{\text{H}} [\text{Ru}]=\text{CHR}$	Trial 1			Trial 2			Trial 3			average
		% 6	% 7	Σ	% 6	% 7	Σ	% 6	% 7	Σ	%6+7
HII	16.72 (s)	12	18	30	12	19	31	-	-	-	30 $\pm$ 1
nG	16.38 (s)	9	30	39	10	28	38	-	-	-	39 $\pm$ 1
PII	17.83 (d, $^2J_{\text{HP}} = 35.8$ Hz)	0	28	28	0	18	18	0	36	36	27 $\pm$ 9
DA	18.99 (s)	7	19	26	4	20	24	-	-	-	25 $\pm$ 2
GIII	19.66 (s)	0	0	0	0	0	0	-	-	-	0

^aConditions as in Figure 4.1; in C_6D_6 except for **PII** (in CD_2Cl_2 , as **PII** is insoluble in C_6D_6). NMR spectra at 300 MHz; for a representative spectrum, see Figure A17. **6** = β -methylstyrene; **7** = propene. Not observed: 1,3-diphenylpropene, $\text{ArCH}=\text{CHMe}$, $\text{ArCH}=\text{CHCH}_2$ (Ar = isopropoxyphenyl).¹⁵

4.5.3 Quantification of propenyl species formed during methyl 10-undecenoate metathesis

The following experiments were carried out to assess the extent of “false” propenyl products generated via isomerization–metathesis during metathesis of a representative aliphatic 1-olefin (Scheme 4.8). A J. Young tube was charged with **III** (21 mg, 0.034 mmol) and DMT (ca. 1 mg) in 0.70 mL C₆D₆, and methyl 10-undecenoate **8** (1.00 mL, 4.45 mmol, 130 equiv) was added via syringe. The tube was shaken to effect mixing, and the progress of reaction was examined after 1 h, when no further catalyst signals remained

Scheme 4.8. Propenes generated during metathesis of methyl 10-undecenoate **8.**



After 1 h: ¹H NMR (C₆D₆, 300 MHz; diagnostic signals only): δ 16.72 (s, 1H, [Ru]=CHAr of **III**; none remaining), 5.73 (m, 1H, =CHR of **8**), 5.37 (m, 2H, =CHR of **9**), 5.28 (s, 4H, C₂H₄), 4.95 (dq, ³J_{HH} = 17.0, ⁴J_{HH} = 1.8 Hz, 1H, RCH=CH_aH_b of **8**), 4.89 (dm, ³J_{HH} = 10.3 Hz, 1H, RCH=CH_aH_b of **8**), 1.51 (m, 2H, CH₂CH₂CO₂Me of **8**). Signals due to **8** obscure any propene formed (for literature³ values, see text).

GC-FID of **8**: 5.62 (0.1%), 6.07 (0.1%), 6.24 (99.6%, **8**), 6.32 (0.2%) min.

After 1 h: see Table 4.2. The combined yield of assigned chain-lengthened or chain-shortened products is 6%, well above the 0.7% theoretical maximum for β -elimination from metallacyclobutane **Ru-B**.

Table 4.2. GC signals observed in self-metathesis of methyl 10-undecenoate 8.^a

Retention time (min)	Assignment	Area %	Basis of Assignment
5.03	8–28 Da*	0.8	GC-MS
5.63	8–14*	3.0	GC-M
6.19	8	70.8	Co-injection / GC-MS
6.95	8+14*	2.1	GC-MS
10.48	Inconclusive (weak)*	2.0	-
10.53	Inconclusive (weak)*	1.5	-
10.80	(<i>E</i>)-7	17.6	NMR
11.08	Inconclusive (weak)*	0.3	-
11.18	Inconclusive (weak)*	0.5	-
11.37	Inconclusive (weak)*	0.3	-

^a Known or suspected isomerization–metathesis products are denoted with (*).

4.5.4 Identification of Ru species formed on metathesis of styrene by **GIII**

In a representative experiment, a solution of **GIII** (7.3 mg, 0.010 mmol) and anthracene (ca. 1 mg; internal standard) in 385 μL C_6D_6 was added to a J. Young NMR tube. A ^1H NMR spectrum was measured to establish the starting ratio of **GIII** vs anthracene, and styrene (115 μL , 1.0 mmol, 100 equiv) was then added. A colour change from green to orange was observed within the first 30 min, followed by a change back to green. No signals for **GIII** or other $[\text{Ru}]=\text{CHR}$ species were evident after 35 min: ^1H NMR (C_6D_6 , 300 MHz; diagnostic signals only; Figure A18): δ 19.66 (s, 1H, $[\text{Ru}]=\text{CHPh}$ of **GIII**; none remaining), 9.62 (dt, $^3J_{\text{HH}} = 5.2$ Hz, $^4J_{\text{HH}} = 1.5$ Hz, 4H, py *o*-CH of **Ru-2**, 45%), 9.25 (br d, 2H, py *o*-CH of **Ru-3**, 19%), 9.16 (br s, 2H, py *o*-CH of **Ru-2'**, 14%), 8.19 (s, 2H, CH of anthracene). Adding pyridine (5 μL , 6 equiv) effected immediate conversion to **Ru-2** as the sole py species present (98% yield).

^1H NMR data for the individual complexes are given below.

RuCl₂(H₂IMes)(py)₃ Ru-2: ^1H NMR (C_6D_6 , 300 MHz; Figure A21): δ 9.62 (dt, $^3J_{\text{HH}} = 5.2$ Hz, $^4J_{\text{HH}} = 1.5$ Hz, 4H, py *o*-CH), 9.39 (dt, $^3J_{\text{HH}} = 4.9$ Hz, $^4J_{\text{HH}} = 1.6$ Hz, 2H, py *o*-CH), 6.53 (tt, $^3J_{\text{HH}} = 7.5$ Hz, $^4J_{\text{HH}} = 1.6$ Hz, 1H, py *p*-CH), 6.41 (tt, $^3J_{\text{HH}} = 7.4$ Hz, $^4J_{\text{HH}} = 1.5$ Hz, 2H, py *p*-CH), 6.28 (m, 2H, py *m*-CH; overlaps with Mes CH), 6.28 (s, 4H, Mes CH; overlaps with py *m*-CH), 5.98 (m, 4H, py *m*-CH), 3.64 (s, 4H, NCH₂), 2.77 (s, 12H, *o*-CH₃), 1.88 (s, 6H, *p*-CH₃). Values in CD_2Cl_2 are in excellent agreement with those reported in the same solvent.^{8a}

RuCl₂(H₂IMes)(py)₂ Ru-2': ¹H NMR (C₆D₆, 300 MHz; Figure A21): δ 9.42 (br s, 2H, py *o*-CH; overlaps with py *o*-CH of **Ru-2**), 9.15 (br s, 2H, py *o*-CH), 6.67–6.35 (br s, 6H, Mes CH and py CH; overlaps with py *m/p*-CH of **Ru-2**), 6.28 (s, 2H, Mes CH; overlaps with Mes CH of **Ru-2**), 6.03 (br s, 2H, py *m*-CH; overlaps with py *m*-CH of **Ru-2**), 3.48 (br s, 4H, NCH₂), 2.75 (br s, 12H, *o*-CH₃), 1.99 (br s, 6H, *p*-CH₃). ¹H NMR (CD₂Cl₂, 300 MHz): δ 8.94 (br s, 2H, py *o*-CH), 8.60 (br s, 2H, py *o*-CH), 7.51 (br s, 1H, py *p*-CH), 7.25 (s, 1H, py *p*-CH), 7.00 (br s, 2H, py *m*-CH), 6.59 (br s, 2H, py *m*-CH), 6.34 (s, 4H, Mes CH), 3.97 (s, 4H, NCH₂), 2.48 (s, 12H, *o*-CH₃), 2.15 (s, 6H, *p*-CH₃). All ¹H NMR signals for **Ru-2'** are broad (ω_{1/2} ~5–50 Hz) at RT, indicating fluxionality. A monomeric formulation is supported by DOSY-NMR analysis, which shows slightly faster diffusion for **Ru-2'** than **Ru-2**. Key ¹³C NMR signals (located by ¹H–¹³C HMQC; C₆D₆, 300 MHz): 154.0 (py *o*-CH), 152.6 (py *o*-CH), 121.7 (py *m*-CH), 52.4 (NCH₂), 20.6 (Mes *p*-CH₃), 19.2 (Mes *o*-CH₃).

RuCl(H₂IMes)(C₂H₄)(py) Ru-3: ¹H NMR (C₆D₆, 300 MHz; Figure A18): δ 9.30 (br d, ³J_{HH} = 5.3 Hz, 2H, py *o*-CH), 6.63 (py *m*-CH; overlaps with styrene =CH; 2D-detected via COSY), 3.59 (br s, 4H, NCH₂), 3.05 (br s, 3H, Mes CH₃), 2.67 (br s, 3H, Mes CH₃), 2.49 (br s, 6H, Mes CH₃), 2.11 (br s, 3H, Mes CH₃), 1.70 (br s, 3H, Mes CH₃). Signals for Mes CH, py *p*-CH, and C₂H₄ are masked by overlap with **Ru-2/2'** and styrene. ¹H–¹H NOESY: δ 9.30 (py *o*-CH) and 6.63 (py *m*-CH), 9.30 and 2.67 (Mes CH₃). Stirring a mixture of **Ru-2/2'/3** in C₆D₆ at RT under N₂ for 3 h resulted in a colour change from green to orange, and complete consumption of **Ru-3** (Figure A19). At t₀: 45% **Ru-2**, 19% **Ru-2'**, 34% **Ru-3**. After 3 h: 22% **Ru-2**, 66% **Ru-2'**, 0% **Ru-3**; 11% missing Ru. Adding ethylene (1 atm) resulted in reformation of **Ru-3**. After ethylene addition: 51% **Ru-2**, 4% **Ru-2'**, 29% **Ru-3**; 16% missing Ru.

4.5.5 Bimolecular Coupling of **GIII**

In a representative reaction, solid **GIII** (9.6 mg, 0.013 mmol) and ca. 1 mg DMT were dissolved in 0.66 mL C₆D₆ in a J. Young NMR tube, to give a final Ru concentration of 20 mM. A ¹H NMR spectrum was recorded to establish the initial integration ratio of **GIII** relative to DMT. The NMR tube was heated to 60 °C in a thermostatted oil bath, and decomposition of **GIII** was monitored by ¹H NMR analysis over 5 d, during which time the color changed from green to orange. After this time, no **GIII** remained. ¹H NMR (C₆D₆, 300 MHz; diagnostic signals; Figures A20, A21): δ 19.66 (s, 1H, [Ru]=CHPh of **GIII**; none remaining), 9.62 (dt, ³J_{HH} = 5.2 Hz, ⁴J_{HH} =

1.5 Hz, 4H, py *o*-CH of **Ru-2**; 34%), 9.16 (br d, $^3J_{\text{HH}} = 4.2$ Hz, 2H, py *o*-CH of **Ru-2'**; 28%), 9.06 (dt, $^3J_{\text{HH}} = 5$ Hz, $^4J_{\text{HH}} = 1.5$ Hz, 8H, py *o*-CH of **Ru-4**; 1.6%), 8.00 (s, 4H, CH of DMT), 7.33 (m, 4H, *o*-CH of (*E*)-stilbene; 74%), 7.24 (m, 4H, *o*-CH of (*Z*)-stilbene; none present).

(*E*)-*PhCH=CHPh*: ^1H NMR (C_6D_6 , 300 MHz): δ 7.33 (m, 4H, *o*-CH), 7.17 (m, 4H, *m*-CH), 7.08 (m, 2H, *p*-CH), 7.01 (s, 2H, =CH). EI MS, m/z : [M^+] 180.1 (simulated: 180.1 for $\text{C}_{14}\text{H}_{12}$). The ^1H NMR and GC-MS data matched those of a commercial sample (Sigma-Aldrich).

(*Z*)-*PhCH=CHPh* (Alfa Aesar, not observed): ^1H NMR (C_6D_6 , 300 MHz): δ_{H} 7.24 (m, 4H, *o*-CH), 7.06–6.93 (m, 6H, *m*- and *p*-CH), 6.47 (s, 2H, =CH).

4.5.6 Synthesis of $\text{RuCl}_2(\text{H}_2\text{IMes})(\text{py})_2(=\text{CHMe)$, **GIIf**

Synthesis of **GIIf** was carried out by a modified version of the method reported¹⁷ for the 3-bromopyridine analog. Decomposition of **GIIf** was minimized by performing the reaction in C_6H_6 at near-freezing temperatures, and then subliming the solvent by freeze-drying. On the Schlenk line, a solution of **GIIf** (100 mg, 0.138 mmol) in C_6H_6 (2 mL) was freeze/pump/thaw degassed, then thawed at 6 °C. Cis-2-butene (1 atm) was admitted via the side-arm of the Schlenk flask, and the reaction was stirred for 10 min, over which time it turned from green to brown, and a red-brown solid precipitated. Pyridine (100 μL) was then injected, and the solution was frozen and lyophilized. The resulting tan powder was suspended in pentane (2 mL) in the glovebox, filtered, washed with pentane (3 x 1 mL), and dried in vacuo. Repeating the entire process with the crude product afforded **GIIf** as a reddish-tan powder (85 mg, 93%), containing trace **Ru-2** and **GIIf** (each $\leq 1\%$). Re-subjecting to reaction with butene, or reprecipitating from CH_2Cl_2 –pentane at 0 °C, led to competing decomposition. **GIIf** is sufficiently stable to observe at RT by ^1H NMR spectroscopy, but its spectrum degrades noticeably over the longer collection times required for ^{13}C NMR analysis (3–4 h).

^1H NMR (C_6D_6 , 300 MHz, Figure A22): δ 19.53 (q, $^3J_{\text{HH}} = 5.9$ Hz, [Ru]=CHMe), 8.64 (br s, 4H, py *o*-CH), 6.78 (s, 2H, Mes CH), 6.75 (s, 2H, Mes CH), 6.71 (br s, 2H, py *p*-CH), 6.42 (br s, 4H, py *m*-CH), 3.50–3.37 (m, 2H, NCH_2), 3.37–3.23 (m, 2H, NCH_2), 2.78 (s, 6H, Mes CH_3), 2.57 (s, 6H, Mes CH_3), 2.11 (br s, 3H, Mes CH_3), 2.10 (d, $^3J_{\text{HH}} = 5.9$ Hz, 3H, [Ru]=CHCH₃; overlaps with Mes CH_3), 2.06 (br s, 3H, Mes CH_3).

^1H NMR (CDCl_3 , 300 MHz, $-20\text{ }^\circ\text{C}$): δ 19.10 (br q, $^3J_{\text{HH}} = 5.7\text{ Hz}$, $[\text{Ru}]=\text{CHMe}$), 8.70 (br d, $^3J_{\text{HH}} = 3.7\text{ Hz}$, 2H, py *o*-CH), 8.06 (br s, 2H, py *o*-CH), 7.52 (br t, $^3J_{\text{HH}} = 7.5\text{ Hz}$, 1H, py *p*-CH), 7.43 (br t, $^3J_{\text{HH}} = 6.6\text{ Hz}$, 1H, py *p*-CH), 7.06 (br s, 2H, py *m*-CH), 6.96 (br s, 4H, Mes CH), 6.79 (br s, 2H, py *m*-CH), 4.20–4.02 (m, 2H, NCH_2), 4.04–3.87 (m, 2H, NCH_2), 2.55 (s, 6H, Mes CH_3), 2.42 (s, 6H, Mes CH_3), 2.32 (br s, 3H, Mes CH_3), 2.21 (br s, 3H, Mes CH_3), 1.72 (d, $^3J_{\text{HH}} = 5.7\text{ Hz}$, $[\text{Ru}]=\text{CHCH}_3$, 3H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 300 MHz, $-20\text{ }^\circ\text{C}$; Figure A23): δ 330.1 ($[\text{Ru}]=\text{CHMe}$; ^1H -detected via HSQC), 219.4 (C_{NHC}), 150.8 (py *o*-CH), 149.9 (py *o*-CH), 139.0, 138.5, 138.1, 137.9, 136.4, 136.2 (py *p*-CH), 135.0 (py *p*-CH), 129.2 (Mes CH), 128.9 (py *m*-CH), 128.2, 123.5 (Mes CH), 123.2 (py *m*-CH), 51.0 (NCH_2), 50.7 (NCH_2), 46.4 ($[\text{Ru}]=\text{CHCH}_3$), 21.1 (Mes CH_3), 20.9 (Mes CH_3), 19.7 (Mes CH_3), 18.5 (Mes CH_3). IR (ATR, cm^{-1}): $\nu(\text{C-H})$ 2864 (w), $\nu(\text{CH}_3)$ 1484 (m), $\nu(\text{CH}_3)$ 1405. MALDI-TOF MS (pyrene matrix), m/z : $[\text{RuCl}(\text{H}_2\text{IMes})(\text{pyrene})]^{*+}$ 645.12 (42%; calc'd: 645.16), $[\text{Ru}(\text{H}_2\text{IMes-H})(\text{pyrene})]^{*+}$ 609.14 (67%; calc'd: 609.18), $[\text{RuCl}(\text{H}_2\text{IMes-H})]^{*+}$ 442.05 (100%; calc'd: 442.08). Sample decomposition precluded satisfactory microanalysis.

4.5.7 Bimolecular Coupling of **GIIIe**: Quantification of Butene and Ru-2/2'

Caution! Thermal expansion in these variable-temperature experiments results in an explosion hazard, because it is essential to minimize the headspace in the NMR tube in order to measure as much as possible of the volatile products evolved (e.g., propene, butene). To minimize this risk, the headspace volume required to accommodate thermal expansion of the solvent and evolution of butene was calculated (see SI), and quadrupled to provide a safety margin. Any potential for damage to personnel or the NMR probe was limited further by warming the sample only behind a blast shield (not in the probe), and using a face shield when transferring the tube to and from the NMR probe.

In a representative experiment, a solution of **GIIIe** (13.9 mg, 0.0209 mmol) and DMT (ca. 1 mg) in C_6D_6 (2.75 mL) was added to a J. Young tube. A ^1H NMR spectrum was recorded to establish the initial integration ratio of **GIIIe** relative to DMT. The full length of the NMR tube was heated to $60\text{ }^\circ\text{C}$ in a thermostatted water bath behind a blast shield. A colour change from brown to orange was observed within 25 min. After this time, the tube was removed from the $60\text{ }^\circ\text{C}$ bath, cooled in a room-temperature water bath (1 min), and then immediately inserted into the probe for ^1H NMR analysis.

^1H NMR (C_6D_6 , 300 MHz; diagnostic signals; Figures A24–A26): δ 19.53 (q, $^3J_{\text{HH}} = 5.9$ Hz, $[\text{Ru}]=\text{CHMe}$; none remaining), 9.62 (dt, $^3J_{\text{HH}} = 5.2$ Hz, $^4J_{\text{HH}} = 1.5$ Hz, 4H, py *o*-CH of **Ru-2**; 30%), 9.16 (br d, $^3J_{\text{HH}} = 4.2$ Hz, 2H, py *o*-CH of **Ru-2'**; 48%), 8.00 (s, 4H, CH of DMT), 5.52–5.30 (overlapping m, 2H, $=\text{CH}$ of (*E*)/(*Z*)-2-butene and 2-pentene, 53% total), 5.25 (s, 4H, C_2H_4 , <1%), 5.06–4.90 (m, 2H, $=\text{CH}_2$ of propene, 23%). The overlapping olefinic signals for 2-butene and 2-pentene were deconvoluted by re-running the spectrum at 600 MHz (Figure A25). The observed proportion of butene, pentene, and propene increased on warming the sample to 60 °C in the probe, perhaps reflecting pressure buildup in the headspace on warming. ^1H NMR (C_6D_6 , 300 MHz, 60 °C; diagnostic signals): δ 5.52–5.30 (m, 2H, $=\text{CH}$ of (*E*)/(*Z*)-butene and 2-pentene, 69%), 5.06–4.88 (m, 2H, $=\text{CH}_2$ of propene, 24%). Adding 2 equiv pyridine to the reaction resulted in conversion of the Ru products to **Ru-2** (85%). The identities of the butene, pentene, and propene products were confirmed by ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR, ^1H – ^1H COSY, ^1H – ^{13}C HSQC, and ^1H – ^{13}C HMBC analysis. The key NMR shifts are provided below.

(E)-2-butene: ^1H NMR (C_6D_6 , 600 MHz): δ 5.38 (m, 2H, $=\text{CH}$), 1.57 (m, 6H, CH_3). $^{13}\text{C}\{^1\text{H}\}$ NMR (C_6D_6 , 150 MHz): δ 124.5, 17.8. *(Z)*-2-butene: ^1H NMR (C_6D_6 , 600 MHz): δ 5.48 (m, 2H, $=\text{CH}$), 1.51 (d, $^3J_{\text{HH}} = 5.0$ Hz, 6H, CH_3). $^{13}\text{C}\{^1\text{H}\}$ NMR (C_6D_6 , 150 MHz): δ 125.7, 12.0. The NMR signals are slightly shifted relative to the reported values in CDCl_3 ,⁵⁰ but are otherwise in good agreement.

Propene: ^1H NMR (C_6D_6 , 600 MHz): δ 5.76–5.67 (m, 1H, $=\text{CH}$), 5.01 (dm, $^3J_{\text{HH}} = 17.0$ Hz, $=\text{CH}_2$), 4.95 (dm, $^3J_{\text{HH}} = 10.3$ Hz, $=\text{CH}_2$), 1.55 (dt, $^3J_{\text{HH}} = 6.5$ Hz, $^4J_{\text{HH}} = 1.5$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (C_6D_6 , 150 MHz): δ 134.0 ($=\text{CH}$), 115.6 ($=\text{CH}_2$), 19.4 (CH_3). The observed shifts are in excellent agreement with the reported values.⁴⁹

(E)-2-pentene: ^1H NMR (C_6D_6 , 600 MHz): δ 5.52–5.33 (m, 2H, $=\text{CH}$), 1.94 (dq, $^3J_{\text{HH}} = 7.5$ Hz, $^3J_{\text{HH}} = 1.3$ Hz, 2H, $=\text{CHCH}_2$). $^{13}\text{C}\{^1\text{H}\}$ NMR (C_6D_6 , 150 MHz): δ 133.0 ($=\text{CH}$), 122.8 ($=\text{CH}$), 26.0 ($=\text{CHCH}_2$). The NMR signals are slightly shifted relative to the reported values in CDCl_3 , but are otherwise in good agreement.⁵¹ A predominantly (*E*)-configuration is assigned on the basis of the downfield location of the $=\text{CHCH}_2$ singlet (δ_{C} 26.0, vs. 25.2 in CDCl_3 ; cf. 20.0 for (*Z*)-pentene in CDCl_3).⁵¹

4.5.8 NMR-scale synthesis of $\text{RuCl}_2(\text{H}_2\text{IMes})(\text{o-dianiline})(=\text{CH}_2)$, **Ru-5**

(a) *In situ* generation of metallacyclobutane **Ru-B**. In a representative experiment, the Piers catalyst **PII** (23.9 mg, 0.0260 mmol) and dimethyl terephthalate (DMT; internal standard; ca. 0.5 mg) were dissolved in 0.65 mL CD_2Cl_2 in a screw-cap NMR tube (Figure A47), to give a final Ru concentration of 40 mM. The solution was frozen with $\text{N}_2(\text{l})$, and the tube was evacuated via a needle connected to the Schlenk line. The solution was thawed under static vacuum at -50°C (MeCN–dry ice bath). Ethylene (1 atm) was introduced, the pierced septum was protected with a dab of grease and Parafilm, and the full length of the NMR tube was immersed in the cold-bath. After 1–2 min, the NMR tube was removed, shaken rapidly (1–2 sec), and returned to the cold-bath. Repeating this mixing procedure 3–4x caused the solution to change colour from dark brown to intense dark pink. ^1H NMR (CD_2Cl_2 , 300 MHz, -50°C ; diagnostic signals for integration; Figures 4.3 and A27): δ 18.00 (d, $^2J_{\text{HP}} = 36.8$ Hz, 1H, $[\text{Ru}]=\text{CHPCy}_3$ of **PII**, none remaining), 8.09 (s, 4H, CH of DMT), 6.44–6.01 (m, 2H, $=\text{CH}_2$ of $[\text{H}_2\text{C}=\text{CHPCy}_3]^+$; 100%), -2.64 (br s, 2H, H_β , **Ru-B**; 100%). The ^1H NMR data for **Ru-B** and $[\text{H}_2\text{C}=\text{CHPCy}_3]\text{OTf}$ (the organic product of ethenolysis) are shifted slightly relative to the reported values,⁴ but are otherwise in good agreement.

$\text{RuCl}_2(\text{H}_2\text{IMes})(\kappa^2\text{-C}_3\text{H}_6)$, Ru-B. ^1H NMR (CD_2Cl_2 , 300 MHz, -50°C): δ 6.91 (s, 4H, Mes CH), 6.67 (m, 4H, H_α), 4.28 (s, 4H, NCH_2), 2.45 (s, 12H, Mes o-CH_3), 2.28 (s, 6H, Mes p-CH_3), -2.64 (br s, 2H, H_β).

$[\text{H}_2\text{C}=\text{CHPCy}_3]\text{OTf}$. ^1H NMR (CD_2Cl_2 , 300 MHz, -50°C): δ 6.76 (dd, $^3J_{\text{HP}} = 41.3$ Hz, $^3J_{\text{HH}} = 13.4$ Hz, 1H, $=\text{CH}_2$; overlaps with H_α of **Ru-B**), 6.44–6.01 (m, 2H, $=\text{CH}_2$ and $=\text{CHPCy}_3$), 2.50 (m, 3H, PCH ; overlaps with Mes o-CH_3 of **Ru-B**), 2.00–1.64 (m, 15H, Cy), 1.57–1.13 (m, 15H, Cy). $^{13}\text{C}\{^1\text{H}\}$ NMR (CD_2Cl_2 , 77.5 MHz, 23°C ; cation only): δ 142.7 (s, $\text{H}_2\text{C}=\text{CHP}$), 114.1 (d, $^1J_{\text{PC}} = 70.6$ Hz, $\text{H}_2\text{C}=\text{CHP}$), 29.7 (d, $^1J_{\text{PC}} = 42.4$ Hz, 3C, Cy), 26.5–26.0 (overlapping, 12C, Cy), 25.2 (d, $^4J_{\text{PC}} = 1.4$ Hz, 3C, Cy).

^1H NMR (CDCl_3 , 300 MHz, -50°C): δ 6.76 (dd, $^3J_{\text{HP}} = 41.3$ Hz, $^3J_{\text{HH}} = 11.7$ Hz, 1H, $=\text{CH}_2$; overlaps with H_α of **Ru-B**), 6.48–6.19 (m, 2H, $=\text{CH}_2$ and $=\text{CHPCy}_3$), 2.37 (br m, 3H, PCH), 2.03–1.62 (m, 15H, Cy), 1.60–1.13 (m, 15H, Cy). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 77.5 MHz, -50°C ; cation only): δ 142.8 (s, $\text{H}_2\text{C}=\text{CHP}$), 114.3 (d, $^1J_{\text{PC}} = 70.1$ Hz, $\text{H}_2\text{C}=\text{CHP}$), 29.1 (d, $^1J_{\text{PC}} = 42.8$ Hz, Cy), 26.3 (s, Cy), 26.2 (d, $^2J_{\text{PC}} = 9.0$ Hz, 6C, Cy), 25.3 (s, Cy).

(b) *Transformation of Ru-B into methyldiene adduct Ru-5.* In the second step of reaction, a solution of *o*-dianiline (5.3 mg, 0.029 mmol, 1.1 equiv) in CD₂Cl₂ (50 μL) was dribbled down the cold internal surface of the NMR tube at –50 °C, at a rate sufficiently slow to chill it over the timescale of addition (ca. 1 min). The solution was agitated as above, and returned to the cold-bath. A colour change to green was observed over ca. 30 min, accompanied by the disappearance of signals for **Ru-B**, and appearance of signals for **Ru-5**. ¹H NMR (CD₂Cl₂, 300 MHz, –50 °C, 30 min; diagnostic signals for reaction progress, excluding those for the phosphonium salt): δ 19.34 (s, 2H, [Ru]=CH₂ of **Ru-5**; 97%), 8.09 (s, 4H, CH of DMT), –2.62 (br s, 2H, H_β, **Ru-B**; <1% remaining).

RuCl₂(H₂IMes)(*o*-dianiline)(=CH₂), Ru-5. ¹H NMR (CD₂Cl₂, 300 MHz, –50 °C): δ 19.34 (s, 2H, [Ru]=CH₂), 7.39 (s, 1H, Mes CH), 7.32–6.74 (m, Mes CH, *o*-dianiline CH), 6.51 (br d, ³J_{HH} = 6.9 Hz, 1H, *o*-dianiline CH), 6.42 (br d, 1H, *o*-dianiline CH; overlaps with =CH of [H₂C=CHPCy₃]), 4.29 (br s, 2H, NH₂), 4.06–3.70 (m, 4H, NCH₂), 3.56 (br s, 2H, NH₂), 2.62 (s, 3H, CH₃), 2.48 (s, 3H, CH₃), 2.32 (s, 9H, CH₃), 2.19 (s, 3H, CH₃).

4.5.9 Synthesis of RuCl₂(H₂IMes)(*o*-dianiline)(=CH₂), Ru-5

In a 10 mL Schlenk flask, a 60 mM solution of **PII** (75 mg, 0.081 mmol) in CH₂Cl₂ (1.10 mL) was prepared and frozen in N₂(*l*). The headspace was evacuated, the flask was sealed, and the solution was allowed to thaw at –50 °C. Ethylene gas (1 atm) was then admitted via the side-arm, after which the flask was sealed again, and the reaction was stirred at –50 °C for 10 min, over which time the colour changed from dark brown to bright pink. A solution of *o*-dianiline (15.8 mg, 0.0855 mmol, 1.05 equiv) in CH₂Cl₂ (250 μL) was then added dropwise. Care was taken to dribble the solution down the cold wall of the flask, to avoid warming the reaction mixture. A colour change from pink to green occurred within 10 min. The solution was stirred for an additional 20 min, then cooled further to –78 °C (acetone–dry ice), after which cold pentane (30 mL; –78 °C) was added via cannula. To avoid warming, the cannula was kept cold with dry ice. The resulting precipitate was decanted and dried in vacuo to afford 74 mg of a pale green solid containing a near-equimolar mixture (1.2:1.0) of **Ru-5** and [H₂C=CHPCy₃]OTf,^{10a} with ca. 10–15% unidentified Ru-H₂IMes impurities. Yield of crude **Ru-5**: 75%. Attempts at reprecipitation or washing caused decomposition into **Ru-6**. Given below are NMR details for **Ru-5** alone; those for the phosphonium salt appear in the supporting information.

^1H NMR (CDCl_3 , 300 MHz, $-50\text{ }^\circ\text{C}$; Figure A28): δ 19.46 (s, 2H, $[\text{Ru}]=\text{CH}_2$), 7.39 (s, 1H, Mes CH), 7.32–6.92 (m, 13H, Mes CH and *o*-dianiline CH; overlaps with residual CHCl_3), 6.57 (br d, $^3J_{\text{HH}} = 7.8\text{ Hz}$, 1H, *o*-dianiline CH), 6.44 (br d, $^3J_{\text{HH}} = 7.8\text{ Hz}$, 1H, *o*-dianiline CH), 4.37 (br s, 2H, NH_2), 4.14–3.70 (m, 4H, NCH_2), 3.68 (br s, 1H, NH_aH_b), 3.41 (br s, 1H, NH_aH_b), 2.67 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 2.35 and 2.34 (overlapping s, 9H, CH_3), 2.23 (s, 3H, CH_3). Assignment of the NH_2 signals was confirmed by adding ca. 5 μL D_2O at $-50\text{ }^\circ\text{C}$, and rapidly shaking the tube (1-2 sec) before re-immersing in the cold-bath.

$^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 77.5 MHz, $-50\text{ }^\circ\text{C}$; Figure A29): δ 314.2 ($[\text{Ru}]=\text{CH}_2$, ^1H -detected by HMQC), 218.5 (C_{NHC}), 143.6, 139.8, 139.0, 138.9, 138.6, 138.4, 137.1, 134.8, 134.3, 131.1, 130.6, 130.4, 129.4, 129.2, 128.9, 128.4, 119.1, 115.8, 50.6 (NCH_2), 49.8 (NCH_2), 21.5 (CH_3), 21.4 (CH_3), 19.2 (CH_3), 19.0 (CH_3), 18.6 (CH_3), 18.5 (CH_3).

4.5.10 Synthesis of $\text{RuCl}_2(\text{H}_2\text{IMes})(\text{py})_n(=\text{CH}_2)$ (**GIII m** : $n = 2$; **GIII m'** : $n = 1$)

The synthesis was undertaken using the method for **Ru-5** above, with several modifications to prevent decomposition and enable precipitation of the product: (i) use of lower temperatures (down to $-116\text{ }^\circ\text{C}$); (ii) immediate workup after adding pyridine; and (iii) higher Ru concentrations (ca. 110 mM starting **PII**), to aid in precipitating the product. Use of stoichiometric pyridine was likewise essential, to prevent oiling out of the product.

In a 10 mL Schlenk flask, a 110 mM solution of **PII** (60 mg, 0.065 mmol) in CH_2Cl_2 (0.60 mL) was prepared and frozen in $\text{N}_2(l)$. The headspace was evacuated, the flask was sealed, and the solution was allowed to thaw at $-50\text{ }^\circ\text{C}$. Ethylene gas (1 atm) was then admitted via the side-arm, after which the flask was sealed again, and the reaction was stirred at $-50\text{ }^\circ\text{C}$ for 10 min. A colour change from dark brown to bright pink occurred over this time. The solution was cooled further, to $-78\text{ }^\circ\text{C}$, and a solution of pyridine (10.3 μL , 0.132 mmol, 2.0 equiv) in pentane (150 μL) was added dropwise. A colour change from pink to green occurred over the course of the addition. Cold pentane (8 mL; $-116\text{ }^\circ\text{C}$; $\text{N}_2(l)$ –ethanol bath) was then added via a cannula chilled with dry ice. The resulting precipitate was decanted and dried in vacuo to afford 59 mg of the mustard-yellow product accompanied by $[\text{H}_2\text{C}=\text{CHPCy}_3]\text{Cl}$, in a 2:3 ratio. Also present are unidentified Ru- H_2IMes impurities, which give rise to additional mesityl CH_3 peaks (Figure A33). Integration of the alkylidene singlets at $-50\text{ }^\circ\text{C}$ indicates a ca. 1:2 ratio of **GIII m** and

GIII^m'. Crude yield: ca. 60% based on **GIII^m/m'**. Attempts to purify by washing with cold pentane (−116 °C) afforded no improvement. ¹H NMR analysis was carried out at 0 °C in CDCl₃ (in which the complex is more stable than in CD₂Cl₂). Exchange averaging at this temperature results in a single alkylidene peak, greatly simplifying analysis. Sample decomposition occurs over 3–4 h, precluding ¹³C{¹H} NMR analysis.

¹H NMR (CDCl₃, 300 MHz, 0 °C; Figure A33): δ 18.83 (s, 2H, [Ru]=CH₂), 8.67 (br s, 0.6H, py *o*-CH), 7.82 (br s, 2H, py *o*-CH), 7.51 (br s, 0.6H, py *m*-CH), 7.37 (br t, 0.3H, ³J_{HH} = 7.0 Hz, py *p*-CH), 7.15 (br t, ³J_{HH} = 7.0 Hz, 1H, py *p*-CH), 7.01 (s, 4H, Mes CH and py *m*-CH), 6.95 (s, 2H, Mes CH), 4.12 (m, 2H, NCH₂), 4.02 (m, 2H, NCH₂), 2.55 (s, 6H, CH₃), 2.35 (s, 6H, CH₃), 2.32 (s, 6H, CH₃). Exchange averaging of the bis- and mono-pyridine complexes results in a single set of signals at 0 °C (as also seen for **GIII** and its mono-pyridine derivative **GIII'**; see below). At −50 °C, pyridine exchange is retarded and two sets of signals emerge. ¹H NMR (CDCl₃, −50 °C; key signals only): δ 19.35 (br s, [Ru]=CH₂ for **GIII^m**, 30%), 18.63 (br s, [Ru]=CH₂ for **GIII^m'**, 70%). Adding pyridine (10 μL) to the NMR sample at −50 °C caused clean conversion to **GIII^m**. Key ¹³C NMR signals (detected via ¹H–¹³C HMQC in CDCl₃ at 0 °C): 305.1 (s, [Ru]=CH₂), 129.7 (s, Mes CH), 129.4 (s, Mes CH), 51.1 (s, NCH₂), 49.9 (s, NCH₂).

4.5.11 Bimolecular coupling of Ru-5: quantification of ethylene and formation of Ru-6

These experiments were carried out with the precautions against explosion described above. The sample was prepared in the glovebox, so that the septum-sealed, screw-capped NMR tube could be replaced with a J. Young NMR tube (see Figure A47; 2.15 mL capacity), and perturbation by oxygen could be more rigorously inhibited. While the lower operating temperature is then limited to −35 °C (the temperature of the glovebox freezer), this was deemed acceptable given rapid manipulation, as decomposition commences only at ca. −10 °C. In a representative experiment, crude **Ru-5** (ca. 30 mg, 0.022 mmol) and 1.7 mg DMT (40 μL of a 0.22 M stock solution in CD₂Cl₂) were added to a cold NMR tube bedded in a chilled (−35 °C) sand-bath. Cold CD₂Cl₂ (1.72 mL; used instead of C₇D₈ to improve the solubility of **Ru-5**) was added, and the solution was mixed using a chilled pipette. The tube was sealed, transferred to the instrument room in an ethylene glycol–dry ice bath (−20 °C), and inserted into an NMR probe pre-cooled to −20 °C, to measure the initial integration ratio of **Ru-5** vs. DMT. The sample was then ejected from the NMR probe, mixed briefly by shaking, and allowed to warm in a 23 °C water bath

(blast shield; see above). Decomposition of **Ru-5** was monitored over 1 h at RT (^1H NMR). During this time the colour changed from green to brown. After 6 min: ^1H NMR (CD_2Cl_2 , 300 MHz, RT; diagnostic signals only): δ 19.53 (s, 2H, $[\text{Ru}]=\text{CH}_2$ of **Ru-5**; 27%), 8.09 (s, 4H, CH of DMT), 5.40 (s, 4H, C_2H_4 ; 63%), 4.91 (d, $^2J_{\text{HH}} = 10.3$ Hz, 1H, NH_2 of **Ru-6**; 55%). At 1 h: 2% **Ru-5**, 52% C_2H_4 , 61% **Ru-6**. At 85 min: no **Ru-5** remaining, 53% C_2H_4 , 55% **Ru-6**.

$\text{RuCl}_2(\text{H}_2\text{IMes})(o\text{-dianiline})$ Ru-6. ^1H NMR (CD_2Cl_2 , 300 MHz; Figure A31): δ 7.29–6.95 (m, 9H, Ar CH of *o*-dianiline and Mes CH), 6.94 (s, 2H, Mes CH), 6.86 (d, 1H, $^3J_{\text{HH}} = 7.7$ Hz, Ar CH of *o*-dianiline), 6.18 (m, 1H, Ar CH of *o*-dianiline), 4.89 (d, $^2J_{\text{HH}} = 10.4$ Hz, 1H, NH_aH_b), 4.20 (d, $^2J_{\text{HH}} = 10.4$ Hz, 1H, NH_aH_b), 4.12–3.89 (m, 6H, NCH_2 and NH_aH_b), 2.56 (br s, 6H, Mes *o*- CH_3), 2.41 (s, 6H, Mes *o*- CH_3), 2.25 (s, 6H, Mes *p*- CH_3). The two NH doublets that overlap with the backbone NCH_2 protons of H_2IMes were located from their ^1H – ^1H COSY correlations with the well-separated NH signals further downfield. The diastereotopic NH_aH_b pairs thus identified appear at: 4.89 / 3.95 ppm, and 4.20 / 4.04 ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (CH_2Cl_2 , 77.5 MHz; Figure A32): δ 213.8 (C_{NHC}), 140.0, 139.7, 138.9 (br), 138.3 (br), 138.0, 130.7, 129.8 (br), 129.8 (Mes CH), 129.7, 129.4, 128.1, 127.9, 127.54, 127.45, 124.8, 124.2, 123.7, 122.9, 122.6, 122.3, 52.3 (NCH_2), 20.6 (Mes *p*- CH_3), 18.6 (br, Mes *o*- CH_3), 18.3 (Mes *o*- CH_3). MALDI-TOF MS (pyrene matrix), m/z : [**Ru-6**–H] $^+$ 661.141 (calc'd: 661.144).

4.5.12 Bimolecular coupling of **GIIIm**: quantification of ethylene (Figure A34)

Experiment carried out as for **Ru-5** above, using solid **GIIIm**/**m'** (ca. 60 mg, 0.038 mmol) and TMB (0.47 mg) in CD_2Cl_2 (1.72 mL). After 20 min: δ 18.80 (s, 2H, $[\text{Ru}]=\text{CH}_2$ of **GIIIm**; none remaining), 8.99 (br d, $^2J_{\text{HH}} = 5.6$ Hz, 2H, py *o*-CH of **Ru-2**, 12%), 8.60 (br s, 2H, py *o*-CH of **Ru-2'**, 4%), 6.07 (s, 3H, Ar CH of TMB), 5.40 (s, 4H, C_2H_4 ; 70%).

4.5.13 Kinetic studies

The rate of disappearance of the methylidene signal for **Ru-5** vs. DMT internal standard was measured as in the ethylene quantitation experiments above, but using a standard NMR-tube headspace, as quantification of evolved gases is irrelevant.

*Kinetics at High $[\text{Ru}]_0$ (ca. 20 mM **Ru-5**).* A J. Young tube was chilled in a sand-bath in the glovebox, loaded with solid **Ru-5** (17 mg, 0.012 mmol), cold CD_2Cl_2 (600 μL), and DMT (ca. 1 mg) in the glovebox, to give a Ru concentration of approximately 20 mM (based on **Ru-5** is 48%

pure, based on ^1H NMR analysis indicating 1.15 equiv $[\text{H}_2\text{C}=\text{CHPCy}_3]\text{OTf}$ and ca. 15% Ru- H_2IMes impurities in this particular sample). Decomposition of **Ru-5** was monitored over three half-lives. A linear dependence on $[\text{Ru-5}]^{-1}$ (Figures 4.6 and 4.10) indicates that coupling is second-order at this concentration ($k_{\text{obs}} = 0.12 \pm 0.02 \text{ M}^{-1} \text{ s}^{-1}$, based on two trials).

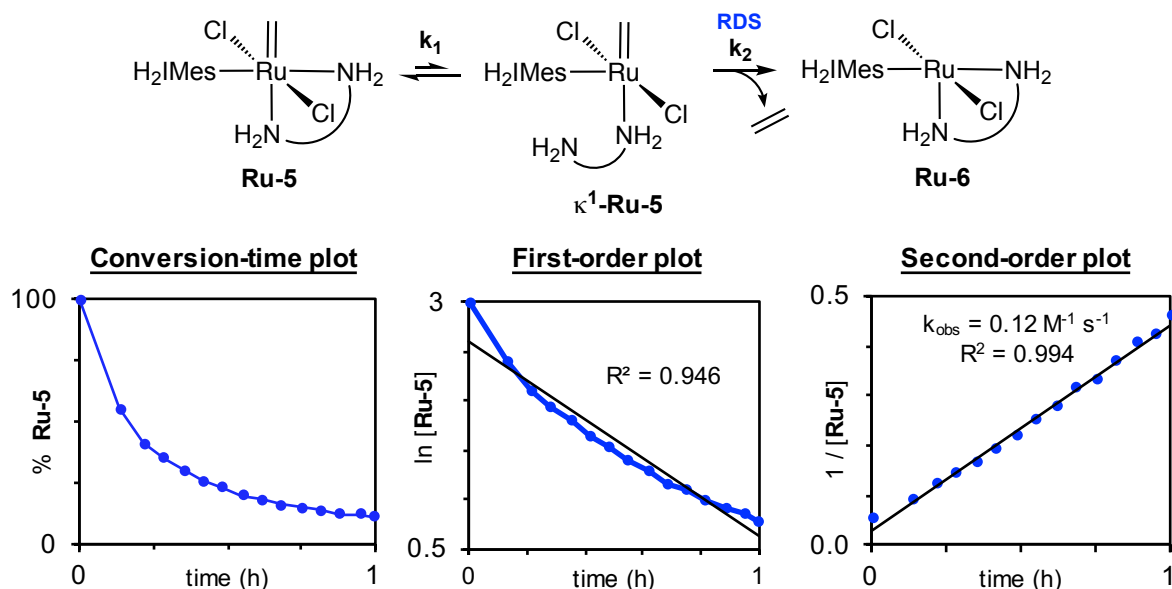


Figure 4.10. Exemplary kinetic plots for bimolecular coupling of **Ru-5** at high initial concentrations (20 mM **[Ru-5]**). Experiments in CD_2Cl_2 at 23 °C; $\text{H}_2\text{N}-\text{NH}_2 = o\text{-dianiline}$. The conversion–time and second-order plots are reproduced from Figure 4.6 above, for ease of reference. K_{obs} values shown are the average of two trials.

*Kinetics at Low $[\text{Ru}]_0$ (ca. 1 mM **Ru-5**).* As above, but with ca. 1 mg solid **Ru-5** and DMT (0.024 mg, 0.125 nmol; 5.0 μL of a 26 mM stock solution in CD_2Cl_2) in 600 μL CD_2Cl_2 . A starting Ru concentration of ca. 1 mM was established via integration of the methylidene singlet vs. DMT at -20 °C. Decomposition of **Ru-5** was monitored at $+10$ °C to permit collection of sufficient scans for good signal-to-noise ratios (Figures 4.6 and 4.11). Analysis as above revealed a linear dependence on $\ln[\text{Ru-5}]$, indicating that bimolecular coupling is first-order in **Ru-5** at low concentrations ($k_{\text{obs}} = (1.9 \pm 0.3) \times 10^{-4} \text{ s}^{-1}$, based on two trials).

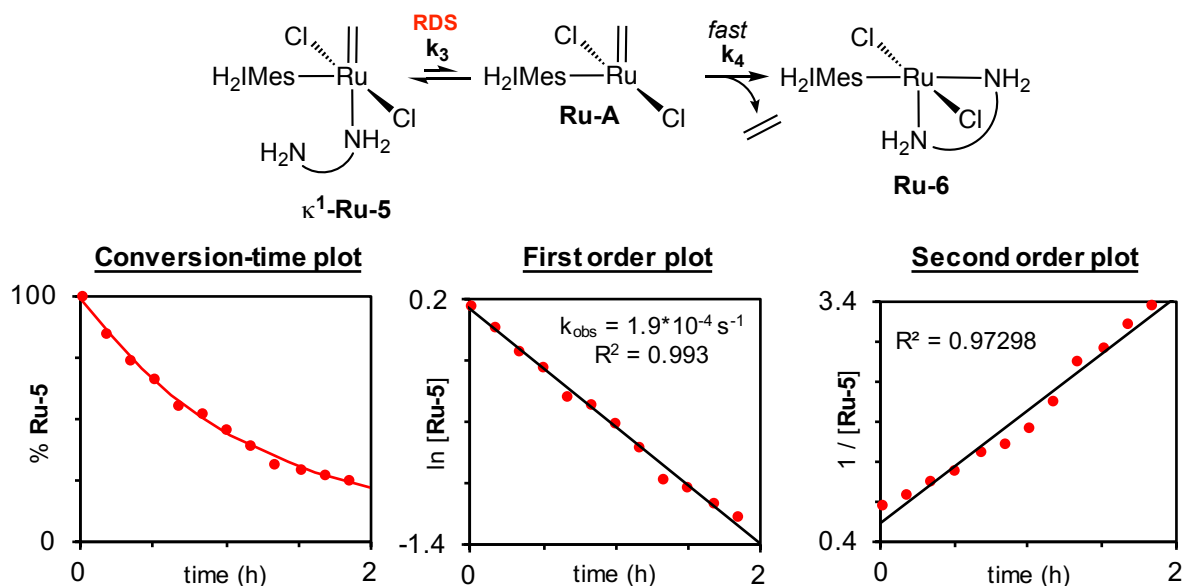


Figure 4.11. Exemplary kinetic plots for bimolecular coupling of **Ru-5** at low initial concentrations (1 mM [**Ru-5**]; CD_2Cl_2 , 10 °C; $\text{H}_2\text{N-NH}_2 = o\text{-dianiline}$). Conversion–time and first-order plots are reproduced from Figure 4.6 above for ease of reference. K_{obs} values are the average of two trials.

*Rate Inhibition by Added *o*-Dianiline at Low $[\text{Ru}]_0$.* Experiments with and without exogenous *o*-dianiline were conducted at RT, under conditions that otherwise correspond to the 1 mM experiments above (Figure 4.12). The proportion of **Ru-5** was assessed after 1 h. Control: 5% **Ru-5** remaining. With 4 equiv *o*-dianiline: 21% **Ru-5**.

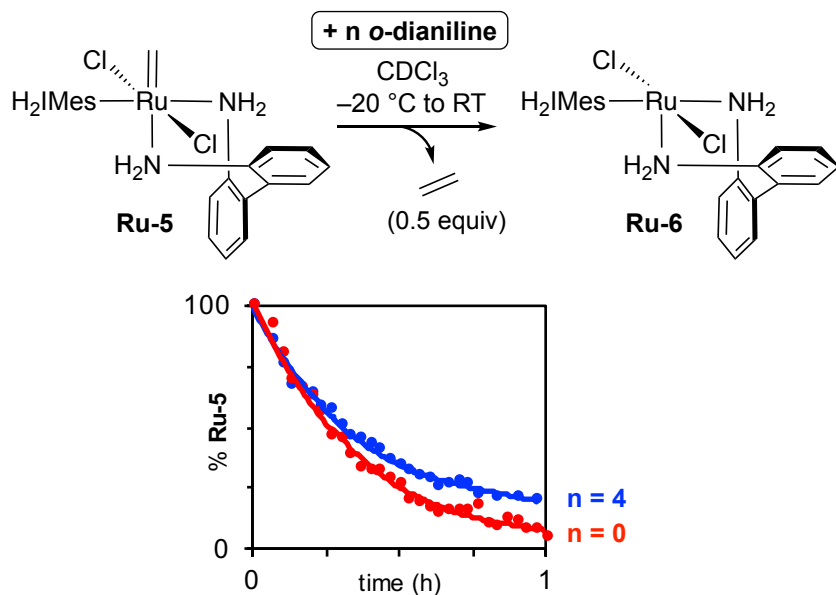


Figure 4.12. Rate inhibition by added *o*-dianiline. Exemplary kinetic plots showing bimolecular coupling of **Ru-5** at low concentrations (1 mM) with and without 4 equiv added *o*-dianiline.

4.5.14 Computational methods

Geometry optimization. All DFT calculations were performed with the Gaussian 09 suite of programs.⁵² Geometry optimization were performed using Head-Gordon's long-range- and dispersion-corrected hybrid density functional ω B97XD⁵³⁻⁵⁵ as implemented in Gaussian 09. This functional was chosen as it provides geometries in very good agreement with those of X-ray diffraction analysis of Ru metathesis catalysts and other homogeneous catalysts.⁵⁶ Ruthenium was described by the Stuttgart 28-electron relativistic effective core potential, termed ECP28MDF and retrieved from the Stuttgart/Cologne group website,^{57,58} in combination with the accompanying correlation-consistent valence double- ζ plus polarization basis set (cc-pVDZ-PP)⁵⁷ retrieved from the EMSL basis set exchange database.⁵⁹ All remaining atoms were described by Dunning's correlation-consistent valence double- ζ plus polarization basis sets (cc-pVDZ),^{60,61} as retrieved from the EMSL basis set exchange database.⁵⁹ Numerical integration was performed using the “ultrafine” grid of Gaussian 09. This grid specification defaults to the coarser “SG1” grid for analytical Hessian calculations using the CPHF procedure. The built-in Gaussian 09 stability check was carried out for all self-consistent field solutions prior to geometry optimization. Instable solutions were re-optimized to real, spin-restricted solutions. Geometries were then optimized using tight convergence criteria (max. force $1.5 \cdot 10^{-5}$ a.u., RMS force $1.0 \cdot 10^{-5}$ a.u., max. force $6.0 \cdot 10^{-5}$ a.u., RMS force $4.0 \cdot 10^{-5}$ a.u.), without symmetry constraints, and using default convergence criteria for the self-consistent field (SCF) optimization procedure (RMS change in density matrix $< 1.0 \cdot 10^{-8}$, max. change in density matrix = $1.0 \cdot 10^{-6}$).

All stationary points were characterized by the eigenvalues of the analytically calculated Hessian matrix, confirming either a single imaginary frequency (for the transition state) or no imaginary frequencies (for minima). The only exception was **Ru-R**, for which the procedure described above returned an imaginary frequency $i13\text{cm}^{-1}$. This imaginary frequency was confirmed to be an artifact resulting from the above-mentioned default reduction of the grid quality in analytical frequency calculations in Gaussian 09.⁶² Specifically requesting the “ultrafine” grid also in the CPHF-based frequency calculation confirmed all-positive curvature for this intermediate as well. The thermal correction for **Ru-R** was thus obtained from the latter vibrational analysis using the

“ultrafine” integration grid, while the standard procedure described above was used for all species for which artifacts from the grid were not detected. The translational, rotational, and vibrational components of the thermal corrections to enthalpies and Gibbs free energies were calculated within the ideal-gas, rigid-rotor, and harmonic oscillator approximations, except that all frequencies below 100 cm^{-1} were shifted to 100 cm^{-1} when calculating the vibrational component of the entropy,^{63,64} to prevent asymptotic behavior of the harmonic approximation for modes of very low frequencies (an approach termed the “quasi-harmonic approximation” in the following).

Intrinsic reaction coordinate (IRC)⁶⁵ calculations (using the local quadratic approximation algorithm (LQA))⁶⁶ connected intermediate **Ru-S** with transition state **TS-T**.

Single-point energy calculations. All single-point energy calculations were performed with the Gaussian 09 implementation of the generalized gradient approximation functional of Perdew, Burke and Ernzerhof (PBE),⁶⁷ and included Grimme’s D3 empirical dispersion term⁶⁸ with revised Becke-Johnson⁶⁹ damping parameters (together labeled PBE-D3M(BJ), for brevity).⁷⁰ Ruthenium was described by the ECP28MDF relativistic effective core potential,⁵⁷ accompanied by a correlation-consistent valence quadruple- ζ plus polarization basis set (ECP28MDF_VQZ),⁵⁷ both obtained from the Stuttgart/Cologne group website. Carbon and hydrogen atoms were described by valence quadruple- ζ plus polarization (EML: cc-pVQZ)⁵⁹ basis sets.⁶⁰ All other atoms were described by the valence quadruple- ζ plus polarization augmented with diffuse functions (EML: aug-cc-pVQZ),^{59,60,71} Electrostatic and non-electrostatic solvation effects in dichloromethane were taken into account using the polarizable continuum model (PCM), in combination with the “Dis”, “Rep”, and “Cav” keywords and the built-in program values (dielectric constant, number density, etc.).⁷² The solute cavity was constructed using the united atom topological model with atomic radii optimized for Hartree–Fock (termed “UAHF”)^{72d,73} Numerical integrations were performed with the “ultrafine” grid of Gaussian 09 and the self-consistent field (SCF) density-based convergence criterion was set to 10^{-5} (RMS change in density matrix $< 1.0 \cdot 10^{-5}$, max. change in density matrix = $1.0 \cdot 10^{-3}$).

Calculation of Gibbs free energies. Gibbs free energies were calculated at 298.15 K according to

$$\text{equation 1. } G_{\text{PBE-D3M(BJ)}}^{\text{CH}_2\text{Cl}_2} = E_{\text{PBE-D3M(BJ)}}^{\text{CH}_2\text{Cl}_2} + \Delta G_{\text{B97XD,qh}}^{\text{T=298.15K}} + \Delta G_{\text{1atm} \rightarrow \text{1M}}^{\text{T=298.15K}} \quad (1)$$

Here $E_{\text{PBE-D3M(BJ)}}^{\text{CH}_2\text{Cl}_2}$ corresponds to the potential energies resulting from single point calculations with PBE-D3M(BJ), including the contributions from the implicit solvation model; $\Delta G_{\text{B97XD,qh}}^{\text{T=298.15K}}$ is the thermal correction to the Gibbs free energy, calculated at the geometry optimization level with the quasi-harmonic approximation, and $\Delta G_{\text{1atm} \rightarrow \text{1M}}^{\text{T=298.15K}}$ is the standard-state correction corresponding to 1 M solution (but exhibiting infinite-dilution, ideal-gas-like behavior). The latter is equal to $1.89 \text{ kcal mol}^{-1}$ ($= RT \cdot \ln(24.46)$). Table S5 reports all these values, together with the single-point energy calculated at the geometry optimization level (E_{B97XD}) and the corresponding Gibbs free energy including thermal corrections from the harmonic approximation ($G_{\text{B97XD}}^{\text{T=298.15K}}$).

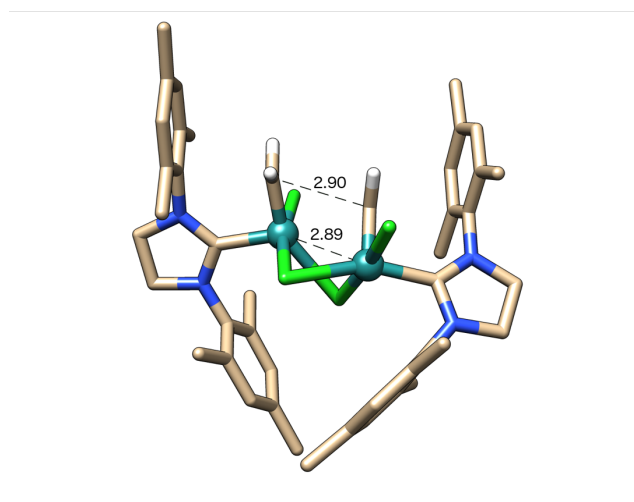


Figure 4.13. Optimized geometry of intermediate **Ru-S**. Only the hydrogen atoms of the methylidene moieties are shown. Colour code: C: brown; N: blue; H: white; Cl: light green; Ru: turquoise.

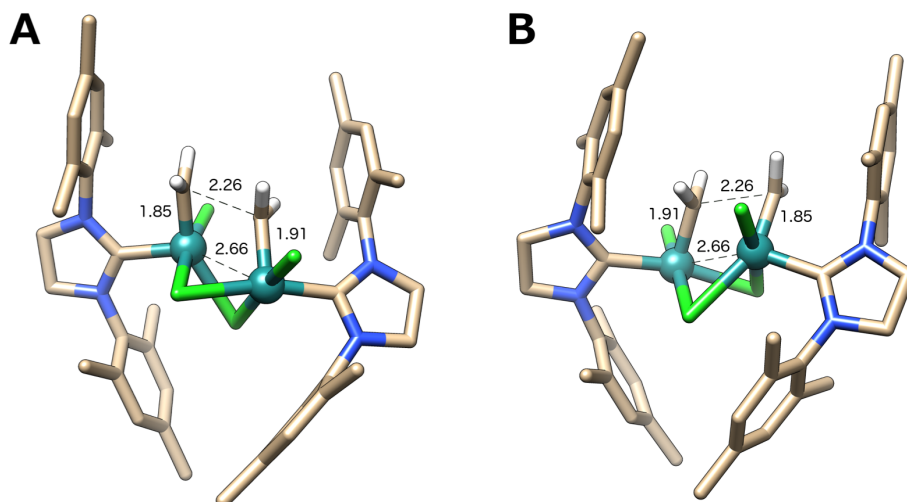


Figure 4.14. Two different views of the optimized geometry of transition state **TS-T**. Only the hydrogen atoms of the methylidene moieties are shown. For colour code, see caption to Figure 4.13.

Table 4.3. Calculated Gibbs free energies.^a

Mol. ID	E_{wB97XD} [a.u.]	$G_{\text{wB97XD}}^{T=298.15\text{K}}$ [a.u.]	$\Delta G_{\text{wB97XD;qh}}^{T=298.15\text{K}}$ [a.u.]	$E_{\text{PBE-D3M(BJ)}}^{\text{CH}_2\text{Cl}_2}$ [a.u.]	$G_{\text{PBE-D3M(BJ)}}^{\text{CH}_2\text{Cl}_2}$ [a.u.]	$G_{\text{PBE-D3M(BJ)}}^{\text{CH}_2\text{Cl}_2}$ w.r.t. Ru-5	
						[a.u.]	[kcal/mol]
Ru-A	-1979.586563	-1979.199251	0.395916	-	-	-	-
Ru-5	-2553.521737	-2552.923477	0.608479	-2552.426963	-2551.815466	0.000000	0.0
Ru-6	-2514.254421	-2513.679554	0.585391	-2513.170490	-2512.582080	-0.010051	-6.3
Ru-S	-3959.227635	-3958.420421	0.825375	-3957.609942	-3956.781548	0.026083	16.4
TS-T	-3959.225480	-3958.414550	0.826754	-3957.609588	-3956.779815	0.027816	17.5
Ru-Q	-3959.242925	-3958.437227	0.824155	-3957.628074	-3956.800900	0.006731	4.2
Ru-R	-3959.182742	-3958.376355	0.825470	-3957.600020	-3956.771531	0.036100	22.7
<i>cis</i> - Ru-6^b	-2514.246693	-2513.666597	0.587710	-2513.167383	-2512.576654	0.000800	0.5
<i>o</i> - dianiline	-573.868057	-573.688045	0.180968	-573.595637	-573.411650	-	-
ethylene	-78.560878	-78.531898	0.028980	-78.508821	-78.476822	-	-

^a Energies defined in Computational Methods section. ^b An isomer of **Ru-6** with *cis*-positioned chloride ligands.

Natural bond orbital analysis. The natural bond orbital analyses were performed using the NBO 6.0 program.⁷⁴ Memory restrictions prohibited NBO calculations on the dimeric ruthenium

complexes (**Ru-S** and transition state **TS-T**) using the very large basis sets for single-point calculations described above. Instead, Dunning's correlation-consistent valence triple- ζ plus polarization basis sets (cc-pVTZ-DK)^{57,60,61} were used for all atoms in the single-point, self-consistent field calculations giving the electron density used in the NBO analyses. The remaining settings of the DFT model and the self-consistent field protocol were as described above for the single-point energy calculations, the sole exception being use of the original Becke-Johnson⁶⁹ damping parameters when calculating Grimme's D3 empirical dispersion terms.⁶⁸

To compare NBO-derived properties of **Ru-S**, **TS-T** and the methyldiene complex **Ru-A**, the electron density was analyzed in terms of a single Lewis structure (enforced via the \$CHOOSE keylist) with an intact Ru=CH₂ double bond for **Ru-A**. Other features of this Lewis structure (ionic Ru-Cl bonds, a lone pair on each NHC N atom, Kekulé-structured aromatic rings) are generally optimal by NBO calculations for **Ru-S**, **TS-T**, and **Ru-A**. The selected Lewis structure is thus a reasonable compromise in comparing these three structures, and accounts for > 97.6% of the electron density in each case.

Selected natural charges (in units of the electron charge) from natural population analysis appear in Table S6. Donation from $\pi(\text{Ru}_\text{B}-\text{C}_\text{B})$ increases the electron population on Ru_A and results in a smaller positive charge on Ru_A than on Ru_B (Table S6). This donation also reduces the occupancy of $\pi(\text{Ru}_\text{B}-\text{C}_\text{B})$ to a value (1.86, Table S9) lower than that of $\pi(\text{Ru}_\text{A}-\text{C}_\text{A})$ (1.94) as well as that of the isolated methyldiene **Ru-A** (1.98). The fact that this electron donation gives rise to new bonding interactions is reflected in Wiberg bond indices confirming the presence of a small, shared electron density between Ru_A and C_B (0.14) and between the two Ru atoms (also 0.14), respectively (Table S7).

In comparison, the shared electron density between C_A and C_B in **Ru-S** is smaller as judged from the Wiberg index⁷ (0.06), indicating that this bond formation must be triggered by the initial geometric dissymmetry and $\pi(\text{Ru}_\text{B}-\text{C}_\text{B}) \rightarrow \text{Ru}_\text{A}$ donation. This brings C_B close to the Ru_A=C_A methyldiene and starts to weaken the Ru_B-C_B bond by reducing the $\pi(\text{Ru}_\text{B}-\text{C}_\text{B})$ occupancy. The latter MO, as with all the methyldiene π bonds studied herein (Table S9), is polarized toward Ru, while the corresponding antibonding π^* are polarized in the opposite direction. Thus, with $\pi^*(\text{Ru}_\text{B}-\text{C}_\text{B})$ polarized toward C_B, electron density builds up between the two carbon atoms as a result of $\pi(\text{Ru}_\text{A}-\text{C}_\text{A}) \rightarrow \pi^*(\text{Ru}_\text{B}-\text{C}_\text{B})$ donation (Table S9). This donation increases on going to

transition state **TS-T**, where the $\pi^*(\text{Ru}_\text{B}-\text{C}_\text{B})$ occupancy reaches 0.45 and the atomic carbon s orbitals start contributing more to this MO, as expected for a C–C bond. Even in **TS-T**, however, the shared electron density between Ru_A and C_B (Wiberg bond index⁷ 0.31) is still larger than that between C_A and C_B (0.27), and most of the C–C bond forms after this transition state. Details of post-**TS-T** steps and the liberation of alkene are under further study.

Table 4.4. Selected natural charges (in units of the electron charge) from natural population analysis.^a

Model	Natural charges			
	Ru_A	C_A	Ru_A	C_B
Ru-A	0.32	-0.21	-	-
Ru-S	0.14	-0.16	0.18	-0.26
TS-T	0.13	-0.18	0.21	-0.33

^a See Figure 4.8 for atom labeling.

Table 4.5. Selected Wiberg bond indices (in units of electrons) from natural population analysis.^a

Model	Wiberg bond index					
	$\text{Ru}_\text{A}-\text{C}_\text{A}$	$\text{Ru}_\text{B}-\text{C}_\text{B}$	$\text{Ru}_\text{A}-\text{C}_\text{B}$	$\text{Ru}_\text{B}-\text{C}_\text{A}$	$\text{Ru}_\text{A}-\text{Ru}_\text{B}$	$\text{C}_\text{A}-\text{C}_\text{B}$
Ru-A	1.64	1.64	-	-	-	-
Ru-S	1.41	1.38	0.14	0.02	0.14	0.06
TS-T	1.15	1.10	0.31	0.06	0.34	0.27

^a See Figure 4.8 for atom labeling.

Table 4.6. Occupancy and polarization of selected NBOs of σ symmetry.^a

Model	NBOs σ -component											
	$\sigma(\text{Ru}_\text{A}-\text{C}_\text{A})$			$\sigma(\text{Ru}_\text{B}-\text{C}_\text{B})$			$\sigma^*(\text{Ru}_\text{A}-\text{C}_\text{A})$			$\sigma^*(\text{Ru}_\text{B}-\text{C}_\text{B})$		
	Occ.	% Ru	% C	Occ.	% Ru	% C	Occ.	% Ru	% C	Occ.	% Ru	% C
Ru-A	1.975	53	47	1.975	53	47	0.204	47	53	0.204	47	53
Ru-S	1.955	51	49	1.940	54	46	0.326	49	51	0.264	46	54
TS-T	1.949	51	49	1.919	55	45	0.375	49	51	0.281	45	55

^a See Figure 4.8 for atom labeling.

Table 4.7. Occupancy and polarization of selected NBOs of π symmetry.^a

Model	NBOs π -component											
	π (Ru _A -C _A)			π (Ru _B -C _B)			π^* (Ru _A -C _A)			π^* (Ru _B -C _B)		
	Occ.	% Ru	% C	Occ.	% Ru	% C	Occ.	% Ru	% C	Occ.	% Ru	% C
Ru-A	1.989	65	35	1.989	65	35	0.160	35	65	0.160	35	65
Ru-S	1.936	71	29	1.859	66	34	0.137	29	71	0.236	34	66
TS-T	1.716	74	26	1.690	67	33	0.246	26	74	0.455	33	67

^a See Figure 4.8 for atom labeling.

4.6 References

- (1) (a) Grela, K., *Olefin Metathesis-Theory and Practice*. Wiley: Hoboken, NJ, 2014. (b) Grubbs, R. H.; Wenzel, A. G., *Handbook of Metathesis*. 2nd ed.; Wiley-VCH: Weinheim, 2015.
- (2) (a) Higman, C. S.; Lummiss, J. A. M.; Fogg, D. E. *Angew. Chem., Int. Ed.* **2016**, *55*, 3552–3565. (b) K. R. Fandrick, J. Savoie, N. Y. Jinhua, J. J. Song, C. H. Senanayake, In ref 1a, pp. 349–366. (c) Farina, V.; Horváth, A. In ref 1a, pp 633–658.
- (3) Rate constants for initiation (k_i ; $\times 10^{-3} \text{ s}^{-1}$) at 5 °C: **GII**, 0.0032; **HII**, 2.6; **GIII**, >200. See: Love, J. A.; Morgan, J. P.; Trnka, T. M.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 4035–4037, and references therein. % Recapture = proportion of the resting-state species at 50% catalyst decomposition during styrene metathesis (100 equiv styrene, 22 °C, C₆D₆). Data for selected Class A–C catalysts: **GII**, 15%; **HII**, 100%; **GIII**, 0%. The resting states are, respectively, RuCl₂(H₂IMes)(PCy₃)(=CH₂) **GII**m, **HII** itself, and (see below) RuCl₂(H₂IMes)(py)_n(=CH₂).
- (4) Higman, C. S.; Nascimento, D.; Ireland, B. J.; Audorsch, S.; Bailey, G. A.; Fogg, D. E. *J. Am. Chem. Soc.* **2018**, *140*, 1604–1607.
- (5) For evidence of “boomerang” recapture of isopropoxystyrene, see: (a) Bates, J. M.; Lummiss, J. A. M.; Bailey, G. A.; Fogg, D. E. *ACS Catal.* **2014**, *4*, 2387–2394. (b) Griffiths, J. R.; Keister, J. B.; Diver, S. T. *J. Am. Chem. Soc.* **2016**, *138*, 5380–5391. For the original proposal, see: (c) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.
- (6) The vinylphosphonium salt [H₂C=CHPCy₃]Cl lost on initiation of **PII** does not re-enter metathesis. See: Leitao, E. M.; van der Eide, E. F.; Romero, P. E.; Piers, W. E.; McDonald, R. J. *J. Am. Chem. Soc.* **2010**, *132*, 2784–2794.
- (7) (a) Schrodi, Y., Mechanisms of Olefin Metathesis Catalyst Decomposition and Methods of Catalyst Reactivation. In ref 1b, pp 323–342. (b) 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.
- (8) (a) Hong, S. H.; Wenzel, A. G.; Salguero, T. T.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2007**, *129*, 7961–7968. (b) Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2004**, *126*, 7414–7415.
- (9) (a) McClennan, W. L.; Rufh, S.; Lummiss, J. A. M.; Fogg, D. E. *J. Am. Chem. Soc.* **2016**, *138*, 14668–14677. (b) Lummiss, J. A. M.; McClennan, W. L.; McDonald, R.; Fogg, D. E.

- Organometallics* **2014**, *33*, 6738–6741. (c) Lummiss, J. A. M.; Ireland, B. J.; Sommers, J. M.; Fogg, D. E. *ChemCatChem* **2014**, *6*, 459–463. (d) Lummiss, J. A. M.; Botti, A. G. G.; Fogg, D. E. *Catal. Sci. Technol.* **2014**, *4*, 4210–4218.
- (10) (a) Romero, P. E.; Piers, W. E. *J. Am. Chem. Soc.* **2005**, *127*, 5032–5033. (b) Romero, P. E.; Piers, W. E. *J. Am. Chem. Soc.* **2007**, *129*, 1698–1704. (c) van der Eide, E. F.; Piers, W. E. *Nature Chem.* **2010**, *2*, 571–576.
- (11) Solans-Monfort, X.; Coperet, C.; Eisenstein, O. *J. Am. Chem. Soc.* **2010**, *132*, 7750–7757.
- (12) Nizovtsev, A. V.; Afanasiev, V. V.; Shutko, E. V.; Bessalova, N. B. *NATO Sci. Ser. II* **2007**, *243*, 125–135.
- (13) Propene loss was also reported on reaction of **GII** with ethylene. See: van Rensburg, W. J.; Steynberg, P. J.; Meyer, W. H.; Kirk, M. M.; Forman, G. S. *J. Am. Chem. Soc.* **2004**, *126*, 14332–14333. Methylidene abstraction (refs 8,9) was apparently prevented by oxidation of PCy₃; O=PCy₃ was detected.
- (14) Bailey, G. A.; Lummiss, J. A. M.; Foscatto, M.; Occhipinti, G.; McDonald, R.; Jensen, V. R.; Fogg, D. E. *J. Am. Chem. Soc.* **2017**, *139*, 16446–16449.
- (15) Ireland, B. J.; Dobigny, B. T.; Fogg, D. E. *ACS Catal.* **2015**, *5*, 4690–4698.
- (16) Engel, J.; Smit, W.; Foscatto, M.; Occhipinti, G.; Törnroos, K. W.; Jensen, V. R. *J. Am. Chem. Soc.* **2017**, *139*, 16609–16619.
- (17) Williams, J. E.; Harner, M. J.; Sponsler, M. B. *Organometallics* **2005**, *24*, 2013–2015.
- (18) Pyridine is significantly less nucleophilic than either PPh₃ or PCy₃. *N* values on the logarithmic Mayr nucleophilicity scale: pyridine, 12.90; PPh₃, 14.33; PCy₃, 14.64; all in dichloromethane. See: <http://www.cup.lmu.de/oc/mayr/reaktionsdatenbank/>.
- (19) (a) Schrock, R. R.; Copéret, C. *Organometallics* **2017**, *36*, 1884–1892. An important early analysis noted the striking propensity of M=CH₂ species to eliminate ethylene: (b) Merrifield, J. H.; Lin, G.-Y.; Kiel, W. A.; Gladysz, J. A. *J. Am. Chem. Soc.* **1983**, *105*, 5811–5819. For crystallographically characterized examples of methylidene complexes derived from group 6 metathesis catalysts, see: (c) Arndt, S.; Schrock, R. R.; Muller, P. *Organometallics* **2007**, *26*, 1279–1290. (d) Tsang, W. C. P.; Jamieson, J. Y.; Aeilts, S. L.; Hultsch, K. C.; Schrock, R. R.; Hoveyda, A. H. *Organometallics* **2004**, *23*, 1997–2007.
- (20) (a) 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. (b) Huang, J.; Schanz, H.-J.; Stevens, E. D.; Nolan, S. P. *Organometallics* **1999**, *18*, 5375–5380.
- (21) Adlhart, C.; Chen, P. *Helv. Chim. Acta* **2003**, *86*, 941–949.
- (22) Experiments in 2.00 mL total volume of C₆D₆ plus styrene, in a 2.15 mL J. Young tube. Further reductions in headspace present an explosion hazard (see SI).
- (23) (a) Borguet, Y.; Sauvage, X.; Zaragoza, G.; Demonceau, A.; Delaude, L. *Organometallics* **2011**, *30*, 2730–2738 and references therein. (b) Wolf, J.; Thommes, K.; Briel, O.; Scopelliti, R.; Severin, K. *Organometallics* **2008**, *27*, 4464–4474. (c) Quebatte, L.; Solari, E.; Scopelliti, R.; Severin, K. *Organometallics* **2005**, *24*, 1404–1406.

- (24) Reported pK_a values in acetonitrile. Pyridine: 12.6; NEt_3 : 18.5. See: Cox, B. G., *Acids and Bases: Solvent Effects on Acid-Base Strength*. Oxford University Press: Croydon, 2013, p. 99–115.
- (25) (a) Griffiths, J. R.; Hofman, E. J.; Keister, J. B.; Diver, S. T. *Organometallics* **2017**, *36*, 3043–3052. (b) Galan, B. R.; Pitak, M.; Gembicky, M.; Keister, J. B.; Diver, S. T. *J. Am. Chem. Soc.* **2009**, *131*, 6822–6832. (c) Galan, B. R.; Gembicky, M.; Dominiak, P. M.; Keister, J. B.; Diver, S. T. *J. Am. Chem. Soc.* **2005**, *127*, 15702–15703.
- (26) For computational studies of Buchner insertion of methylenide: (a) Poater, A.; Ragone, F.; Correa, A.; Cavallo, L. *J. Am. Chem. Soc.* **2009**, *131*, 9000–9006. Of benzylenide: (b) Poater, A.; Cavallo, L. *Theor. Chem. Acc.* **2012**, *131*, 1155.
- (27) Primary evidence is the unperturbed H_2IMes ligand in **Ru-2** (quantitative). In addition, reaction of **GIIm/m'** with cyclohexene revealed no norcaradiene resulting from cyclopropanation by 1H NMR or GC-MS analysis. Instead, ethylene is generated, consistent with decomposition by bimolecular coupling. A further possibility suggested by a referee, involving loss of alkylidene as the free carbene on binding a π -acceptor ligand, was explicitly ruled out in the Cavallo study (ref 26a) on the basis of the high energy barriers involved. Diver's studies likewise suggested that alkylidene insertion is intramolecular (see ref 25b).
- (28) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *Organometallics* **2001**, *20*, 5314–5318.
- (29) Walsh, D. J.; Lau, S. H.; Hyatt, M. G.; Guironnet, D. *J. Am. Chem. Soc.* **2017**, *139*, 13644–13647.
- (30) Adding pyridine to the solution, with the intention of converting all Ru species present to **Ru-2**, left a shortfall of ca. 25%. Ru nanoparticles may account for the balance of material: see (a) Higman, C. S.; Lanterna, A. E.; Marin, M. L.; Scaiano, J. C.; Fogg, D. E. *ChemCatChem* **2016**, *8*, 2446–2449. The chief alternative possibility, formation of paramagnetic Ru byproducts, is improbable given the absence of significant signal broadening in the NMR spectrum (Figure A21).
- (31) Lummiss, J. A. M.; Beach, N. J.; Smith, J. C.; Fogg, D. E. *Catal. Sci. Technol.* **2012**, *2*, 1630–1632.
- (32) (a) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100–110. (b) Werner, H.; Stuer, W.; Weberndorfer, B.; Wolf, J. *Eur. J. Inorg. Chem.* **1999**, 1707–1713. (c) Burrell, A. K.; Clark, G. R.; Rickard, C. E. F.; Roper, W. R.; Wright, A. H. *J. Chem. Soc., Dalton Trans.* **1991**, 609–614.
- (33) PCy_3 loss from **GIIm** is >40,000x slower than from **GI**, $RuCl_2(PCy_3)_2(=CHPh)$. See: (a) Lummiss, J. A.; Higman, C. S.; Fyson, D. L.; McDonald, R.; Fogg, D. E. *Chem. Sci.* **2015**, *6*, 6739–6746. (b) Lummiss, J. A.; Perras, F. A.; Bryce, D. L.; Fogg, D. E. *Organometallics* **2016**, *35*, 691–698.
- (34) The excellent Lewis basicity of *o*-dianiline is evident from over a dozen reports of its Ru complexes. Selected examples: (a) Crimmin, M. R.; Bergman, R. G.; Toste, F. D. *Angew. Chem., Int. Ed.* **2011**, *50*, 4484–4487. (b) Faller, J. W.; Fontaine, P. P. *Organometallics* **2005**, *24*, 4132–4138. (c) Aikawa, K.; Mikami, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 5455–5458. A pK_a of 3.81 in 70% aqueous EtOH is reported for the conjugate acid of *o*-dianiline; cf. 3.66 for pyridine. See, respectively: (a) Grantham, P. H.; Weisburger, E. K.; Weisburger, J. H. *J. Org. Chem.* **1961**, *26*,

- 1008–1017. (b) McDaniel, D. H.; Özcan, M. *J. Org. Chem.* **1968**, *33*, 1922–1923. The pK_a reported for pyridine in acetonitrile is considerably higher: see ref 24.
- (35) Nickel, A.; Ung, T.; Mkrtumyan, G.; Uy, J.; Lee, C. W.; Stoianova, D.; Papazian, J.; Wei, W.-H.; Mallari, A.; Schrodi, Y.; Pederson, R. L. *Top. Catal.* **2012**, *55*, 518–523.
- (36) Schweitzer, D.; Snell, K. D. *Org. Process Res. Dev.* **2015**, *19*, 715–720.
- (37) Vignon, P.; Vancompernelle, T.; Couturier, J.-L.; Dubois, J.-L.; Mortreux, A.; Gauvin, R. M. *ChemSusChem* **2015**, *8*, 1143–1146.
- (38) For PCy₃-stabilized catalysts, the greater steric bulk of the ethylidene ligand, vs. methylidene, also retards abstraction of this ligand by phosphine. See ref 9a.
- (39) MacNaughtan, M. L.; Gary, J. B.; Gerlach, D. L.; Johnson, M. J. A.; Kampf, J. W. *Organometallics* **2009**, *28*, 2880–2887.
- (40) Leitao, E. M.; Dubberley, S. R.; Piers, W. E.; Wu, Q.; McDonald, R. *Chem. – Eur. J.* **2008**, *14*, 11565–11572.
- (41) For selected examples of transoid diruthenium complexes arising from decomposition of Ru-H₂IMes catalysts, see refs 39, 40.
- (42) Foster, J. P.; Weinhold, F. *J. Am. Chem. Soc.* **1980**, *102*, 7211–7218.
- (43) Wiberg, K. B. *Tetrahedron* **1968**, *24*, 1083–1096.
- (44) Occhipinti, G.; Jensen, V. R. *Organometallics* **2011**, *30*, 3522–3529.
- (45) Jung, K.-H.; Kim, H.-K.; Lee, G. H.; Kang, D.-S.; Park, J.-A.; Kim, K. M.; Chang, Y.; Kim, T.-J. *J. Med. Chem.* **2011**, *54*, 5385–5394.
- (46) Bottomley, F.; Mukaida, M. *J. Chem. Soc., Dalton Trans.* **1982**, 1933–1937.
- (47) van Lierop, B. J.; Reckling, A. M.; Lummiss, J. A. M.; Fogg, D. E. *ChemCatChem* **2012**, *4*, 2020–2025.
- (48) Dubberley, S. R.; Romero, P. E.; Piers, W. E.; McDonald, R.; Parvez, M. *Inorg. Chim. Acta* **2006**, *359*, 2658–2664.
- (49) Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. *Organometallics* **2010**, *29*, 2176–2179.
- (50) Wang, R.; Groux, L. F.; Zargarian, D. *Organometallics* **2002**, *21*, 5531–5539.
- (51) Lucke, A. J.; Young, D. J. *J. Org. Chem.* **2005**, *70*, 3579–3583.
- (52) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J.

J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J., Gaussian 09, Revision D.01, Gaussian, Inc., Wallingford CT. 2013.

(53) Becke, A. D. *J. Chem. Phys.* **1997**, *107*, 8554–8560.

(54) Wu, Q.; Yang, W. *J. Chem. Phys.* **2002**, *116*, 515–524.

(55) Chai, J.-D.; Head-Gordon, M. *Phys. Chem. Chem. Phys.* **2008**, *10*, 6615–6620.

(56) Minenkov, Y.; Singstad, Å.; Occhipinti, G.; Jensen, V. R. *Dalton Trans.* **2012**, *41*, 5526–5541.

(57) Peterson, K. A.; Figgen, D.; Dolg, M.; Stoll, H. *J. Chem. Phys.* **2007**, *126*, 124101.

(58) Energy-consistent pseudopotentials of the Stuttgart/Cologne Group, <http://www.tc.uni-koeln.de/PP/clickpse.en.html>.

(59) (a) Feller, D. *J. Comput. Chem.* **1996**, *17*, 1571–1586. (b) Schuchardt, K. L.; Didier, B. T.; Elsethagen, T.; Sun, L.; Gurumoorthi, V.; Chase, J.; Li, J.; Windus, T. L. *J. Chem. Inf. Model.* **2007**, *47*, 1045–1052.

(60) Dunning, T. H. *J. Chem. Phys.* **1989**, *90*, 1007–1023.

(61) Woon, D. E.; Dunning, T. H. *J. Chem. Phys.* **1993**, *98*, 1358–1371.

(62) Martin, J. M. L.; Bauschlicher, C. W.; Ricca, A. *Comput. Phys. Commun.* **2001**, *133*, 189–201.

(63) Zhao, Y.; Truhlar, D. G. *Phys. Chem. Chem. Phys.* **2008**, *10*, 2813–2818.

(64) Ribeiro, R. F.; Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2011**, *115*, 14556–14562.

(65) Fukui, K. *Acc. Chem. Res.* **1981**, *14*, 363–368.

(66) (a) Page, M.; Doubleday, C.; McIver, J. W. *J. Chem. Phys.* **1990**, *93*, 5634–5642. (b) Page, M.; McIver, J. W. *J. Chem. Phys.* **1988**, *88*, 922–935.

(67) (a) Perdew, J. P.; Burke, K.; Ernzerhof, M. *Phys. Rev. Lett.* **1996**, *77*, 3865–3868. (b) Perdew, J.; Burke, K.; Ernzerhof, M. *Phys. Rev. Lett.* **1997**, *78*, 1396–1396.

(68) Grimme, S.; Ehrlich, S.; Goerigk, L. *J. Comput. Chem.* **2011**, *32*, 1456–1465.

(69) Johnson, E. R.; Becke, A. D. *J. Chem. Phys.* **2005**, *123*, 024101.

(70) Smith, D. G. A.; Burns, L. A.; Patkowski, K.; Sherrill, C. D. *J. Phys. Chem. Lett.* **2016**, *7*, 2197–2203.

(71) Kendall, R. A.; Dunning, T. H.; Harrison, R. J. *J. Chem. Phys.* **1992**, *96*, 6796–6806.

(72) (a) Cossi, M.; Scalmani, G.; Rega, N.; Barone, V. *J. Chem. Phys.* **2002**, *117*, 43–54. (b) Scalmani, G.; Frisch, M. J. *J. Chem. Phys.* **2010**, *132*, 114110. (c) Tomasi, J.; Mennucci, B.; Cammi, R. *Chem. Rev.* **2005**, *105*, 2999–3093. (d) Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027–2094.

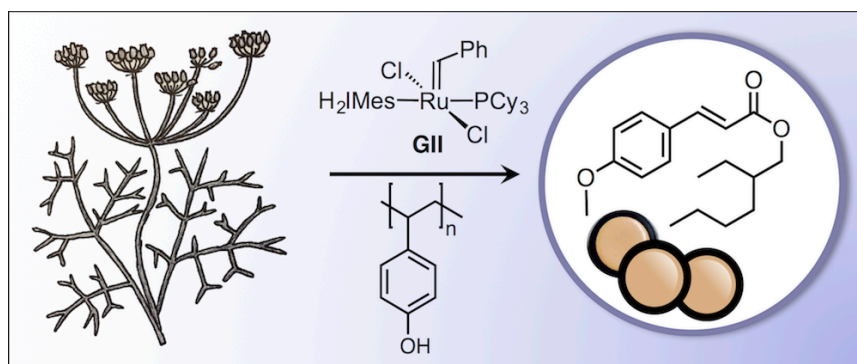
(73) (a) Tomasi, J. *Theor. Chem. Acc.* **2004**, *112*, 184–203. (b) Cramer, C. J.; Truhlar, D. G. *Phys. Chem. Chem. Phys.* **2009**, *11*, 10757–10816. (c) Klamt, A.; Mennucci, B.; Tomasi, J.; Barone, V.; Curutchet, C.; Orozco, M.; Luque, F. J. *Acc. Chem. Res.* **2009**, *42*, 489–492.

(74) Glendening, E. D.; Badenhop, J. K.; Reed, A. E.; Carpenter, J. E.; Bohmann, J. A.; Morales, C. M.; Landis, C. R.; Weinhold, F. *NBO*, 6.0.; Theoretical Chemistry Institute, University of Wisconsin: Madison, WI, 2013.

Chapter 5. Overcoming Catalyst Decomposition in Acrylate Metathesis

5.1 Published Contributions

Overcoming Catalyst Decomposition in Acrylate Metathesis: Polyphenol Resins as Enabling Agents for PCy₃-Stabilized Metathesis Catalysts. Alexandra G. Santos,[†] Gwendolyn A. Bailey,[†] Eduardo N. dos Santos, and Deryn E. Fogg. *ACS Catalysis* **2017**, 3181–3189. (Full paper) [†]*Equal Contributions*



Abstract: Phosphine-stabilized metathesis catalysts are among the most popular and widely used catalysts in organic synthesis. The second-generation Grubbs catalyst **GII**, in particular, dominates synthetic applications of olefin metathesis. This is commonly true even for reactions that are fundamentally incompatible with free PCy₃, which is released upon entry of **GII** into the catalytic cycle. A leading example is cross-metathesis with electron-deficient olefins such as acrylates, for which yields are seriously degraded by a deleterious side reaction involving attack of free PCy₃ on the acrylate olefin, and production of an enolate anion that decomposes the active catalyst. Here we describe a simple, powerful means of upgrading the performance of **GII** and its indenylidene analogue **M2** to levels matching or exceeding that of the important, but more costly, phosphine-free Hoveyda catalyst **III**. Key to this improvement is carrying out the reaction in the presence of a phenol-functionalized polymer resin. We demonstrate that, at standard catalyst loadings (which correspond to low concentrations of PCy₃), the beneficial effect of phenol arises not from protonation of PCy₃ itself, but from protonation of the enolate, thereby converting this aggressive base into an innocuous phosphonium salt. The methodology is showcased in the demanding cross-metathesis of the renewable phenylpropanoid trans-anethole with 2-ethylhexyl acrylate (an efficient route to the high-value antioxidant octylmethoxy-

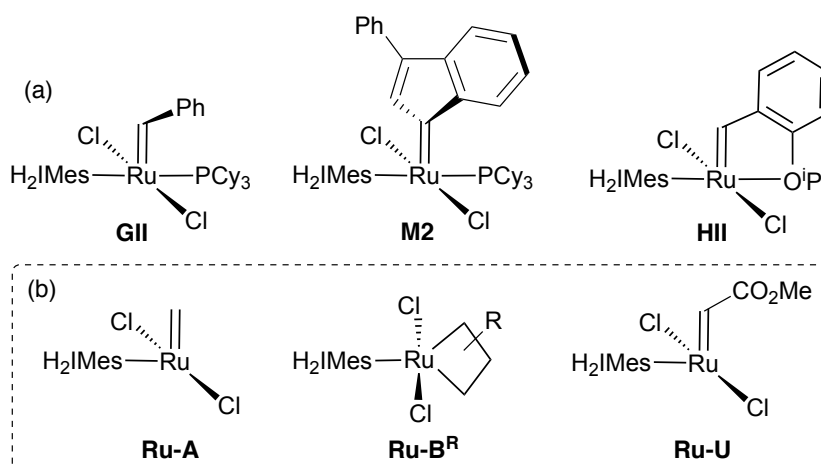
cinnamate, an active ingredient in sunscreen formulations with the tradename Octinoxate), as well as methyl acrylate, a ubiquitous and more sterically accessible coupling partner. Experiments with water-saturated toluene indicate that water cannot be substituted for the resin as a sacrificial proton donor, such treatment resulting in drastically reduced productivity. Control experiments involving macrocyclization indicate that the resin has an additional protective function beyond enolate quenching, potentially due to hydrogen bonding of polar contaminants present as impurities in the reagents or reaction medium.

Author Contributions: This manuscript was formulated, written, edited, and revised by GAB and DEF, with input from ENdS. The use of polyphenols as enabling agents in acrylate metathesis was conceived by ENdS. The initial catalyst screening studies involving PVP-11, PVP-25, PVP-MMA, and Amberlite CG50 (data in Tables 5.1, 5.2, and 5.3) were conducted by AGS. The mechanism of action of polyphenols was proposed by GAB and DEF, and then demonstrated in experiments by GAB. All other experiments were conceived by GAB and DEF, and conducted by GAB.

5.2 Introduction

Olefin metathesis is among the most powerful and general catalytic methodologies now known for the construction of carbon–carbon bonds.^{1–3} Metathesis methodologies are ubiquitous in organic synthesis in academia, while emerging applications in process chemistry range from pharmaceutical manufacturing to the transformation of renewable plant oils into specialty chemicals.^{4–8} The second-generation Grubbs catalyst **GII** remains the dominant catalyst in academic use today, although the past decade has seen expanding use of the indenylidene and phosphine-free catalysts **M2** and **HII** (Chart 5.1a).

Chart 5.1. (a) Dominant metathesis catalysts; (b) Key intermediates in olefin or acrylate metathesis

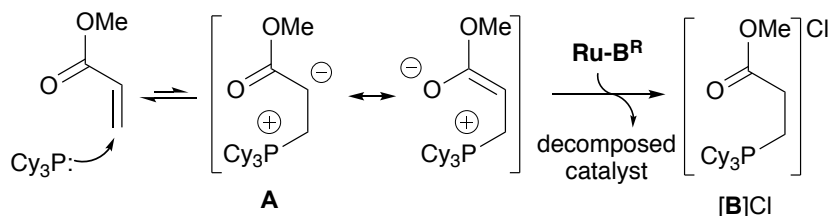


Notwithstanding the transformative impact of **GII** and its analogues on organic and materials synthesis, a steady accumulation of evidence demonstrates that the PCy_3 ligand—which must be dissociated to permit the catalyst to enter the active cycle—has an adverse impact on both activity and productivity.^{9–19} Recoordination of PCy_3 to the methylidene intermediate (**Ru-A**; Chart 5.1b) is profoundly deactivating. Strong binding of PCy_3 traps the catalyst in its off-cycle resting state,¹¹ greatly retarding re-entry into the catalytic cycle.²⁰ Nucleophilic attack of PCy_3 on the methylidene carbon is even more deleterious. This initiates a “ligand stripping” pathway that culminates in loss of the methylidene as $[\text{MePCy}_3]\text{Cl}$ ^{10–16} and formation of isomerization-active species (including Ru nanoparticles).²¹

Less widely recognized, despite prominent developments in nucleophilic phosphine organocatalysis (including phosphine-enabled annulation and other conjugate additions with

electron-deficient olefins, allenes, or alkynes),²²⁻²⁵ is the potential for additional reactions arising from the high nucleophilicity of free PCy₃. We recently described a particularly aggressive decomposition pathway operative in acrylate metathesis.⁹ Nucleophilic attack of PCy₃ on the acrylate olefin generates a stabilized α -carbanion (**A**, Scheme 5.1) or enolate,⁹ as recognized decades ago in Morita–Baylis–Hillman chemistry.²⁶ This potent Brønsted base²⁷ deprotonates the active metallacyclobutane intermediate **Ru-B^R** (see Chapter 3). The resulting decomposition cascade occurs with great rapidity,⁹ accounting for the high catalyst loadings required to maximize product yields when using **GII** for acrylate cross-metathesis.²⁸⁻³⁰ The problem is not limited to **GII**. Because all metathesis catalysts converge on the identical set of active species (examples of which are shown in Chart 5.1b), use of any PCy₃-stabilized precatalyst—whether **M2**, **GII**, or another—results in the same limitations.

Scheme 5.1. Generation of a potent Brønsted base via nucleophilic attack by PCy₃ on methyl acrylate



Such challenges to productivity are especially important given the dominance of **GII** in synthetic applications, as noted above. The enormous popularity of this catalyst is undoubtedly due in part to familiarity, but simple economics are also relevant, **GII** being among the least expensive of the available Ru-NHC metathesis catalysts (see Table A11 in the appendix). Offsetting such gains, however, are the high catalyst loadings required to compensate for its short lifetime in acrylate metathesis. Furthermore, catalyst decomposition has an adverse effect on product selectivity and purity, owing to competing C=C isomerization (the most common side-reaction in metathesis chemistry),^{21,31-33} as well as challenges in removing decomposed ruthenium products from the organic constituents.³⁴ Of note, distillation has been reported to significantly promote product isomerization⁵ or decomposition,^{35,36} while column chromatography is hampered by streaking of the decomposed Ru species on the column.^{37,38}

The present study was aimed at eliminating these problems, and, optimally, at establishing the potency of **GII** in acrylate metathesis. Our initial line of inquiry was inspired by the Sasol

finding that phenols such as *p*-cresol (4-methylphenol) greatly improved yields in **GII**-promoted cross-metathesis of acrylates with 1-decene.^{39,40} The protective effect was proposed to originate in the ability of the phenol to sequester PCy₃ and to stabilize **Ru-A** via hydrogen bonding.^{41,42} The utility of the original protocol was undermined, however, by the need for large amounts of the phenol (500 equiv vs Ru, or 2.5 g of *p*-cresol for cross-metathesis of 9 mL of 1-decene), removal of which by basic extraction or column chromatography is nontrivial. We were therefore intrigued by the potential of poly(vinylphenol) resins as convenient, readily removed, potentially recyclable catalyst promoters.

Here we report that such phenol-functionalized polymer resins dramatically increase metathesis yields in acrylate cross-metathesis, via a previously unconsidered enolate-quenching mechanism. The resin bearing sequestered phosphonium salt is simply filtered off at the end of reaction. This approach offers a straightforward, powerful means of upgrading the metathesis performance of **GII** and **M2** to match—or, in the case of methyl acrylate, to exceed—that of the important, widely used phosphine-free catalyst **HII**.

5.3 Results and Discussion

5.3.1 Impact of Catalyst Loadings on Yields

Synthetic organic chemists regard the Grubbs catalyst as “de rigueur” for the metathesis of electron-deficient olefins. Issues of catalyst performance, while critical in, e.g., pharmaceutical process chemistry, are often viewed with less concern in target-driven synthesis or discovery applications, where catalyst decomposition is normally compensated for by increasing the proportion of catalyst as required. From this perspective, however, the performance in Figure 5.1 is enlightening. The demanding cross-metathesis of anethole **3** with 2-ethylhexyl acrylate (EHA), which yields the high-value cinnamate **4a**, is shown to proceed to ca. 70% yield at a catalyst loading of 0.1 mol %. Complete cessation of metathesis is evident by 30 min, indicating catalyst decomposition. The more striking aspect of the figure, however, is the marginal improvement in yield achieved via a 30-fold increase in catalyst loading, to 3 mol % **GII**. To put this in perspective, performing the latter reaction on 10 g of **3** would require nearly 1 g of **GII** (see Table A11 in the appendix) to achieve <90% capture of the high-value phenylpropanoid moiety as **4a**, accompanied by unfavorable consequences in terms of cost, workup, and isolated yields.

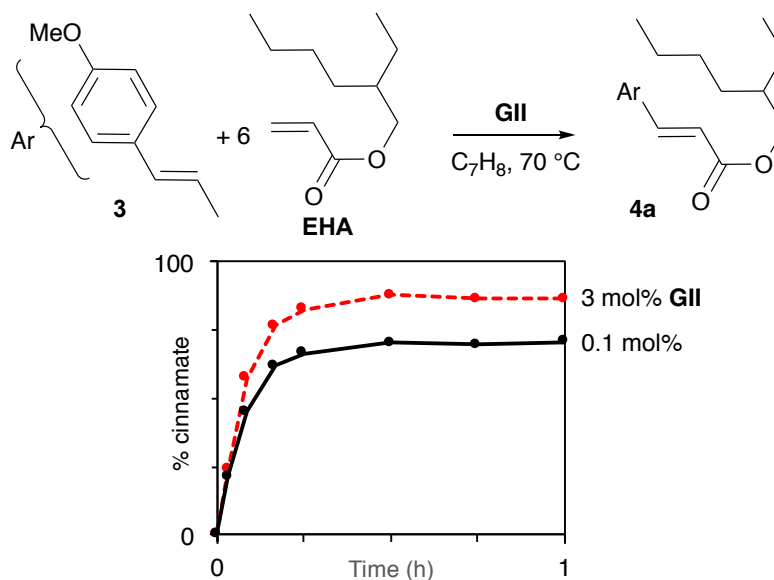
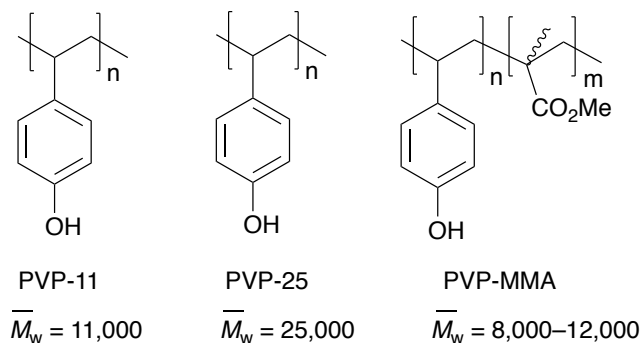


Figure 5.1. Acrylate metathesis via **GII**: limited improvements in yield of (E)-**4a** upon increasing the catalyst loading 30-fold. GC analysis ($\pm 2\%$ in replicate runs). For metathesis byproducts, see below.

5.3.2 Use of Poly(vinylphenols) as Catalyst Promoters.

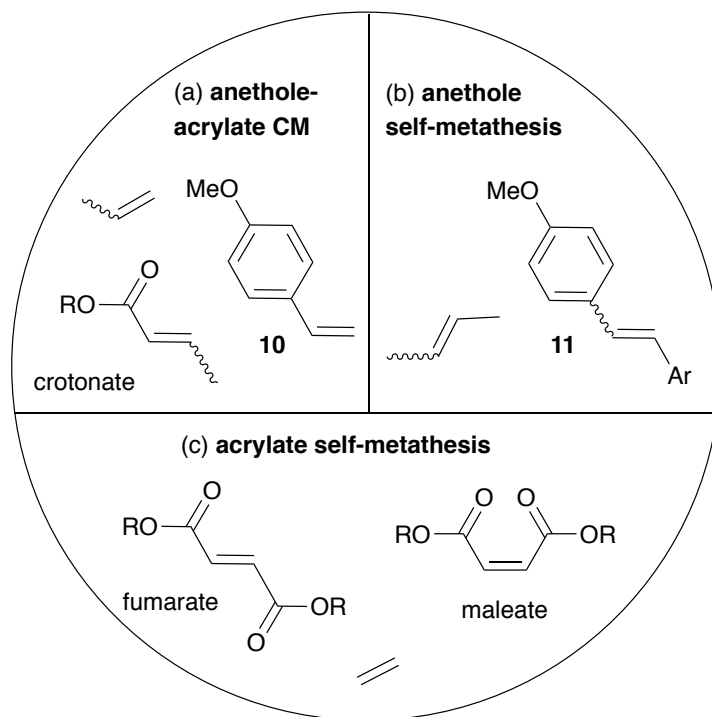
In examining the potential utility of phenol resins in this chemistry, we commenced by repeating the reaction of Figure 5.1 in the presence of commercially available poly(vinylphenols) PVP-11, PVP-25, and PVP-MMA, to assess the impact on product yields and selectivity relative to p-cresol. In all of these polymers, the phenol ring is subtended via the 4-position, providing a functional mimic of p-cresol. The PVP-11 and PVP-25 polymers differ in their average molecular weight, as shown in Chart 5.2, while PVP-MMA contains ca. 50% methyl methacrylate (MMA) as a co-monomer.

Chart 5.2. Poly(vinylphenol) Resins Studied



Expected byproducts from the metathesis reaction of **3** with an acrylate partner are shown in Chart 5.3. Byproducts generated via CM include propylene (formed by the desired reaction of **3** and acrylate), vinylanisole **10**, and methyl or 2-ethylhexyl crotonate. Of these, the styrenyl derivative **10** is of greatest relevance, as it contains the valuable anisole moiety. Compound **10** and crotonate are formed as the undesired cross-products of anethole–acrylate CM; furthermore, **10** may be generated by CM of **3** with propylene or ethylene (primary or secondary metathesis products, respectively). In the presence of active catalyst, however, **10** is readily converted into the target cinnamate **4a** via a further cycle of acrylate coupling. More recalcitrant is the predominantly trans-configured stilbenoid product **11** resulting from self-metathesis of either anethole or **10** (or indeed via their CM reaction). Steric congestion at the double bond in **11** places a high demand on reactivity: while this byproduct can likewise be recycled into **4a** via further metathesis with EHA, the reaction is slow even at 70 °C,⁴³ and catalyst lifetime is therefore critical. Included for completeness in Chart 5.3 are the fumarate and maleate products formed by acrylate self-metathesis. However, these byproducts are expected to be minimal for such Class IV olefins.⁴⁴ This indeed proved the case (<1%; see below), enabling use of acrylate in excess.

Shown in Table 1 is the proportion of cinnamate **4a**, anisole **10**, and stilbenoid **11** formed upon CM of anethole and EHA, and the impact of molecular or polymer-bound phenols on this product distribution. These reactions were carried out using 4 equiv acrylate in 1,2-dichloroethane (DCE) at 70 °C, the conditions originally developed for metathetical synthesis of **4a**.⁴³ Screening was carried out in an adapted seven-well HEL reactor equipped with individual, chilled condensing tips (see Figure 5.4 below), with removal of the volatile olefins via a slow argon purge. Sweeping out the volatile terminal olefins was essential for high yields. Removing these species minimizes secondary/tertiary metathesis reactions leading to **10** rather than cinnamate **4**, and limits decomposition arising from formation of methyldiene **Ru-A**¹⁰⁻¹⁶ and the unsubstituted metallacyclobutane **Ru-B** (R = H).⁴⁵⁻⁵²

Chart 5.3. Primary Metathesis Byproducts Formed by (a) Cross-Metathesis, (b) Anethole Self-Metathesis, and (c) Acrylate Self-Metathesis (Ar = 4-Methoxyphenyl)**Table 5.1. Impact of Phenols on Productivity of **GII** in Anethole–EHA Cross-Metathesis ^a**

	Phenol	Equiv phenol ^b	% Conv ^c	% Yield ^c		
				4a	10	11
1	none	none	99	85	3	11
2	<i>p</i> -cresol	100	100	96	2	2
3	PVP-11	100	99	94	4	2
4	PVP-25	100	100	95	3	2
5	PVP-MMA	100	100	96	2	2
6	PVP-MMA	50	100	91	3	6
7	PVP-MMA	500	100	92	4	4
8 ^d	PVP-MMA	100	100	88	7	5

^a Conditions: 4 equiv EHA vs **3**, 1 mol % **GII**, 1,2-dichloroethane, 70 °C, 4 h. ^b Equiv phenol vs Ru. ^c Yields assessed by GC, based on **3** as the limiting reagent; **4a** is >99% E. Agreement within replicate runs $\pm 1\%$. <1% maleate/fumarate products, accompanied by unreacted acrylate: see fully assigned GC trace (see Figure A45 in the Appendix).⁵³ ^d Reaction time 1 h.

In the absence of phenol, yields of **4a** obtained with **GII** under these conditions reached 85% (Table 5.1, entry 1). In comparison, phosphine-free catalyst **HII** has been shown to deliver essentially quantitative yields of **4a** under similar conditions.⁴³ Addition of a 100-fold excess of

p-cresol to the **GII** reaction improved yields of **4a** to 96% (entry 2). Similar performance was observed for the phenol resins (entries 3–5). While the different structural features in these polymers could potentially affect polymer swelling and hence access to the phenol sites, comparable promoting effects were found with all three resins. Decreasing the proportion of PVP-MMA to 50 equiv proved slightly detrimental (91% **4a**, entry 6). Increasing the proportion of phenol to 500 equiv, unexpectedly, was also slightly deleterious (92%, entry 7), perhaps because the resin sequesters the catalyst to some extent. We therefore adopted 100 equiv PVP-MMA as the standard for subsequent studies. Interrupting the reaction of entry 5 at 1 h (entry 8) showed complete consumption of anethole, but ca. 10% of the high-value arylpropenyl unit remained in the form of anisole **10** and stilbenoid **11**. Finally, use of poly(methacrylic acid) was much less effective (yielding 87% **4a** under conditions corresponding to those of entries 2–5; see Table 5.3 below), possibly because this resin promotes catalyst binding or decomposition.

Subsequent studies examined the impact of PVP-MMA on the performance of different catalysts. In these experiments, the catalyst loading was halved, to highlight differences in behavior. The proportion of EHA was accordingly increased to 6 equiv, relative to **3**.⁴³ Both **GII** and the Umicore catalyst **M2** effected 99% conversion of anethole in the absence of resin, but ca. 10% of the stilbenoid **11** remained, accompanied by smaller amounts of vinylanisole **10** (Table 5.2, entries 1 and 2). Use of 100 equiv PVP-MMA greatly improved performance, increasing yields of **4a** by up to 12%, to levels just short of those attained with **HII** (99%, entry 3). Added phenol had no apparent effect on **HII**, as expected.

Motivated by the classification of DCE as a hazardous solvent by the CHEM21 consortium,⁵⁵ and as a probable human carcinogen by the U.S. Environmental Protection Agency,⁵⁶ we also examined the impact of switching from DCE to toluene as the reaction medium. “Green” ethereal solvents were not explored, however, given the demonstrated inefficiency of anethole CM in THF, relative to toluene.⁵⁷ In toluene, yields of **4a** obtained with **GII** were markedly lower than those in DCE (76%, vs 84%; entry 4 vs 1). Solvent effects in metathesis are notoriously complex,⁵⁸ with different impacts on the rates of initiation, productivity, and deactivation.¹⁰ In the present case, enhanced enolate nucleophilicity in the less-polar solvent may contribute. The phenol resin dramatically improved performance, increasing yields to 96% (entry 4). With **M2**, the improvement was even greater, reaching 99% **4a** (entry 5).⁵⁴ These figures should be compared to a yield of 95% **4a** obtained using **HII** in this solvent. Thus,

poly(vinylphenol) renders the most affordable versions of these second-generation catalysts also the most effective, in an environmentally less hazardous solvent than that originally required. The possible slight improvement in the **HII**-catalyzed reaction (entry 6) should not be overinterpreted, as the difference is within the statistical error in these experiments.

Table 5.2. Impact of PVP-MMA on Performance of Different Catalysts in Anethole-EHA Cross-Metathesis ^a

Catalyst		Equiv resin ^b	% Conv ^c	% Yield ^c		
				4a	10	11
<i>1,2-dichloroethane solvent</i>						
1	GII	0	99	84	4	11
		100	100	96	1	3
2	M2	0	99	88	3	8
		100	100	97	1	2
3	HII	0	100	99	1	0
		100	100	99	1	0
<i>toluene solvent</i>						
4	GII	0	98	76	8	14
		100	100	96	2	2
5	M2 ⁵⁴	0	98	76	9	13
		100	100	99	1	0
6	HII	0	100	95	2	3
		100	100	99	1	0

^a Conditions are as described in Table 5.1, except: 6 equiv EHA vs **3**; solvent as indicated; 0.5 mol % Ru. ^b PVP-MMA resin. ^c Yields assessed by GC, based on **1** as the limiting reagent; $\pm 2\%$ in replicate runs.

5.3.3 Impact of Acrylate Bulk

A major difference between EHA and more routinely employed acrylates such as methyl acrylate is the steric bulk of the 2-ethylhexyl ester substituent. We find that greater acrylate bulk has a positive impact on cross-metathesis productivity at 0.1 mol % **GII** (the reduced catalyst loading is chosen to maximize differences in performance). While the rate curves in Figure 5.2a show rapid deactivation in the reaction of **3** with both EHA and MA, yields of **4a** were ca. 15% higher than those of the corresponding methyl cinnamate **4b**. We attribute the difference to the small size and consequently more aggressive Brønsted basicity of the methyl acrylate-derived enolate, which can more readily approach the catalyst.⁹

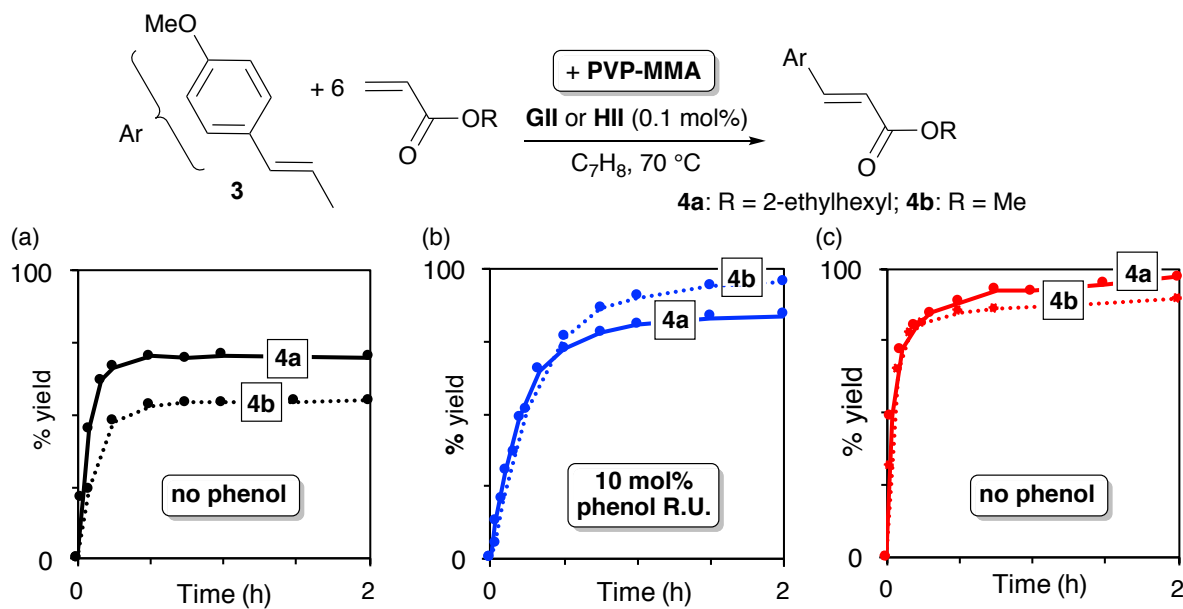


Figure 5.2. Impact of acrylate bulk on efficacy of phenol resin in anethole–acrylate CM, catalyzed by (a) **GII**, no added phenol; (b) **GII**, with 10 mol% added PVP-MMA (i.e. 100 phenol repeat unit (R.U.) vs. **GII**); and (c) **III**, no added phenol. $\pm 2\%$ in replicate runs.

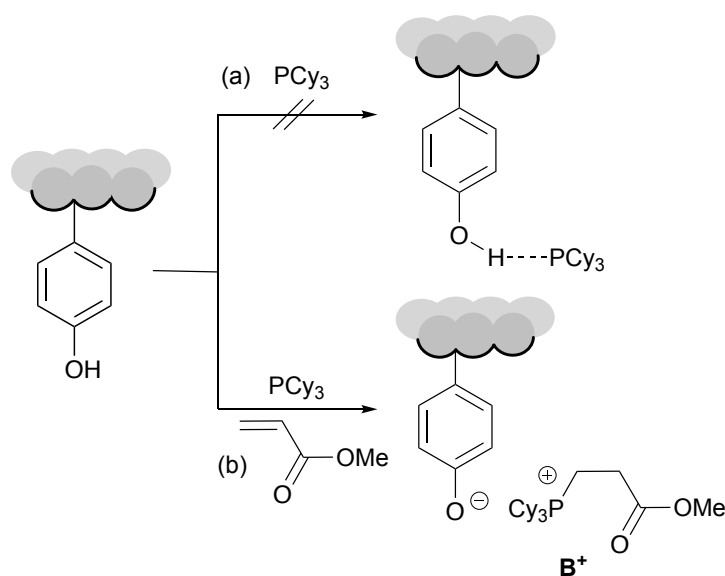
However, this greater steric accessibility also favours protonation of the enolate by resin, as discussed below. Indeed, the resin exerts an even greater protective effect with MA, enabling yields of methyl cinnamate **4b** superior to those of 2-ethylhexyl cinnamate **4a** (95% vs 84%, Figure 5.2b). In comparison, the maximum yield of **4b** attainable with phosphine-free **III** is 90% (Figure 5.2c), a point of keen interest given the ubiquity of methyl acrylate in the cross-metathesis literature.^{59–63} That is, in the presence of the phenol resin, the performance of **GII** for this widely used acrylate does not merely equal, but surpasses, the current state of the art.⁶⁴

5.3.4 Protective Effects of Resin

Additional experiments were carried out to probe whether the protective effect of the phenol resin is due to PCy₃ sequestration, as originally suggested for molecular phenols.^{39,40} Treating a toluene solution of PCy₃ with PVP-MMA (100 equiv phenol; Scheme 5.2a) at 70 °C caused no change in the ³¹P{¹H} NMR spectrum over 4 h, and no diminution of the signal for free PCy₃ vs an integration standard. In the presence of excess methyl acrylate, in contrast, the singlet due to PCy₃ disappeared completely within the same time period, and no new NMR signals were evident. Formation of the phosphonium salt [**B**]⁺ (see Scheme 5.2b) was confirmed by analysis of the resin isolated from this reaction (NMR and infrared (IR) spectroscopy, and matrix-assisted

laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS)). We infer that the resin functions principally as a sacrificial proton source, which intercepts the enolate and prevents catalyst decomposition.⁹ Indeed, experiments with molecular phenols (*p*-cresol and *p*-chlorophenol) likewise showed no evidence of phosphine sequestration, at the PCy₃ concentrations relevant to low catalyst loadings).⁶⁵ In short, we conclude that, under catalytically relevant conditions, using minimal catalyst loadings, sequestration of PCy₃ by the phenol (whether molecular or resin) is minimal.

Scheme 5.2. Exploring the function of PVP-MMA: (a) Sequestration of PCy₃ and (b) protonation of the enolate formed by nucleophilic attack of PCy₃ on acrylate



The resin-bound aryloxide generated in this chemistry (see Scheme 5.2b) is expected to be innocuous, from the perspective of exchange with the chloride ligands on the catalyst. Prior findings indicated that more accessible, molecular aryloxide anions required a heavy-metal counterion to enable efficient salt metathesis.^{38,66}

Additional experiments were conducted to examine whether trace water might provide an alternative proton source that renders resin treatment superfluous. Unexpectedly, small amounts of water were found to dramatically impede anethole–methyl acrylate cross-metathesis. Replacing the PVP-MMA resin with H₂O at its limiting concentration in toluene (330 ppm, or 80 equiv per Ru; Figure 5.3a),⁶⁷ caused yields of **4b** to fall from 95% to 23%. When water and resin were simultaneously present, yields were substantially restored, although use of phenol itself had a limited effect (82% vs 35% **4b**, respectively). The greater efficacy of the resin suggests

operation of a multivalent effect associated with the proximity of multiple phenol functionalities in the resin.

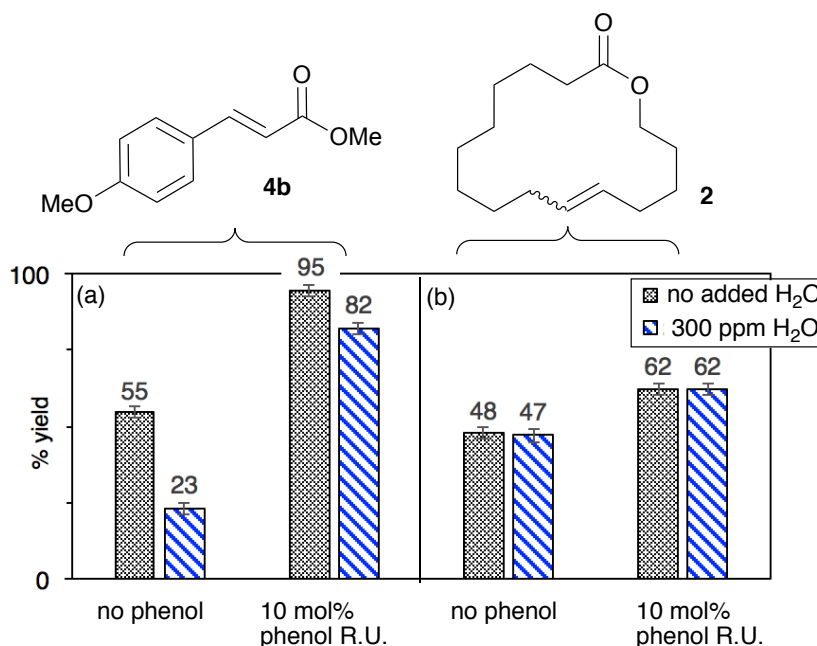


Figure 5.3. Negative impact of added water, and protective effect of PVP-MMA (100 equiv phenol R.U. vs **GII**), in (a) anethole-methyl acrylate CM (200 mM **1**, 6 MA, 0.1 mol% **GII**, 70°C, 4 h); (b) RCM macrocyclization (5 mM **6**, 0.5 mol % **GII**, C₇H₈, 40 °C, 4 h).

The adverse impact of water on Ru-catalyzed olefin metathesis has received rather little attention to date, because it is typically masked by high catalyst loadings. Recent work at 0.1 mol % Ru or lower demonstrated that macroscopic amounts of water (ca. 5% by volume) indeed limit metathesis productivity.^{10,68} To parallel the acrylate metathesis experiments above, we performed RCM macrocyclization of hex-5-enylundec-10-enoate **1** (the α,ω -diene precursor to **2**; see Figure 5.3b) with **GII** in water-saturated toluene (330 ppm of H₂O; Appendix H). Yields of the 16-membered macrolactone **2** were identical to those in anhydrous toluene. The sensitivity of this reaction to water is clearly much less than that of acrylate CM, despite the nearly 10-fold lower Ru concentration (25 ppm, vs 200 ppm in the CM reactions; see appendix H).

Catalyst decomposition during RCM of **1** is due to water-accelerated methylidene abstraction by PCy₃: it is associative in donor, accounting for its operation only at high water concentrations.¹⁰ Cyclization of **1**, although challenging, does not involve an electron-deficient olefin. We propose that the much more negative impact of water in the presence of acrylate and PCy₃ is due to a

different catalyst decomposition pathway: specifically, deprotonation of water by enolate, and catalyst degradation by the hydroxide ion thus formed. The reduced water-sensitivity of acrylate metathesis in the presence of resin indicates that the pendant phenol groups on the polymer effectively compete with water for reaction with enolate.

The positive impact of the resin in the macrocyclization experiments indicates that the role of the phenolic resin is not limited to enolate quenching. In these reactions, no enolate formation can occur. Rather, the phenolic groups may act to bind polar impurities present at ppm levels in the substrate or solvent. Sequestering of contaminants via hydrogen bonding would inhibit donor-accelerated decomposition of **GII**^{10,12} and base-induced decomposition of **III**.^{5,32,46} This finding may indicate a generally beneficial role for such resins for metathesis in minimally purified media, where contaminants introduced via the solvent and/or substrate feed threaten catalyst longevity.

5.4 Conclusions

Metathesis of electron-deficient olefins is an enabling tool in organic synthesis, widely used to introduce functional groups in conjugation with the C=C bond, and/or to access directly functionalized olefins for subsequent transformation. Of particular importance are conjugated esters accessed via acrylate metathesis, and used in the assembly of structurally complex products or functional materials. **GII** is widely used for this purpose, this catalyst offering a less expensive alternative to the leading phosphine-free catalyst **III**. Unfortunately, however, PCy₃-stabilized catalysts such as **GII** and its indenylidene analogue **M2** deliver limited yields of the synthetic targets in acrylate cross-metathesis. A major cause is catalyst decomposition by reactive enolates generated by nucleophilic attack of free PCy₃ on the electron-deficient olefin. As shown for **GII** above, catalyst performance is only marginally improved even by large (30-fold) increases in catalyst loadings, because rates of decomposition increase in parallel.

The foregoing describes a simple, straightforward means of transforming the performance of PCy₃-stabilized catalysts in acrylate cross-metathesis. As exemplified by the demanding CM of anethole, use of **GII** and **M2** in the presence of a poly(vinylphenol) resin delivered near-quantitative yields of a high-value ethylhexyl cinnamate, at catalyst loadings as low as 0.5 mol %. This level of efficiency is comparable to that obtained with **III**. For the small, widely used coupling partner methyl acrylate, use of **GII** in conjunction with the resin enables performance

superior to that of **III**. Because the enolate anion formed by attack of PCy₃ on methyl acrylate is considerably less bulky than that derived from EHA, it is both highly reactive toward the catalyst, and also more readily protonated by the phenolic resin. In either case, resin removal is straightforward, requiring simply filtration.

As this suggests, the protective influence of phenols does not involve sequestration of PCy₃ itself. We find that protonation of PCy₃, even by molecular phenols, can indeed occur at high phosphine concentrations (60 mM; 50–100-fold excess phenol). At the low catalyst and phenol loadings commensurate with efficient metathesis, however, the resin functions as a sacrificial proton source that converts the strongly basic enolates into unreactive, resin-bound, readily removed phosphonium salts. Therefore, its chief function is to prevent deprotonation and decomposition of the catalyst.

Importantly, water cannot be used as an alternative proton source. Replacing the resin with water caused significant further degradation in metathesis productivity, most probably because of the formation of the small hydroxide ion, which can react with the catalyst. In the presence of phenol resin, however, the deleterious impact of water is substantially reduced, indicating that the resin is able to compete with water as a proton source, presumably by furnishing an innocuous aryloxide byproduct in place of hydroxide.

Additional protective effects of the resin emerged in an RCM macrocyclization reaction that does not involve enoic carbene or other electron-deficient Ru intermediates. No enolates can be formed in these reactions: rather, we suspect that the resin removes polar contaminants via hydrogen bonding. Resin treatment thus not only transforms the efficiency of PCy₃-stabilized catalysts in acrylate metathesis, but offers a potential means of reducing extensive prepurification protocols in the metathesis of acrylates and other olefins.

5.5 Experimental Details

5.5.1 General Procedures

Procedures requiring an inert atmosphere, including charging of reactors, were carried out in a glovebox under Ar or N₂, unless otherwise indicated. **GII**, **III**, **M20**, *p*-xylene (99%), dodecane (99%, anhydrous), dimethyl terephthalate (99%), 4-vinyl anisole (97%), 1,2-dichloroethane (99.8%, anhydrous), and the poly(4-vinylphenol) resins PVP-11, PVP-25, PVP-MMA, and Amberlite CG50 were purchased from Aldrich and used as received. Catalyst **M2** was provided

by Umicore. Anethole (99%, FG Aldrich) and 2-ethylhexyl acrylate (EHA; 98%, Aldrich) were passed through neutral alumina and degassed by sparging with Ar (10 min). Toluene was sparged with Ar (30 min) and passed through an MBraun solvent purification system. Hex-5-enylundec-10-enoate **1**,⁶⁹ 2-ethylhexyl cinnamate **4b**,⁴³ methyl cinnamate **4a**,⁴³ and stilbenoid **11**⁴³ (authentic samples, for GC-FID calibration) were synthesized as previously described.

NMR spectra were recorded on a Bruker Avance 300 NMR spectrometer at 23 ± 2 °C and referenced against the residual proton signals of the deuterated solvents (¹H), or triethyl phosphate (³¹P capillary: 72 mM in C₆D₆; 0.583 ppm, relative to external 85% H₃PO₄ at 0 ppm).

Catalyst screening was carried out in an argon-swept, seven-well multitest HEL 7 reactor (Figure 5.4), in which each glass-lined well is equipped with an individual condenser tip, a customized PTFE ring to inhibit cross-contamination, and a magnetic stir bar. In the standard configuration, some cross-contamination between wells was observed under conditions of catalysis. This was eliminated by adding customized PTFE gaskets (white rings in Figure 5.4) between each condenser tip and glass well-liner. The gaskets are sufficiently loose to permit escape of ethylene.



Figure 5.4. Photograph of the HEL7 Reactor, showing (left) temperature-controlled condenser tips, (right) glass-lined reactor wells sealed with white PTFE gaskets, and (center) an individual glass well liner.

Samples for analysis were quenched with KTp⁷⁰ or diluted with nondegassed chlorinated solvents. Control experiments indicated that dilution in air was sufficient to quench acrylate metathesis (in contrast to other metathesis reactions);⁷⁰ see section 5.5.8.

5.5.2 Analyte Quantification by GC analysis

Analyte quantification was effected using Shimadzu Model GC2010 Plus or Agilent Model 7683B series gas chromatographs (GCs) equipped with autosamplers and flame ionization detectors (FIDs) and, respectively, a Restek Rtx-5 polysiloxane or Agilent HP-5 polysiloxane column (30 m length, 250 or 320 μm diameter). Calibration curves of peak areas versus concentration in the relevant concentration regimes were established with ca. 1:1 (w/w) sample versus dodecane or *p*-xylene as internal standard. Yields were determined from the integrated peak areas versus internal standard. Separation was achieved as follows:

(a) *Shimadzu GC2010 Plus GC*: The inlet temperature was 310 °C, with a split ratio of 50:1, and H₂ (UHP grade) as the carrier gas. Separation was achieved by heating the Restek RTx-5M polysiloxane column to 50 °C for 3 min, then increasing the temperature by 10 °C/min to 310 °C, and holding for 5 min at this temperature (total separation time: 24 min). The flame ionization detector (FID) was heated to 310 °C.

(b) *Agilent 7890A Series GC*: The inlet temperature was maintained at 250 °C, with a split ratio of 10:1, and He (UHP grade) as the carrier gas. Separation was achieved by heating the HP-5 column to 80 °C for 2 min, then increasing the temperature by 30 °C / min to 320 °C, and holding for 2 min at this temperature (total separation time: 12 min). The FID was heated to 275 °C.

For representative GC traces and retention times, see Figures A45–A46 and Tables A7–A8.

5.5.3 Alternative Protocol: Analyte Quantification by ¹H NMR Analysis

Chemical shifts used for quantification (300 MHz, CDCl₃) were as follows: anethole, 6.73 ppm (dt, ²J_{HH} = 9 Hz, ⁴J_{HH} = 2 Hz, 2H); (E)-**4a**, 7.55 ppm (d, ²J_{HH} = 16 Hz, 1H).⁵⁷ To prevent metathesis post-sampling, aliquots (ca. 50 μL) for ¹H NMR analysis were diluted six-fold in cold (-35 °C) CDCl₃, and then quenched by shaking vigorously under an aerated atmosphere (see control experiments above). Catalysis was carried out according to the representative protocol for kinetic studies (see section 5.5.4), but using C₇D₈ as the reaction solvent, and dimethyl terephthalate (DMT) as the internal standard (δ_{H} 8.01 ppm, s). For representative spectra, see Figures A35 and A36.

5.5.4 Acrylate CM Reactions

Representative Procedure for Catalyst Screening. In a representative procedure using the HEL reactor, each well was charged with a magnetic stir bar, **GII** (4.2 mg, 5×10^{-3} mmol, 1 mol %), anethole (75 μ L, 0.50 mmol), 2-ethylhexyl acrylate (420 μ L, 2.0 mmol), PVP-MMA (110 mg, 100 equiv phenol), and 1,2-dichloroethane (2.5 mL). The reactor was sealed, removed from the glovebox, connected to a steady stream of Ar, and transferred to a preheated aluminum block at 70 °C. The heating block extends over only the lower 3 mL of the reactor wells, enabling efficient condensation in each well via an individual condenser tip maintained at 5 °C via a recirculating water-ethylene glycol chiller. Control experiments indicated no cross-contamination under these conditions. After 4 h, the reactor was cooled and opened to air; *p*-xylene (internal standard: 62 μ L, 0.50 mmol) was added via an Eppendorf-style micropipette, and samples were removed for GC analysis.

Representative Procedure for Kinetic Studies. To permit sampling throughout catalysis, a Schlenk flask in the glovebox was used. Stock solutions of catalyst and substrates were prepared by dissolving **GII** (12.2 mg, 0.0144 mmol) in 1.00 mL C₇H₈ (14.4 mM), or dissolving anethole (535 μ L, 3.60 mmol), 2-ethylhexyl acrylate (4.49 mL, 21.6 mmol, 6 equiv) and dodecane (818 μ L, 3.60 mmol, 1 equiv) to 10.0 mL total volume in C₇H₈ (resulting in a final anethole concentration of 360 mM). An aliquot was removed for analysis of the initial substrate/dodecane ratio. A 20 mL Schlenk flask equipped with a magnetic stir bar was then charged with the substrate solution (2.00 mL, 0.72 mmol 1), toluene (1.55 mL), PVP-MMA (15.8 mg, 0.072 mmol, 100 equiv vs **GII**), and **GII** (50 μ L, 0.72 nmol, 0.1 mol %). The reaction was heated to 70 $\pm$ 1 °C in a thermostatted oil bath. Aliquots (ca. 10 μ L) were periodically withdrawn, quenched, and subjected to GC analysis.

5.5.5 Protective Effect of the Resin

Sequestration of PCy₃ by Resin. Solid PVP-MMA (785 mg, 3.56 mmol) was added to a 10 mL Schlenk flask equipped with a magnetic stir bar. To this was added a solution of PCy₃ in toluene (3.56 mL, 0.0356 mmol PCy₃; 0.01 equiv, from a 10.0 mM stock solution containing 14.0 mg PCy₃ in 5.00 mL C₇H₈). The sealed vessel was heated to 70 °C for 1 h, cooled to room temperature (RT), and gravity-filtered through Celite to avoid evaporation. The concentration of free PCy₃ in the original stock solution, and that in the filtrate, was measured by ³¹P{¹H} NMR

integration versus a triethyl phosphate standard in a glass capillary. $^{31}\text{P}\{^1\text{H}\}$ NMR (C_7H_8 , 121.5 MHz) for the resin experiment: δ 10.4 (s, PCy_3 ; 100% relative to the PCy_3 stock solution).

Sequestration of Phosphonium Enolate by Resin. As above, but with methyl acrylate (906 μL , 10.0 mmol, 200 equiv) added to the PCy_3 stock solution. The resin was filtered off, washed with hexanes (5×5 mL), and dried in vacuo.

Analysis of filtrate: no $^{31}\text{P}\{^1\text{H}\}$ NMR signals. Analysis of isolated resin: $^{31}\text{P}\{^1\text{H}\}$ NMR (THF, 121.5 MHz): δ 31.9 (s, 79%, $[\text{Cy}_3\text{PCH}_2\text{CH}_2\text{CO}_2\text{Me}]^+$, $[\text{B}]^+$), 31.7 (s, 21%, $[\text{Cy}_3\text{PCH}_2\text{CH}(\text{CO}_2\text{Me})(\text{CH}_2\text{CH}_2\text{CO}_2\text{Me})]^+$) ppm. MALDI-TOF MS (pyrene): m/z 367.32, 100% ($[\text{B}]^+$; simulated, 367.28), 453.37, 13% ($[\text{Cy}_3\text{PCH}_2\text{CH}(\text{CO}_2\text{Me})(\text{CH}_2\text{CH}_2\text{CO}_2\text{Me})]^+$; simulated, 453.31). IR (ATR, cm^{-1}): $\nu(\text{C}=\text{O})$ 1725 ($[\text{B}]^+$), 1699 (PVP-MMA). Cf. 1726 cm^{-1} for independently prepared $[\text{B}]\text{Cl}$;⁹ 1698 cm^{-1} for fresh commercial PVP-MMA.

5.5.6 Assessing the Impact of Added Water

Anethole–Acrylate CM. Toluene (20 mL) and freshly degassed H_2O (1 mL) were stirred for 16 h at RT to obtain a water-saturated toluene solution, which was used to prepare stock solutions as above, and assessed for the kinetics of acrylate metathesis, as indicated in the Representative Procedure (Section 5.5.4 above).

RCM Macrolactonization. A water-saturated toluene solution was prepared as above, and used to prepare a stock solution of hex-5-enylundec-10-enoate **1** (20.2 mg, 0.080 mmol) and dodecane (18.2 μL , 0.080 mmol, 1 equiv) in toluene; total volume of 1.00 mL (80 mM **1**). Similarly, a stock solution of **GII** was prepared (12.7 mg, 0.0150 mmol in 500 μL , diluted 10-fold in toluene; 6.0 mM). The solution of **1** (225 μL , 0.018 mmol 5), toluene (3.32 mL), PVP-MMA (2.0 mg) and **GII** (60 μL of the stock solution, 0.09 nmol, 0.5 mol %) were mixed in a 20 mL Schlenk flask and heated to 40 °C. Yields of lactone **2** were assessed by GC-FID, and compared to the corresponding reactions in which no PVP-MMA was added.

5.5.7 Use of Poly(acrylic acid) Resins as Catalyst Promoters

For comments regarding the poorer performance of poly(methacrylic acid), see Section 5.3.2 above. The data are provided in Table 5.3 below; Entries 1 and 3 are reproduced from Table 5.1, for convenience.

Table 5.3. Impact of Poly(acrylic acid) on productivity of GII in anethole–EHA cross-metathesis. ^a

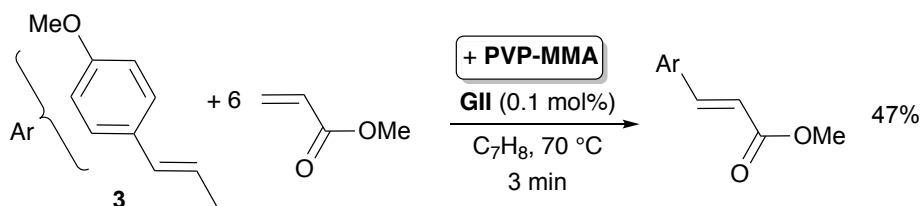
	Additive	Equiv acid ^b	% Conv ^c	% Yield ^c		
				4a	10	11
1	none	none	99	86	3	10
2	PVP-MMA	10	100	89	3	8
3	PVP-MMA	100	100	96	2	2
4	Amberlite CG50 ^d	10	99	89	4	6
5	Amberlite CG50 ^d	100	99	87	5	7

^aConditions: 4 equiv EHA vs. **3**, 1 mol% **GII**, 1,2-dichloroethane, 70 °C, 4 h. ^bEquiv of phenolic or carboxylic repeat units vs. Ru. ^cYields assessed by GC, based on **3** as the limiting reagent; **4a** is > 99% *E*. ^dMacroporous, cross-linked (4%) poly(methacrylic acid).

5.5.8 Control Experiments: Catalyst Quenching by Air

In anethole–acrylate cross-metathesis reactions, control experiments demonstrated rapid, complete loss of catalyst activity on exposure to air. For example, in the anethole–methyl acrylate cross-metathesis reaction of Figure 5.2b, analysis of an aliquot removed at 3 min and diluted with non-degassed CH₂Cl₂ revealed 47% cinnamate **4b** (Scheme 5.3). This is approximately half of the 95% yield ultimately achieved: i.e., the catalyst is still active prior to air-exposure. No increase was observed on reanalysis of the GC sample after 24 h, confirming the efficacy of catalyst quenching by air.

Scheme 5.3. Reaction used to assay catalyst quenching by non-degassed CH₂Cl₂ (10 mol% PVP-MMA, i.e. 100 phenol repeat unit (R.U.), vs. **GII).**



5.6 References

- (1) Grela, K., *Olefin Metathesis-Theory and Practice*. Wiley: Hoboken, NJ, 2014.
- (2) Grubbs, R. H.; Wenzel, A. G., *Handbook of Metathesis*. 2nd ed.; Wiley-VCH: Weinheim, 2015.
- (3) Cossy, J.; Arseniyadis, S.; Meyer, C., *Metathesis in Natural Product Synthesis: Strategies, Substrates and Catalysts*. Wiley-VCH: Weinheim, 2010.
- (4) Higman, C. S.; Lummiss, J. A. M.; Fogg, D. E. *Angew. Chem., Int. Ed.* **2016**, 55, 3552–3565.

- (5) Farina, V.; Horváth, A., Ring-Closing Metathesis in the Large-Scale Synthesis of Pharmaceuticals. In *Handbook of Metathesis*, Grubbs, R. H.; Wenzel, A. G., Eds. Wiley-VCH: Weinheim, 2015; Vol. 2, pp 633–658.
- (6) Hughes, D. L. *Org. Process Res. Dev.* **2016**, *20*, 1008–1015.
- (7) Chikkali, S.; Mecking, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 5802–5808.
- (8) Biermann, U.; Bornscheuer, U.; Meier, M. A. R.; Metzger, J. O.; Schafer, H. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 3854–3871.
- (9) Bailey, G. A.; Fogg, D. E. *J. Am. Chem. Soc.* **2015**, *137*, 7318–7321.
- (10) McClennan, W. L.; Rufh, S. A.; Lummiss, J. A. M.; Fogg, D. E. *J. Am. Chem. Soc.* **2016**, *138*, 14668–14677.
- (11) Lummiss, J. A. M.; Higman, C. S.; Fyson, D. L.; McDonald, R.; Fogg, D. E. *Chem. Sci.* **2015**, *6*, 6739–6746.
- (12) Lummiss, J. A. M.; McClennan, W. L.; McDonald, R.; Fogg, D. E. *Organometallics* **2014**, *33*, 6738–6741.
- (13) Lummiss, J. A. M.; Botti, A. G. G.; Fogg, D. E. *Catal. Sci. Technol.* **2014**, *4*, 4210–4218.
- (14) Lummiss, J. A. M.; Ireland, B. J.; Sommers, J. M.; Fogg, D. E. *ChemCatChem* **2014**, *6*, 459–463.
- (15) Hong, S. H.; Wenzel, A. G.; Salguero, T. T.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2007**, *129*, 7961–7968.
- (16) Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2004**, *126*, 7414–7415.
- (17) Zhao, Z.-X.; Wang, H.-Y.; Guo, Y.-L. *Rapid Commun. Mass Spectrom.* **2011**, *25*, 3401–3410.
- (18) Galan, B. R.; Pitak, M.; Gembicky, M.; Keister, J. B.; Diver, S. T. *J. Am. Chem. Soc.* **2009**, *131*, 6822–6832.
- (19) Galan, B. R.; Pitak, M.; Keister, J. B.; Diver, S. T. *Organometallics* **2008**, *27*, 3630–3632.
- (20) The rate constant for loss of PCy₃ from RuCl₂(H₂IMes)(PCy₃)(=CH₂) **GIIIm** is 4.7 x 10⁻⁴ s⁻¹, 300 times lower than the value of 0.13 s⁻¹ reported for **GII**. For measurements on the methyldiene complex **GIIIm**, see ref 11. For measurements on **GII**, see: Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543–6554.
- (21) Higman, C. S.; Lanterna, A. E.; Marin, M. L.; Scaiano, J. C.; Fogg, D. E. *ChemCatChem* **2016**, *8*, 2446–2449.
- (22) Ye, L.-W.; Zhou, J.; Tang, Y. *Chem. Soc. Rev.* **2008**, *37*, 1140–1152.
- (23) Fan, Y. C.; Kwon, O. *Chem. Commun.* **2013**, *49*, 11588–11619.
- (24) Wang, Z.; Xu, X.; Kwon, O. *Chem. Soc. Rev.* **2014**, *43*, 2927–2940
- (25) Gimbert, C.; Lumbierres, M.; Marchi, C.; Moreno-Mañas, M.; Sebastián, R. M.; Vallribera, A. *Tetrahedron* **2005**, *61*, 8598–8605.

(26) For the original report, see: (a) Morita, K.-I.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815. (b) Baylis, A. B.; Hillman, M. E. D. Ger. Pat. DE2155113A, 1972. For reviews showcasing recent advances for this and related phosphine-catalyzed methodologies, see: refs 22-25 and (c) Wei, Y.; Shi, M. *Chem. Rev.* **2013**, *113*, 6659–6690. For a review describing early advances specific to the Morita-Baylis-Hillman reaction, see: (d) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–892.

(27) While pK_a values have not, to our knowledge, been measured for [B]Cl or related phosphonium salts (Scheme 1), a value of 18.0 was measured for the related ammonium salt $[\text{Me}_3\text{NCH}_2\text{CO}_2\text{Me}]^+$ in water. See: (a) Rios, A.; Amyes, T. L.; Richard, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 9373–9385. In broad agreement is the range of 17.4–22.0 reported for the DABCO-derived ammonium salt $[\text{R}_3\text{NCH}_2\text{CH}_2\text{CO}_2\text{Me}]^+$ (DABCO = 1,4-diazabicyclo[2.2.2]octane) in methanol. See: (b) Plata, R. E.; Singleton, D. A. *J. Am. Chem. Soc.* **2015**, *137*, 3811–3826. Enhanced basicity is expected for the phosphonium enolate in the present work, on the assumption that the negative charge is less effectively stabilized by a nearby positive charge on phosphorus, vs. nitrogen.

(28) For selected comparisons of the yields attainable in acrylate CM using **GII**, **HII**, and other catalysts, see: (a) Miao, X.; Fischmeister, C.; Dixneuf, P. H.; Bruneau, C.; Dubois, J. L.; Couturier, J. L. *Green Chem.* **2012**, *14*, 2179–2183. (b) Bilel, H.; Hamdi, N.; Zagrouba, F.; Fischmeister, C.; Bruneau, C. *RSC Adv.* **2012**, *2*, 9584–9589. (c) Rybak, A.; Meier, M. A. R. *Green Chem.* **2007**, *9*, 1356–1361. (d) Abbas, M.; Slugovc, C. *Tetrahedron Lett.* **2011**, *52*, 2560–2562.

(29) (a) Lin, T.-Y.; Zhu, C.-Z.; Zhang, P.; Wang, Y.; Wu, H.-H.; Feng, J.-J.; Zhang, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 10844–10848; (b) Pritchett, B. P.; Kikuchi, J.; Numajiri, Y.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2016**, *55*, 13529–13532; (c) Wang, W.; Cencic, R.; Whitesell, L.; Pelletier, J.; Porco, J. A. *Chem. Eur. J.* **2016**, *22*, 12006–12010; (d) Yasuda, Y.; Ohmiya, H.; Sawamura, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 10816–10820; (e) Peng, Y.; Totsingan, F.; Meier, M. A. R.; Steinmann, M.; Wurm, F.; Koh, A.; Gross, R. A. *Eur. J. Lipid Sci. Technol.* **2015**, *117*, 217–228. (f) De Joarder, D.; Jennings, M. P. *Eur. J. Org. Chem.* **2015**, *2015*, 3303–3313; (g) Kinzurik, M. I.; Hristov, L. V.; Matsuda, S. P. T.; Ball, Z. T. *Org. Lett.* **2014**, *16*, 2188–2191; (h) Basu, S.; Waldmann, H. *Bioorg. Med. Chem.* **2014**, *22*, 4430–4444.

(30) In early work, the poor performance of **GII** in acrylate metathesis was proposed to arise from strong PCy₃ binding – effectively, formation of $\text{RuCl}_2(\text{H}_2\text{IMes})(\text{PCy}_3)(=\text{CHCO}_2\text{R})$ as an excessively stable resting-state species. (See: Hoveyda, A. H.; Gillingham, D. G.; Van Veldhuizen, J. J.; Kataoka, O.; Garber, S. B.; Kingsbury, J. S.; Harrity, J. P. A. *Org. Biomol. Chem.* **2004**, *2*, 8–23). This is difficult to reconcile, however, with the fact that no such complex is spectroscopically observable. Indeed, we find that the resting-state methyldiene complex $\text{RuCl}_2(\text{H}_2\text{IMes})(\text{PCy}_3)(=\text{CH}_2)$ **Ru-A** is the only $[\text{Ru}]=\text{CHR}$ species observed, other than **GII**. In an early report, a trace signal (<7% of alkylidene integration) was attributed to the enoic alkylidene (see: Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783–3784). No supporting data were reported, however, and the transient nature of this signal is inconsistent with a stable resting state.

(31) Larionov, E.; Li, H.; Mazet, C. *Chem. Commun.* **2014**, *50*, 9816–9826.

(32) van Lierop, B. J.; Lummiss, J. A. M.; Fogg, D. E., Ring-Closing Metathesis. In *Olefin Metathesis-Theory and Practice*, Grell, K., Ed. Wiley: Hoboken, NJ, 2014; pp 85–152.

- (33) Higman, C. S.; Plais, L.; Fogg, D. E. *ChemCatChem* **2013**, *5*, 3548–3551.
- (34) For recent leading reviews on ruthenium contamination of metathesis products, and purification methods, see: (a) Wheeler, P.; Phillips, J. H.; Pederson, R. L. *Org. Process Res. Dev.* **2016**, *20*, 1182–1190. (b) Skowerski, K.; Gułajski, Ł., Purification Strategies in Olefin Metathesis. In *Olefin Metathesis-Theory and Practice*, Wiley: Hoboken, NJ, 2014; pp 559–571. (c) Vougioukalakis, G. C. *Chem. – Eur. J.* **2012**, *18*, 8868–8880. An alternative, extensively explored option is immobilization of metathesis catalysts on polymer or other solid supports. A recent review surveys this approach, with a robust critique of the impact on catalyst activity and productivity. See: (d) Hubner, S.; de Vries, J. G.; Farina, V. *Adv. Synth. Catal.* **2016**, *358*, 3–25.
- (35) Maynard, H. D.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 4137–4140.
- (36) Yee, N. K.; Farina, V.; Houpis, I. N.; Haddad, N.; Frutos, R. P.; Gallou, F.; Wang, X.-J.; Wei, X.; Simpson, R. D.; Feng, X.; Fuchs, V.; Xu, Y.; Tan, J.; Zhang, L.; Xu, J.; Smith-Keenan, L. L.; Vitous, J.; Ridges, M. D.; Spinelli, E. M.; Johnson, M.; Donsbach, K.; Nicola, T.; Brenner, M.; Winter, E.; Kreye, P.; Samstag, W. *J. Org. Chem.* **2006**, *71*, 7133–7145.
- (37) Cho, J. H.; Kim, B. M. *Org. Lett.* **2003**, *5*, 531–533.
- (38) Conrad, J. C.; Parnas, H. H.; Snelgrove, J. L.; Fogg, D. E. *J. Am. Chem. Soc.* **2005**, *127*, 11882–11883.
- (39) Forman, G. S.; Tooze, R. P. *J. Organomet. Chem.* **2005**, *690*, 5863–5866.
- (40) 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.
- (41) Phosphine sequestration is the dominant strategy used to address the limitations associated with the PCy₃ ligand in **GII** and related metathesis catalysts. Sequestration agents used include copper (I) halides (see: (a) **CuCl**: Dias, E. L.; Grubbs, R. H. *Organometallics* **1998**, *17*, 2758–2767. (b) **CuI**: Voigtritter, K.; Ghorai, S.; Lipshutz, B. H. *J. Org. Chem.* **2011**, *76*, 4697–4702. (c) Abbasa, M.; Leitgebb, A.; Slugovc, C. *Synlett* **2013**, *24*, 1193–1196) and fluorous or charge-tagged phosphine ligands in biphasic media (see: (c) Corrêa da Costa, R.; Gladysz, J. A. *Chem. Commun.*, **2006**, 2619–2621 and, for recent developments: (d) Balogh, J.; Hlil, A. R.; Su, H.-L.; Xi, Z.; Bazzi, H. S.; Gladysz, J. A. *ChemCatChem* **2016**, *8*, 125–128).
- (42) Added phenol (up to 3.6 M) or benzoic acid reportedly enhanced the initiation efficiency of **GII** in ring-opening metathesis polymerization, an effect attributed to protonation of PCy₃. See: Slugovc, C.; Demel, S.; Riegler, S.; Hobisch, J.; Stelzer, F. *J. Mol. Catal. A* **2004**, *213*, 107–113.
- (43) Lummiss, J. A. M.; Oliveira, K. C.; Prankevicus, A.; Santos, A.; dos Santos, E. N.; Fogg, D. E. *J. Am. Chem. Soc.* **2012**, *134*, 18889–18891.
- (44) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.
- (45) Vignon, P.; Vancompernelle, T.; Couturier, J.-L.; Dubois, J.-L.; Mortreux, A.; Gauvin, R. M. *ChemSusChem* **2015**, *8*, 1143–1146.
- (46) Ireland, B. J.; Dobigny, B. T.; Fogg, D. E. *ACS Catal.* **2015**, *5*, 4690–4698.
- (47) Skowerski, K.; Czarnocki, S. J.; Knapkiewicz, P. *ChemSusChem* **2014**, *7*, 536–542.

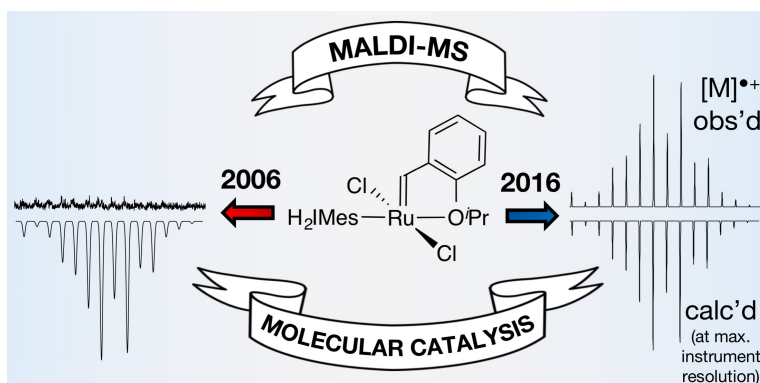
- (48) Monfette, S.; Eyholzer, M.; Roberge, D. M.; Fogg, D. E. *Chem. – Eur. J.* **2010**, *16*, 11720–11725.
- (49) van der Eide, E. F.; Romero, P. E.; Piers, W. E. *J. Am. Chem. Soc.* **2008**, *130*, 4485–4491.
- (50) Romero, P. E.; Piers, W. E. *J. Am. Chem. Soc.* **2007**, *129*, 1698–1704.
- (51) van Rensburg, W. J.; Steynberg, P. J.; Meyer, W. H.; Kirk, M. M.; Forman, G. S. *J. Am. Chem. Soc.* **2004**, *126*, 14332–14333.
- (52) 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.
- (53) A referee suggests that PCy₃ could potentially cause transesterification, or anionic polymerization of the acrylate. The mass balance (Table 1) and GC-FID evidence argue against transesterification. The fully assigned GC-FID spectrum for a representative reaction (Figure A45 in the Appendix) shows that the volatile constituents are composed of solely metathesis products and unreacted acrylate. If any acrylate polymers are formed, the extent is minimal, as indicated by the absence of any significant ¹H NMR signals at the diagnostic locations (2.29 and 1.91 ppm; Figure A36 in the Appendix). See: Baugh, L. S.; Sissano, J. A.; Kacker, S.; Berluche, E.; Stibrany, R. T.; Schulz, D. N.; Rucker, S. P. *J. Polym. Sci., A* **2006**, *44*, 1817–1840.
- (54) Comparable performance was observed for catalyst **M20** (the PPh₃ analogue of **M2**) in the absence of resin, with 97% yield of cinnamate **4a**. In related experiments with PPh₃, no phosphonium salt is evident, suggesting that this phosphine is insufficiently basic to trigger enolate formation. This catalyst clearly warrants more attention in the metathesis of electron-deficient olefins. We note, however, that PPh₃ remains competent to effect methyldiene abstraction: see ref 10.
- (55) Prat, D.; Wells, A.; Hayler, J.; Sneddon, H.; McElroy, R.; Abou-Shehada, S.; Dunn, P. J. *Green Chem.* **2016**, *18*, 288–296.
- (56) U.S. Environmental Protection Agency, Integrated Risk Information System (IRIS) on 1,2-Dichloroethane. National Center for Environmental Assessment, Office of Research and Development: Washington, DC, 1999.
- (57) Higman, C. S.; de Araujo, M. P.; Fogg, D. E. *Catal. Sci. Technol.* **2016**, *6*, 2077–2084.
- (58) Collins, S. K., Solvent and Additive Effects on Olefin Metathesis. In *Handbook of Metathesis*, Grubbs, R. H.; Wenzel, A. G., Eds. Wiley-VCH: Weinheim, 2015; Vol. 1, pp 343–377.
- (59) Prunet, J.; Grimaud, L., Cross-Metathesis in Natural Products Synthesis. In *Metathesis in Natural Product Synthesis: Strategies, Substrates and Catalysts*, Cossy, J.; Arseniyadis, S.; Meyer, C., Eds. Wiley-VCH: Weinheim, 2010; pp 287–312.
- (60) A Web of Science search indicates 132 results for acrylate and "cross-metathesis", of which 93 are retained on refinement with methyl acrylate as an additional term.
- (61) Dixneuf, P. H.; Bruneau, C.; Fischmeister, C. *Oil Gas Sci. Technol.* **2016**, *71*, 19.
- (62) Winkler, M.; Meier, M. A. R. *Green Chem.* **2014**, *16*, 3335–3340.
- (63) Spiccia, N. D.; Solyom, S.; Woodward, C. P.; Jackson, W. R.; Robinson, A. J. *J. Org. Chem.* **2016**, *81*, 1798–1805, and references therein.

- (64) A recent report describes improved yields in cross-metathesis of methyl oleate with **GII**, on replacing methyl acrylate with maleic acid as the cross partner. See: Ferreira, L.; Schrekker, H.; *Catal. Sci. Technol.* **2016**, 6, 8138-8147. One potential benefit lies in the absence of Ru-methylidene intermediates. (For nucleophilic abstraction of the methylidene ligand by PCy₃, see ref 10). As well, however, maleic acid could potentially limit catalyst decomposition by protonating a PCy₃-generated enolate. To probe this point, we undertook CM of anethole **3** with maleic acid (6 equiv; 0.5 mol % **GII** vs. **3**; THF, 66 °C, 4 h). Cinnamate yields reached only 65%, however, as compared with near-quantitative conversions of **4b** for the resin-augmented **GII** reaction, at catalyst loadings five-fold lower. The poorer performance of maleic acid may be due in part to its insolubility in aromatic or halogenated solvents, which constrains use of THF as solvent.
- (65) The corresponding reaction with 100 equiv *p*-cresol with 20 mM PCy₃ in toluene resulted in a <2 ppm shift in the location of the ³¹P{¹H} NMR singlet for PCy₃ (from 10.4 to 8.8 ppm). As these results appear to conflict with those reported in ref 41, we repeated the experiment with *p*-chlorophenol, as in the literature study. A downfield shift to 14.4 ppm was observed. The higher acidity of the phenol (pK_a 9.42, vs. 10.26 for *p*-cresol, both in H₂O; see: Pearce, P. J.; Simkins, R. J. J. *Can. J. Chem.* **1968**, 46, 241–248), clearly has an impact, albeit minor. Tripling the PCy₃ concentration, however (to 60 mM, a figure that would correspond to 30 mol% **GII** under the conditions of Tables 1 and 2), caused a downfield shift to 31.7 ppm, in good agreement with the literature value of 30.0 ppm. We conclude that while phenols indeed protonate PCy₃ at high concentrations, protonation is minimal under normal catalytic conditions, irrespective of whether the phenol is molecular or resin-supported.
- (66) Conrad, J. C.; Amoroso, D.; Czechura, P.; Yap, G. P. A.; Fogg, D. E. *Organometallics* **2003**, 22, 3634–3636.
- (67) This simulates use of non-dried toluene, as the limiting concentration of water in toluene at 25 °C is 330 ppm. See: László, K.; Demé, B.; Czakkel, O.; Geissler, E. *J. Phys. Chem. C* **2014**, 118, 23723–23727.
- (68) Guidone, S.; Songis, O.; Nahra, F.; Cazin, C. S. J. *ACS Catal.* **2015**, 5, 2697–2701.
- (69) Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792–803.
- (70) Blacquiere, J. M.; Jurca, T.; Weiss, J.; Fogg, D. E. *Adv. Synth. Catal.* **2008**, 350, 2849–2855.

Chapter 6. MALDI Mass Spectrometry as a Core Tool for Analysis of Labile Transition-Metal Complexes and Catalysts

6.1 Published contributions

Confronting Neutrality: Maximizing Success in the Analysis of Transition-Metal Catalysts by MALDI Mass Spectrometry. Gwendolyn A. Bailey and Deryn E. Fogg. *ACS Catalysis* **2016**, 4962–4971. (Full paper)



Abstract: The elucidation of molecular identity is a central challenge in homogeneous transition-metal catalysis. Most exacting, despite advances in electrospray-ionization mass spectrometry (ESI-MS), are neutral complexes, which encompass the vast majority of metal catalysts. Insight into molecular constitution, readily achieved in other areas of the chemical sciences, is commonly thwarted by fragmentation of inorganic and organometallic compounds, particularly for highly reactive species. MALDI-MS, where coupled with charge-transfer ionization, stands out from all other current MS methods in its unique capacity to report on the molecular identity of intact metal complexes irrespective of their initial charge state. Identified in the present work are methods that enable routine, unambiguous identification of such complexes across a wide range of standard MALDI mass spectrometers. The origin of fragmentation during MALDI-MS analysis is explored on 13 different instruments at 9 facilities and across a range of mass analyzers, from TOF, TOF-TOF, and Q-TOF to Orbitrap. Selected as test analytes were the second-generation Hoveyda and Grubbs metathesis catalysts and the Grubbs resting-state methyldiene complex, which span a very broad range in terms of ligand lability, and hence susceptibility to fragmentation. Three critical parameters emerge: (1) using the minimum applied laser energy necessary for sample volatilization; (2) minimizing the

absorption cross-section of the analyte at the laser wavelength: (a) by appropriate laser choice, where options exist, (b) by using a matrix that absorbs as strongly as possible at the laser wavelength, in significant excess relative to the analyte (e.g., 500-fold), and (c) by prompt analysis, to limit matrix sublimation in the ion source; (3) using a charge-transfer matrix devoid of reactive protic or donor sites. A final, forward-looking section highlights relevant advances in state-of-the-art instrumentation, and instrumental features that would contribute to the optimization of next-generation MALDI mass spectrometers for this emerging application. These include fast-firing, contoured-profile, and, potentially, wavelength-tunable lasers, high-resolution mass analyzers, automatic plate rastering with software to support retroactive compilation of spectra from optimal sampling locations, and soft-vacuum or atmospheric-pressure sources, in conjunction with a standardized anaerobic interface.

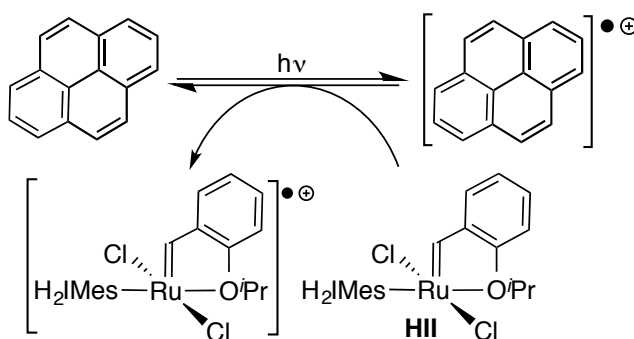
Author Contributions: The experiments for this paper were carried out in extensive field trials by GAB. The manuscript was conceived, written, edited, and revised by GAB and DEF.

6.2 Introduction

Soft-ionization mass spectrometric (MS) tools can afford powerful insight into the molecular constitution of transition-metal complexes and catalysts, including species formed in situ during catalysis.¹⁻⁵ Electrospray-ionization MS (ESI-MS), the dominant ionization method in current use, has been widely embraced for its sensitivity, softness, and dynamic range.⁶⁻¹⁰ Still challenging, however, is the analysis of neutral metal complexes, which represent the majority of organometallic catalysts.

Such complexes can be observed intact, without recourse to charged surrogate ligands or additives, via MALDI mass spectrometry (MALDI = matrix-assisted laser desorption-ionization). Use of a charge-transfer (CT) matrix transforms neutral analytes into their radical cations via one-electron oxidation, as depicted in Scheme 6.1.^{11,12} CT-MALDI MS can yield clear, unambiguous spectra enabling confident assignment of discrete metal complexes,¹³⁻²⁰ resting-state species formed during catalysis,^{11,21} and catalyst deactivation products.²¹

Scheme 6.1. Charge-Transfer MALDI-MS Analysis, Illustrated with the Hoveyda Catalyst HII and Pyrene^a



^a H₂IMes = 1,3-bis(mesityl)-4,5-dihydroimidazol-2-ylidene.

To date, however, MALDI-MS remains underutilized in organometallic chemistry and catalysis. This is not due to the scarcity of MALDI spectrometers, or to the sensitivity of the analytical method to extraneous contaminants. Indeed, because MALDI-MS involves analysis of solid samples, it is in many ways more robust and user-friendly than ESI-MS, which is normally carried out on solutions containing analytes at micro- to nanomolar concentrations.⁶ At these dilutions, aerial oxidation, decomposition, and background noise can all present difficulties. Particularly challenging is the analysis of reactive transition-metal complexes on shared

instruments also used for incompatible applications. Residues from proteomics analysis, for example (typically carried out in water or acetonitrile, with an added proton source such as trifluoroacetic or formic acid), have the potential to trigger hydrolysis, protonolysis, and/or ligand exchange.²²

Given the potential of charge-transfer MALDI-MS to address these issues, we have been surprised not to see MALDI methods more widely adopted in transition-metal chemistry. Our recent experience has been instructive. We now believe that uptake has been discouraged by one simple problem: excessive analyte fragmentation. Studies on instruments of different vintages, ranging from state-of-the-art to widely available workhorse spectrometers, revealed such problems in the majority of cases, when standard analytical methods were used.

Notwithstanding enormous advances in the optimization of MALDI MS methodologies for the life sciences, understanding of the processes that trigger fragmentation of organometallic analytes remains rudimentary, and potential means of inhibiting fragmentation are largely unexplored. The importance of preserving organometallic molecules intact also profoundly differentiates this application from the dominant context of biopolymer analysis, where fragmentation is prized for its ability to yield essential insights into repeat-unit structure.^{23,24} Indeed, a painful correspondence exists between the importance of observing organometallic structures intact, and their susceptibility to fragmentation. This susceptibility is exacerbated by the reactivity inherent to many transition-metal catalysts (for which activity commonly depends on ligand lability), as well as the common presence of chromophores that absorb at the laser energy.

Here we identify key analytical parameters that contribute to fragmentation, and modifications that prove decisive in observing the molecular ion intact. Optimized MALDI-MS analysis represents a potentially transformative tool for the rapid, confident assignment of molecular identities in organometallic chemistry and catalysis.

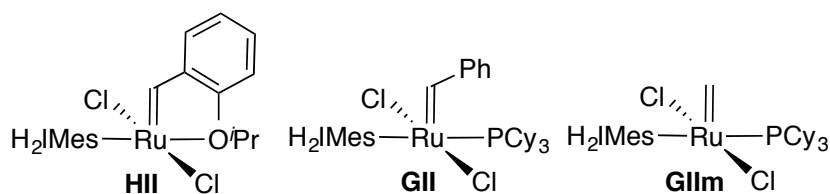
6.3 Results and Discussion

The present work originated in recent trials on state-of-the-art MALDI mass spectrometers, in which the performance routinely achievable on our original instrument (a Bruker Omnixflex MALDI-TOF MS of 2004 vintage) could not readily be reproduced. This unexpected discovery

impelled us to explore the origin of the performance differences. A systematic study of probe analytes on a range of instruments enabled identification of parameters that must be controlled to ensure the robust deployment of MALDI-MS analysis. These experiments were carried out using 13 different spectrometers at 9 facilities. The spectra presented below are those that best illustrate the phenomenon in question, preferentially acquired on the highest-resolution time-of-flight (TOF) instruments available, given the popularity of the TOF mass analyzer for MALDI-MS. Importantly, however, the findings are not limited to MALDI-TOF instruments: the optimized protocols developed herein were replicated on MALDI Orbitrap and Q-TOF (Q = quadrupole) spectrometers with excellent results. These data were acquired without anaerobic equipment any more specialized than an N₂-filled glovebag.²⁵ That is, they are relevant to general use in shared facilities without elaborate precautions to exclude air and water.

The complexes selected for study (Chart 6.1) include the Hoveyda metathesis catalyst **HII**, the Grubbs catalyst **GII**, and the Grubbs methyldiene complex **GIIIm**, the last of which is formed as the resting state in metathesis reactions promoted by **GII**.^{26,27} These complexes are of central importance in olefin metathesis, a highly topical area of modern catalytic chemistry,²⁸ but serve more broadly as models for reactive, coordinatively unsaturated transition-metal complexes. They are characterized by widely differing susceptibilities to fragmentation, a key asset in gauging the importance of the experimental parameters discussed below.

Chart 6.1. Analytes Examined by MALDI MS



6.3.1 Origin of Fragmentation

In initial experiments, we sought to identify the stage at which fragmentation predominantly occurs.²⁹ As a simple test, we compared spectra collected in two different instrument configurations: specifically, the reflector and linear TOF modes depicted in Figure 6.1. The spectrum obtained in linear mode shows only in-source decay (ISD). That is, it reveals only the fragmentation that occurs in the ionization chamber itself. The reflector configuration, in contrast, reveals both ISD and additional fragments arising from post-source decay (PSD).³⁰ PSD

is initiated during ion acceleration and reacceleration (i.e., in the ionization chamber and at the reflectron), but occurs in the field-free drift tube. Importantly, however, any PSD that occurs in linear mode goes unobserved, because momentum is conserved during flight. The parent and fragment ions thus travel down the flight tube with the same velocity, and are detected together. Key to their separation in reflector mode is reacceleration of the ions by the reflectron.³¹

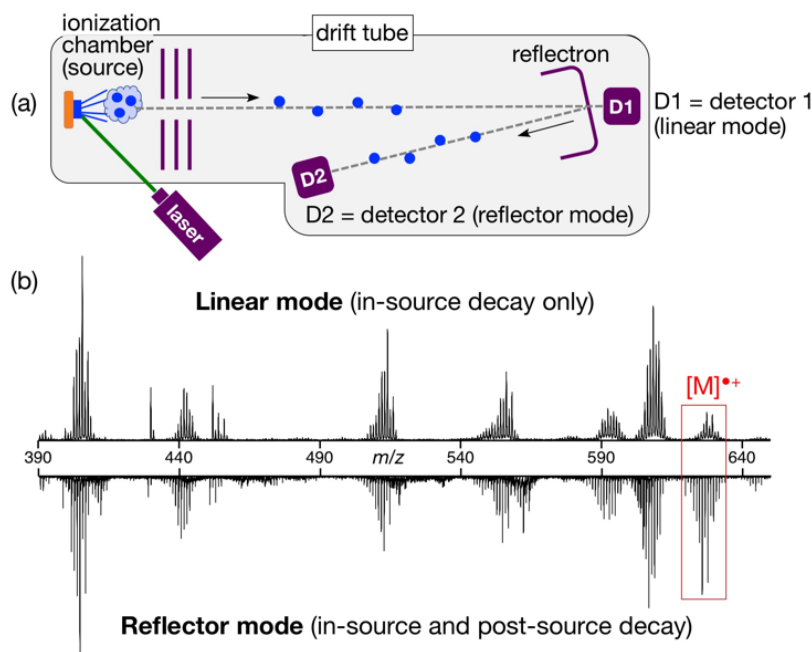


Figure 6.1. (a) Mass spectrometer schematic showing linear and reflector MALDI-TOF modes. (b) Linear and reflector-mode mass spectra of **HII**, showing the predominance of in-source decay (ISD).³²

The linear-mode spectrum of the Hoveyda catalyst **HII** maps almost precisely onto the reflector-mode spectrum (see Figure 6.1b), indicating that minimal added decomposition occurs via PSD. Instead, the majority of fragmentation takes place in the ion source. It should be noted that the reduced intensity of the parent radical cation $[M]^{*+}$ evident in the linear-mode experiment is an artifact of partial evaporation of the matrix prior to analysis. Indeed, this experiment brought out the critical importance of the matrix:analyte ratio, and the rapidity with which matrix evaporation can occur. Both points are treated in more detail below.

In-source decay points toward fragmentation of the analyte by absorption of laser energy.²⁹ Consistent with this, the intensity of the molecular ion $[\mathbf{HII}]^{*+}$ declines sharply as the laser energy is ramped up: see Figure 6.2a. Here the integrated intensity of $[M]^{*+}$ is shown as a percentage of the total intensity for all ions between m/z 390 and 640. This region was chosen to

capture the majority of Ru ions, while excluding organic fragments that would over-report on net fragmentation.

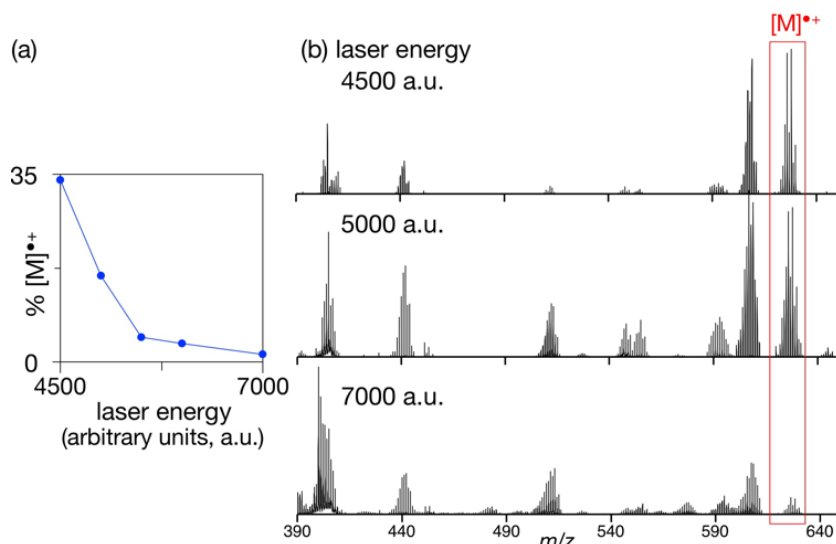


Figure 6.2. (a) Impact of laser energy on fragmentation, illustrated by analysis of **HII**. A laser energy of 4500 au (arbitrary units) was identified as the threshold for observation in this experiment. (b) Representative MALDI-MS spectra at selected laser energies.³²

The decrease in $[\text{HII}]^{++}$ as a function of laser energy is nonlinear, with extensive decomposition of the molecular cation once the laser energy is increased beyond the minimum required to observe a signal. Thus, comparison of the top two spectra in Figure 6.2b reveals a significant increase in fragmentation on increasing the laser energy by ca. 10%, from 4500 to 5000 au. The bottom spectrum illustrates the extreme difficulty in observing the molecular ion at laser energies 40% higher (7000 au).

These experiments pinpoint the laser energy as the primary cause of analyte fragmentation, and indicate the critical importance of identifying the minimum energy that can be applied.³³ Laser-induced fragmentation may result from direct laser excitation of the analyte and/or from excitation resulting from collisions in the gaseous ion plume.²⁹ Direct excitation is of particular concern for organometallic species, which commonly contain chromophores that absorb to some extent at the laser wavelength. Figure 6.3 illustrates this point. Evident here is the much more extensive fragmentation of **GII** relative to **GIIIm**,³⁴ behavior that correlates with the higher molar absorptivity of **GII** at the laser wavelength (ϵ_A). The reduced lability of the PCy₃ ligand in **GIIIm**, relative to **GII**,^{35,36} undoubtedly also contributes. (It may be noted that even **GII** is

considerably more robust than typical organometallic analytes, however, owing to the inverse trans effect exerted by the H₂IMes ligand.³⁶⁾

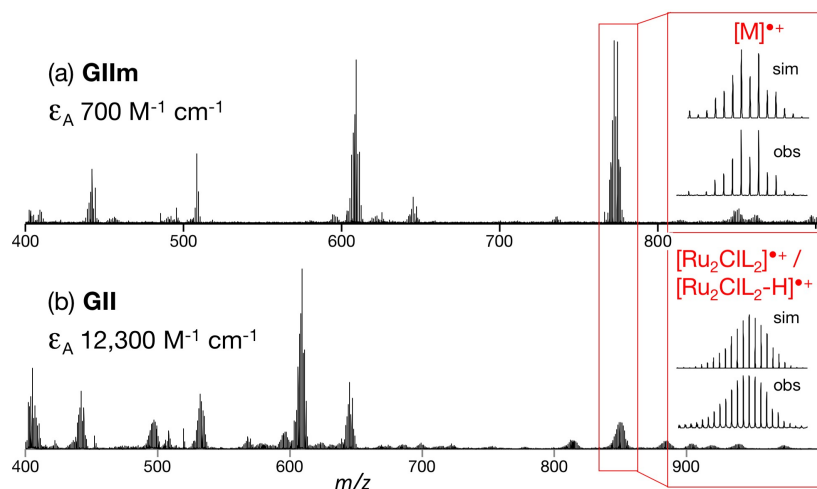


Figure 6.3. Impact of analyte ϵ_A on fragmentation: (a) for **GIIIm**; (b) for **GII** (L = H₂IMes; Nd:YLF laser, λ 349 nm). Insets show simulated³⁷ (sim) and observed (obs) isotope patterns. Spectra were obtained at the minimum laser energy required for sample volatilization.

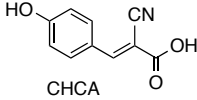
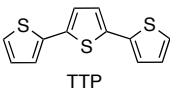
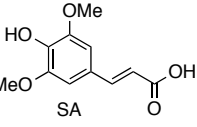
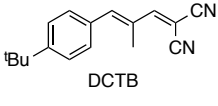
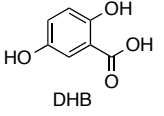
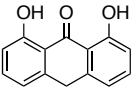
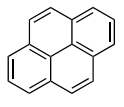
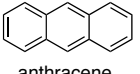
The extent of fragmentation of **GII** is in fact even greater than initial inspection suggests. Closer examination (see inset, Figure 6.3b) reveals complete disappearance of the signal for **[GII]^{•+}**. Instead, the signal observed is due to overlapping isotope patterns for a diruthenium complex, **[Ru₂Cl(H₂IMes)₂]^{•+}**, and a related species containing one less proton. These entities necessitate loss of **[PhCH₂PCy₃]Cl** from **GII**, behavior that parallels the well-established liberation of **[CH₃PCy₃]Cl** on decomposition of **GII** and **GIIIm** in solution.^{36,38-41} MALDI-MS analysis offers potentially valuable insights into the nature of the ruthenium coproducts, previously observable only where fortuitous crystallization enabled single-crystal X-ray crystallographic analysis.

6.3.2 Matrix Roles in Limiting Fragmentation

The extensive decomposition of **GII** in Figure 6.3, above attributed only to high ϵ_A , may alternatively be regarded as due to the very limited absorptivity of the pyrene matrix at the laser wavelength of 349 nm (ϵ_M ; Table 6.1). Strongly absorbing matrices are expected to confer 2-fold protection. By maximizing the efficiency with which laser energy is absorbed, they limit the applied laser energy required for sample volatilization,⁴² hence reducing plume temperatures and, in turn, excitation of the analyte.^{43,44} High- ϵ_M matrices are also expected to limit direct absorption of laser energy by the analyte. Dreisewerd has pointed out that, in peptide analysis,

optimal ion yields (i.e., enhanced $[M]^+$ signal intensity) are obtained where the matrix absorption is well matched to the laser wavelength.^{45,46} Examined below is the capacity of high- ϵ_M matrices to limit fragmentation of organometallic species. More specifically, we examine the impact of the relative absorptivity of the matrix versus the analyte ($\epsilon_{\text{rel}} = \epsilon_M/\epsilon_A$).

Table 6.1. Matrix Classes, Structures, and Reported Molar Absorptivities at Instrument Laser Wavelengths

ϵ_M ($M^{-1}cm^{-1}$)				ϵ_M ($M^{-1}cm^{-1}$)			
Matrix	337 nm; N ₂	349 nm; Nd:YLF	355 nm; Nd:YAG	Matrix	337 nm; N ₂	349 nm; Nd:YLF	355 nm; Nd:YAG
Class A: Acidic matrices^a				Class B: Brønsted (Lewis) base matrices^b			
 CHCA	24,600	24,800	23,500	 TTP	26,400	32,300	33,500
 SA	16,150	8,410	5,100	 DCTB	22,270	29,850	31,410
 DHB	3,550	900	400	Class C: Charge-transfer matrices			
 DT	1,490	1,910	2,100	 pyrene	42,100	2,830	2,240
				 anthracene	3,892	2,830	5,250

^a Abbreviations: CHCA = α -cyano-4-hydroxycinnamic acid; SA = sinapinic acid; DHB = 2,5-dihydroxybenzoic acid; DT = dithranol. ^b Abbreviations: DCTB = trans-2-[3-(4-tert-butylphenyl)-2-methyl-2-propenylidene]malononitrile; TTP = 2,2':5',2''-terthiophene. For the original matrix class assignments, see ref 16.

An unavoidable limitation in this study is the fact that almost all of the candidate matrices (the structures of which are given in Table 6.1) contain potentially non-innocent functionalities.¹¹ Thus, class A matrices,¹⁶ containing acidic groups, are classically used to ionize by protonation, and can potentially trigger ligand protonolysis. Class B matrices¹⁶ are Brønsted bases, designed to ionize by deprotonation. Their Lewis basicity, however, may enable ligand exchange. Class C

matrices,¹⁶ in comparison, are able to ionize only by charge transfer. Table 1 shows ϵ_M values for leading examples of each matrix class, at the wavelengths characteristic of the three principal laser types in current use: N₂, Nd:YLF, and Nd:YAG.⁴⁷

To dissect out the impact of ϵ_{rel} on fragmentation of the molecular ion, we chose **GIIm** as a test analyte, as we anticipated that perturbation by undesired matrix–analyte reactions should be limited by the low lability of this complex (see discussion above). Figure 6.4a plots the percent intensity of the **[GIIm]⁺** signal versus ϵ_{rel} . (For this analyte, unlike **III**, few cationic Ru fragments are seen, and the organic fragments are thus used to gauge total decomposition of **[M]⁺**.)

For the functionalized matrices (indicated in red in Figure 6.4a), the plot shows a trend toward greater **[M]⁺** intensity with increasing ϵ_{rel} , although the scatter observed indicates the operation of additional parameters. The non-innocence of these matrices, and the superior performance of “pure charge-transfer” matrices pyrene and anthracene, is probed below. Nevertheless, the correlation between better performance (i.e., stronger **[M]⁺**) and higher ϵ_M is clear, as also illustrated by the spectra observed with TTP and DT (Figure 6.4b), which exhibit extremes of high and low ϵ_{rel} , respectively, among the class A and B matrices examined. The clean signal for the molecular ion in TTP matrix, and the excellent match between the simulated and observed molecular ions, attest to the capacity of the matrix to shield the analyte from direct laser excitation. In contrast, the strongest signal for the spectrum obtained in DT is due to the **[MePCy₃]⁺** cation expected from decomposition of **GIIm**.^{31-34,36} Also evident, in both DT and TTP matrices, is a strong signal for the **[H₂IMes•H]⁺** cation, indicating protonation and loss of the N-heterocyclic carbene (NHC) ligand.

The most significant outliers in the experiments of Figure 6.4 are pyrene and anthracene, for which the signal intensity for the molecular cation is excellent, notwithstanding their relatively low ϵ_{rel} values. The impressive performance of these class C matrices reflects the absence of reactive functional groups. Also of note is the fact that even robust **GIIm** is not immune to gas-phase reaction with functionalized matrices. This point is examined more closely in the following section.

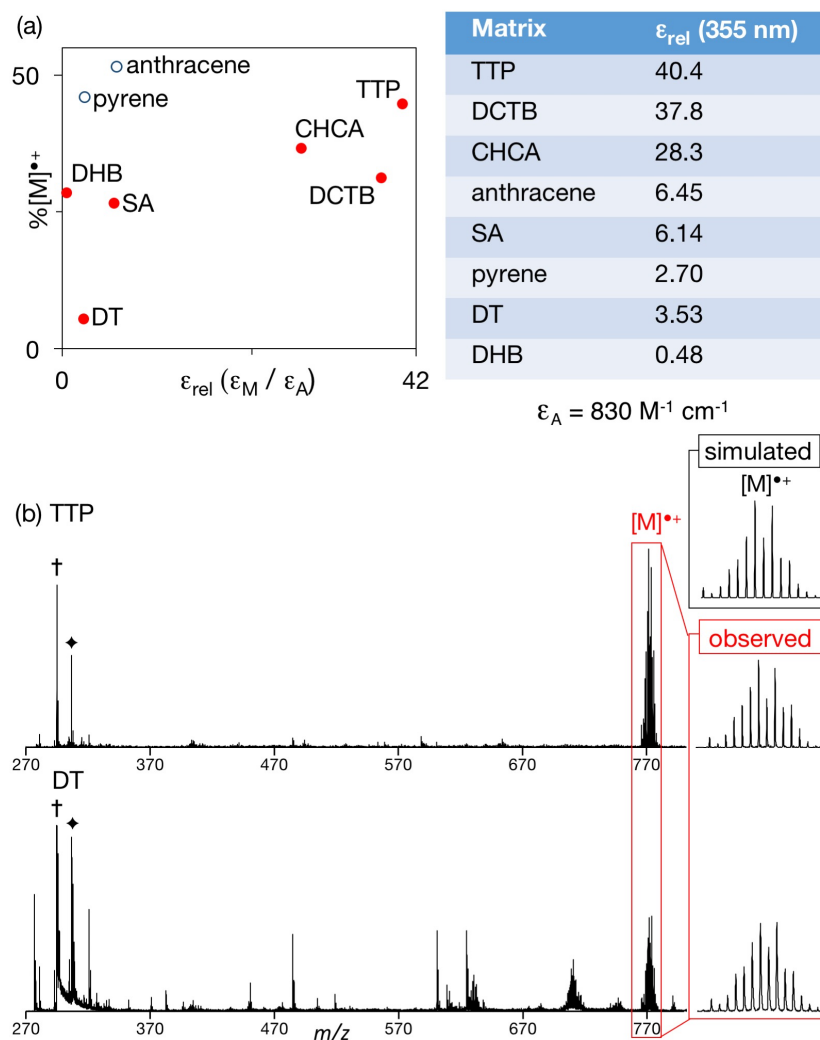


Figure 6.4. Impact of matrix ϵ_M on fragmentation, assessed in analysis of nonlabile **GIIm**. (a) Increasing intensity of $[\text{GIIm}]^{•+}$ signal with increasing ϵ_{rel} .⁴⁷ $\%[M]^{•+}$ = intensity of $[\text{GIIm}]^{•+}$ vs all fragments in the range m/z 270–800. (b) Spectra of **GIIm** in matrices characterized by extremes of high and low ϵ_{rel} . The inset shows simulated and observed isotope patterns. $[\text{MePCy}_3]^+$ and $[\text{H}_2\text{IMes}\cdot\text{H}]^+$ cations arising from ligand loss are indicated by the labels $\dagger$ and $\blacklozenge$, respectively. Nd:YAG laser; λ 335 nm. For spectra in other matrices, see Figure A41 in the Appendix.

More generally, the positive correlation between ϵ_{rel} and the strength of the $[M]^{•+}$ signal implies that, while a matrix of poorer ϵ_M may be tolerated if the analyte is a weak chromophore (i.e., where ϵ_{rel} is high, as in the case of pyrene and **GIIm** at 355 nm), an analyte bearing a strong chromophore mandates use of a high- ϵ_M matrix. Thus, less satisfactory results were seen for the more strongly absorbing **III** in pyrene matrix (see Figure 6.1), and attempts to enhance analyte protection by doubling the matrix:analyte ratio had little effect.

6.3.3 Role of Matrix in Promoting Fragmentation

In the foregoing ϵ_{rel} study, **GII**m was chosen for its low reactivity, to minimize perturbation by extraneous matrix–analyte reactions. A number of reports in fact describe the successful use of polar and protic matrices for MALDI-MS analysis of transition-metal complexes.⁴⁸ However, the analytes are typically coordinatively saturated, 18-electron complexes of the late transition metals, containing nonlabile (often multidentate) ligands. The robustness of such species is expected to significantly surpass that of many catalyst molecules, for which activity typically rests on ligand lability. We therefore chose the Hoveyda metathesis catalyst **HII** as an analyte more representative than nonlabile **GII**m and **GII**,³⁵ in order to gauge the compatibility of class A/B matrices with a relatively reactive organometallic complex.

The spectrum of **HII** in anthracene matrix (used in preference to pyrene for its 2.5-fold higher ϵ_{rel} , and hence improved performance) is provided as a benchmark in Figure 6.5a. In comparison, all class A/B matrices, examined under identical conditions, caused extensive decomposition of **HII** (Figure 6.5b–e). Peak expansions in the molecular ion region are particularly revealing. For DT, signals are visible in this region, but the isotope pattern indicates multiple, unidentifiable species. For CHCA, no molecular ion remains. For TTP, considerable fragmentation and agglomeration is evident, although a strong signal can be seen for $[\text{M} - \text{H}]^+$. For DCTB, the isotope pattern for the molecular ion is surprisingly clean, given the extensive fragmentation observed. However, the extremely cluttered spectrum would undermine confidence in assignment of an unknown compound.

The much poorer performance of DCTB and TTP, relative to anthracene, is particularly striking in view of the protective effect expected from their high ϵ_{M} values (see Table 6.1). This beneficial effect is undermined by the higher absorptivity of **HII**, which results in an ϵ_{rel} value of ca. 3.5 (i.e., at the lowest end of the range shown in Figure 6.4a above), although the harder laser employed with DCTB undoubtedly also contributes to poor performance. The matrices discussed here were chosen for their ubiquity and their utility in other contexts. For additional, less widely used matrices showing even greater decomposition (DHB and SA), readers are referred to Figure A42 in the Appendix. In all cases, non-functionalized matrices are shown to result in cleaner spectra.

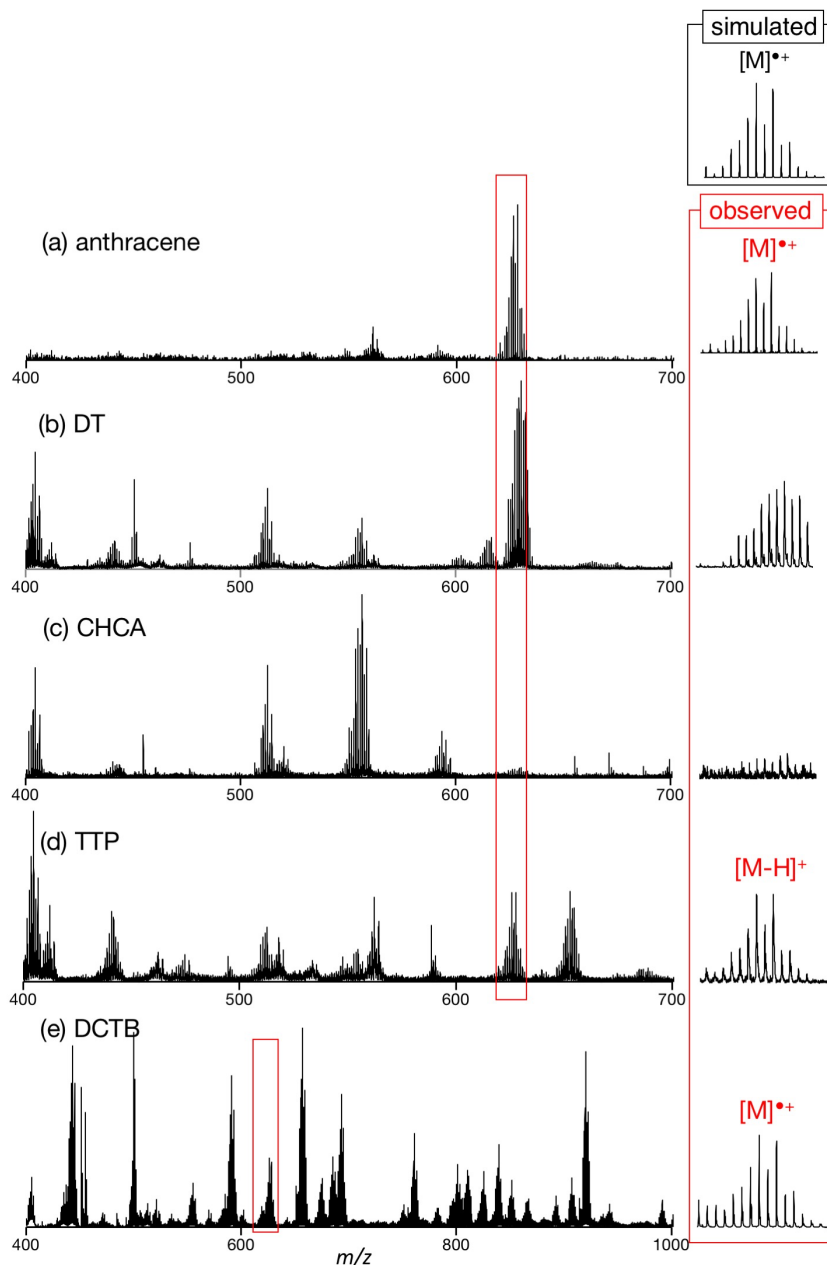


Figure 6.5. MALDI mass spectra showing extensive gas-phase decomposition of **III** by functionalized matrices: (a) benchmark spectrum with non-functionalized anthracene; (b) CHCA; (c) DT; (d) TTP; (e) DCTB. Note that spectra a–d show no signals above m/z 700. For matrix structures, see Table 6.1. Spectra were recorded at 355 nm (a–d) or 349 nm (e),³² using the minimum laser energy essential for volatilization.

Finally, it should be noted that solution stability may not be a reliable gauge of gas-phase stability. Thus, we observed no detectable decomposition of **III** by ^1H NMR analysis after

heating with DT or TTP in C₆D₆ after 24 h at 40 °C, despite the extensive decomposition observed in the MALDI mass spectrum of **III** using these matrices.

We conclude this section with a practical note of considerable importance. The low in-source pressures common in modern MALDI mass spectrometers (often 10⁻⁶–10⁻⁸ mbar) are a risk factor for premature matrix volatilization. Matrix evaporation is associated with increased fragmentation, because it reduces the ratio of matrix to analyte, hence limiting the protective capacity of the matrix. Particular care must be taken with the class C matrices pyrene and anthracene. The absence of functional groups on these polyaromatic hydrocarbon matrices, while fundamental to their selectivity for charge transfer, increases their tendency to sublime under vacuum.⁴⁹ The deleterious effect of matrix evaporation also constitutes an implied warning about using matrix-free, LDI-MS methods to analyze labile organometallic complexes.

Importantly, however, matrix evaporation need not be problematic, if samples are analyzed immediately after inserting the plate. A high-contrast camera is a major asset in detecting matrix evaporation, as shown in Figure 6.6, in which desirable matrix coverage is indicated by dark areas. The useful scan duration in this instance is clearly <15 min, a figure that will vary with the specific matrix, the sample thickness, and the effective vacuum in the ion source. (Recently-proposed fullerene matrices⁵⁰ offer an intriguing potential alternative, but were not explored in this work.)

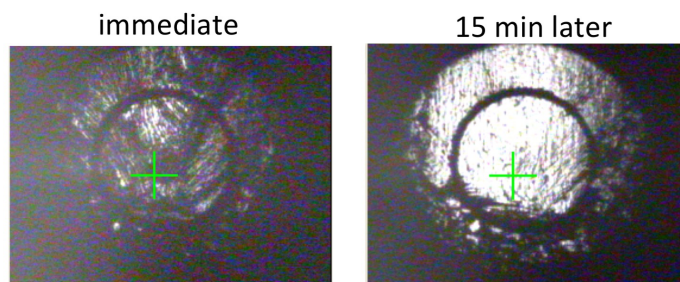


Figure 6.6. Detecting matrix (pyrene) evaporation from a MALDI target plate. Photographs taken immediately on inserting the plate into the spectrometer, and after 15 min, with a high-contrast CCD camera (Applied Biosystems 4800). Desirable matrix coverage is indicated by dark areas. Green cross indicates laser focus point.

6.3.4 New Technology

The discussion thus far has focused on factors that increase fragmentation on widely available spectrometers, and ways to preserve the molecular ion intact. Here we examine relevant

advances in technology relative to the 2004 state of the art, as well as opportunities for organometallic applications created by the latest generation of instruments.

1. Resolution. One of the most immediately obvious advances in the past decade is the improved resolution now routinely available. High resolution is of particular value in recognizing signals arising from fragmentation and subsequent dimerization (a common occurrence for organometallic analytes, owing to the high reactivity of low-valent metal centers generated by ligand loss). Figure 6.7a, for example, shows the $[M]^{++}$ region for **GII**, obtained on an instrument with a rated resolution of $R = 40000$.⁵¹ Two overlapping isotope patterns can be discerned, separated by <0.15 mass unit. One is due to deprotonation of **GII**, and the other to a dinuclear ruthenium complex, the significance of which was noted above. At low resolution (compare the upper and lower traces in Figure 6.7b), the diruthenium species goes unrecognized, masking the extensive fragmentation undergone by the analyte.

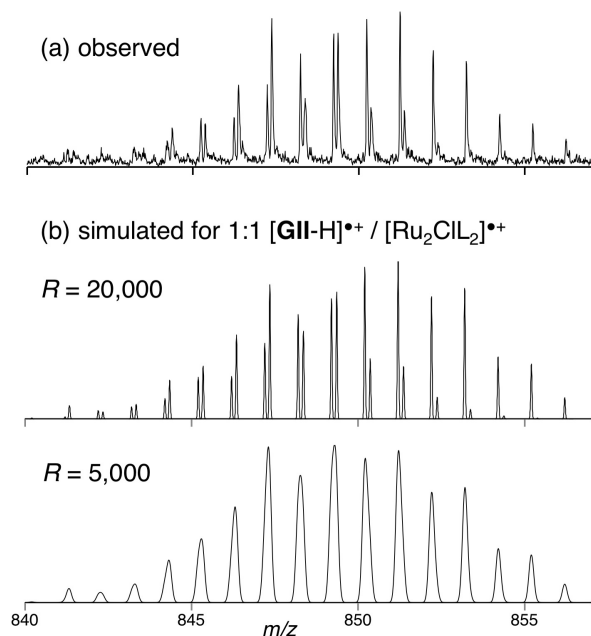


Figure 6.7. Effect of spectrometer resolution on signal assignment for **GII**: (a) observed isotope pattern in the $[M]^{++}$ region;³² (b) simulated pattern at high resolution, revealing overlapping patterns due to $[\text{GII} - \text{H}]^{++}$ and a diruthenium species. The same simulation at low resolution shows that these components cannot be distinguished.

2. Location of Sweet Spots. Minimizing the applied laser energy is critical in limiting fragmentation, as noted above. An important tradeoff, however, is a decrease in the number of sweet spots (crystalline sites that produce intense, readily observed signals on laser irradiation).⁵²

This translates into more time spent locating sites that yield a signal, and yet rapid evaporation of polyaromatic hydrocarbon matrices limits the time that can be spent on the search. Several advances aid in reducing acquisition times, and hence matrix evaporation. This superficially minor issue has major implications for enabling location of sweet spots at lower applied laser energies.

a. Roving Laser Location. A widespread advance is automatic, randomized rastering of the laser focus spot over the target plate. This increases the probability of locating sweet spots, while minimizing ablation of the matrix at any given site.

b. Retroactive Identification of Optimal Sampling Locations. The ThermoFisher Xcalibur platform greatly expands these capabilities, by coupling systematic variation of the laser focal point with an assay of ion count at each xy location, from which a map of signal intensity vs xy coordinate is automatically compiled (Figure 6.8a). After data collection, spectra can be retroactively extracted from the local maxima, from which an optimal spectrum can be chosen (Figure 6.8b). We found that this procedure significantly improved the intensity of the molecular ion with respect to fragments, relative to manual “point-and-shoot” methods. Using these tools, sweet spots could be identified at laser energies that were unproductive in a manual scan, yielding much cleaner spectra.

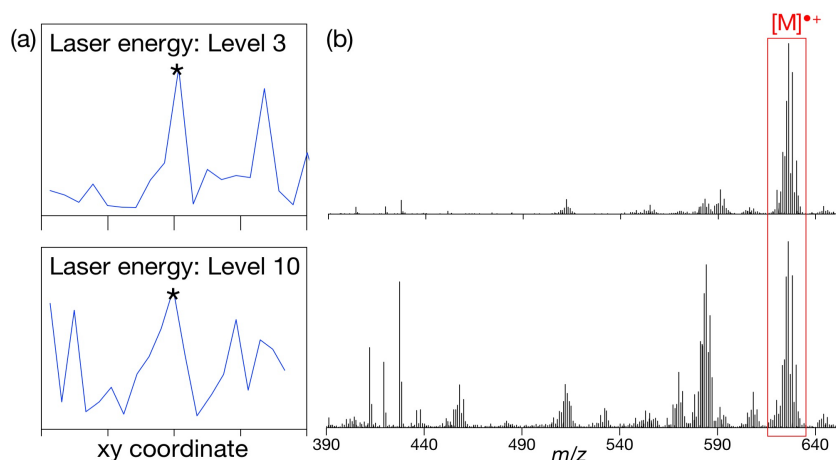


Figure 6.8. Use of signal intensity plots to identify sweet spots at low laser energy levels: (a) signal intensity plots, showing (*) local maxima at sweet spots (xy coordinate = location on target plate); (b) optimized MALDI mass spectra obtained in retroactive analysis at the designated maxima (ThermoFisher MALDI LTQ Orbitrap XL; λ 337 nm).³²

c. Fast-Firing Lasers. The throughput demand of MALDI imaging³³ has driven a move from N₂ lasers to diode-pumped solid-state lasers capable of fast repetition. Laser firing rates up to 2 kHz are now routinely accessible using Nd:YAG or Nd:YLF lasers, while up to 10 kHz can be obtained on state-of-the-art tissue imaging instruments.⁵³ These figures compare with 50 Hz with N₂ lasers. In the present context, rapid firing aids in locating sweet spots prior to matrix evaporation. For analysis of fragile organometallic analytes with fast-firing lasers, a roving laser location takes on additional importance as a means of limiting fragmentation resulting from local heating and matrix ablation.

3. Softer Solid-State Lasers. A breakthrough in MALDI-MS analysis of organometallic complexes is the advent of the contoured-profile laser.^{54,55} This advance, pioneered by Holle and co-workers, involved adaptation of the natural Gaussian laser focus profile of the Nd:YAG laser to give a contour reminiscent of that in the N₂ laser (Figure 6.9, left).⁵⁴ This feature was implemented in the Bruker Daltonics “Smartbeam” laser. The performance of this dappled-contour laser is compared against an unmodulated Nd:YAG laser, and an N₂ laser, in the analysis of **III**: see Figure 6.9. These experiments were controlled for number of shots (a ceiling of 100 shots was imposed, to accommodate the restricted lifetime of the N₂ laser) and time-of-flight mass analyzer. The laser energy was maintained at the lowest possible setting required to observe a signal. To facilitate performance comparisons, the spectra selected in Figure 6.9 are from instruments matched as closely as possible for wavelength and resolution.

The extent of fragmentation is dramatically reduced for the dappled-profile Smartbeam laser (Figure 6.9c), as shown by the relative intensity of the **[III]⁺⁺** signal in the inset for all three laser types. Strikingly, fragmentation is reduced even relative to the N₂ laser (Figure 6.9b), despite a nearly 20-fold drop in matrix ϵ_M (pyrene: $\epsilon_M = 41000 \text{ M}^{-1} \text{ cm}^{-1}$ at 337 nm vs $2240 \text{ M}^{-1} \text{ cm}^{-1}$ at 355 nm; see Table 6.1). The slight reduction in total signal-to-noise ratio is due to the restricted number of shots imposed in this experiment, to enable direct comparison with the N₂ laser: it does not reflect on performance in standard use. Low-threshold laser energies, reduced matrix ablation, improved spectral resolution, and high spot-to-spot reproducibility all contribute to superior performance. The resulting decrease in fragmentation, even in comparison to the N₂ laser, make the Smartbeam laser the current state of the art for MALDI-MS analysis of organometallic complexes.

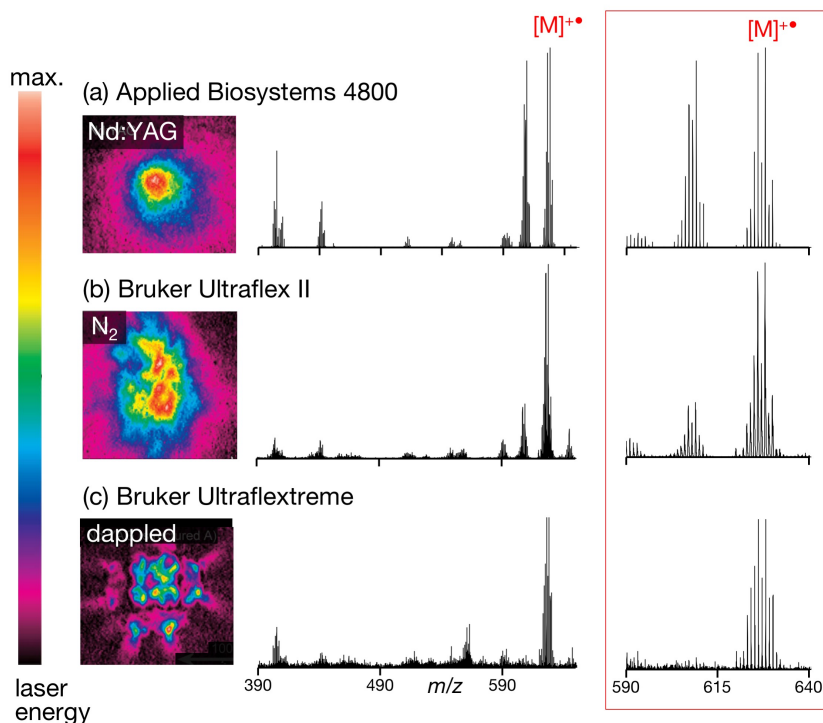


Figure 6.9. Impact of laser beam profile on fragmentation of **HII**. Laser focus profiles and representative spectra for (a) Nd:YAG, (b) N₂, and (c) contoured Nd:YAG (“Smartbeam”) lasers. For additional examples showing increased fragmentation for unmodified lasers (Nd:YAG, Nd:YLF, and N₂), see Figure A43 in the Appendix.³²

6.4 Conclusions

No experienced synthetic chemist seeks to elucidate the structure of an organic compound without first establishing its molecular formula. For transition-metal complexes, such basic, preliminary information was long unattainable, because only highly robust complexes can withstand the high energies of conventional MS methods. The advent of ESI-MS, a breakthrough in soft ionization, led to important advances in the analysis of charged complexes. In comparison, neutral species—by far the majority of metal complexes and catalysts—have been refractory.

Current MALDI-MS instrumentation has enormous potential to aid in the identification of organometallic complexes and catalysts, irrespective of their charge. Ionic complexes are inherently privileged, but charge-transfer ionization can enable straightforward conversion of many neutral complexes into the corresponding radical cations. Despite this potential, and the widespread accessibility of the required instrumentation, CT-MALDI methodologies have not been widely adopted for organometallic analysis. The major deterrent is simply excessive

fragmentation, and a proliferation of peaks arising from both fragmentation and fragment agglomeration. Within our own research group, these challenges long went unrecognized, because our original MALDI-TOF instrument (a Bruker Daltonics Omnistar MS) was fortuitously near-ideal for gentle charge-transfer ionization of neutral organometallics. We are now able to identify the primary factors underlying this excellent performance: a soft laser beam profile and a moderate vacuum in the ion source, which limited sublimation of the charge-transfer matrix.

The foregoing presents a field guide for MALDI-MS analysis of organometallic compounds using widely available, less ideal instrumentation. The single most important factor is minimizing direct excitation of the analyte. This is achieved by (a) using the lowest laser energy at which the sample can be volatilized (greatly facilitated by autoscanning software to identify sweet spots), (b) minimizing overlap between the absorption maxima of the analyte and the laser wavelength, where a choice of instruments exists, (c) using a large (e.g., 500-fold) excess of the matrix, and limiting matrix sublimation by analyzing immediately after inserting the sample plate, and (d) selecting a non-functionalized charge-transfer matrix with maximum absorptivity at the laser wavelength.

As well, however, a tantalizing glimpse can be seen of future instrumental capabilities. With the expanding uptake of transition-metal catalysts in pharmaceutical and fine-chemicals manufacturing, new instrumentation tailored for organometallic analysis represents an emerging market opportunity in a mature business sector. A number of factors can now be identified that should inform the design of next-generation MALDI-MS instruments for this application. Potentially key elements include soft lasers (contoured-beam, or with tunable defocusing capacity); wavelength-tunable lasers; high spectral resolution; high-resolution, high-contrast cameras; and automatic plate rastering with software to support retroactive compilation of spectra from optimal sampling locations. Atmospheric pressure and soft-vacuum sources offer intriguing further possibilities to maximize collisional cooling, and thereby limit fragmentation.

Also desirable is a standardized anaerobic MALDI-glovebox interface, to facilitate reaction monitoring that can afford insight into catalyst turn-on, resting states, and deactivation under operating conditions. Progress has also been made on this front, and a Bruker Daltonics

UltrafleXtreme instrument equipped with such an interface has very recently been installed in our laboratories.

6.5 Experimental Details

6.5.1 General Procedures

MALDI samples were prepared in a N₂-filled glovebag, using anhydrous CH₂Cl₂ or benzene (99%; Sigma-Aldrich). Matrix compounds were purchased from Sigma-Aldrich or Fluka (minimum purity 97%) and used as received. Literature methods were used to prepare the probe analytes **GII**m,⁵⁶ **GII**,⁵⁷ and **HII**⁵⁷ and the RuCl₂(dppe)₂ calibrant.⁵⁸ UV-vis spectra for pyrene, anthracene, **HII**, **GII**, and **GII**m were collected in CH₂Cl₂ on an Agilent Cary 100 UV-visible spectrophotometer, using quartz cuvettes (1.0 cm path length; Figure 6.10). The UV-vis spectrum for sinapic acid was collected in methanol, as this matrix compound is insoluble in CH₂Cl₂. Isotope patterns were simulated using the ChemCalc chemical modeling software.³⁷

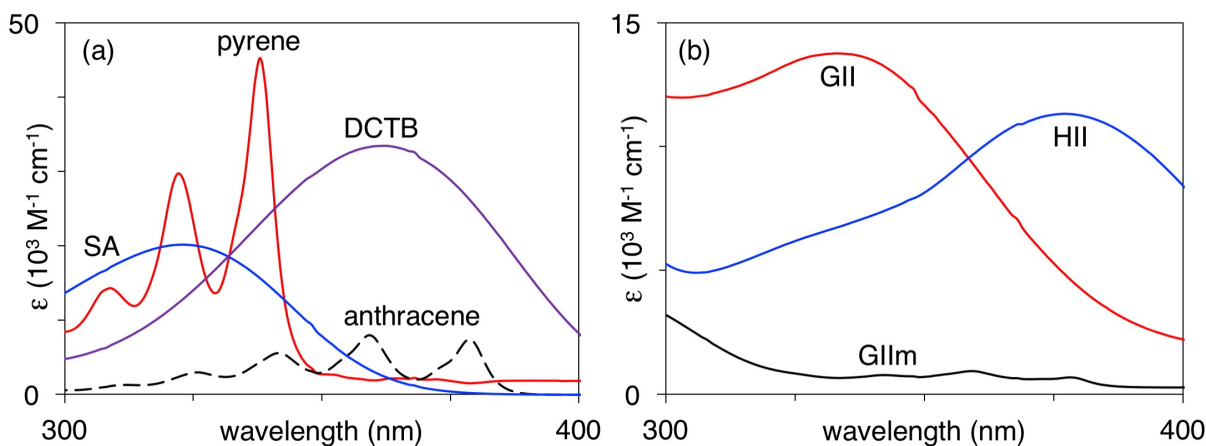


Figure 6.10. (a) UV-vis spectra of the matrices pyrene, anthracene, and DCTB in CH₂Cl₂; spectrum of SA (which is very poorly soluble in CH₂Cl₂) in methanol. (b) UV-vis spectra of the analytes **GII**, **GII**m, and **HII** in CH₂Cl₂.

6.5.2 MALDI Sample Preparation and Analysis

Matrix and analyte solutions were prepared in an N₂-filled glovebag at concentrations of 100 mM and 5 mM or 0.5 mM, respectively. Samples were mixed in a matrix:analyte ratio of 25:1 or 2.5:1, to deliver a final molar ratio of 500:1. A ca. 5 μ L aliquot was spotted on the MALDI target plate and allowed to evaporate by the dried-droplet method. Spotted plates were transported to the spectrometer in sealed Ziploc bags and then rapidly transferred to the source chamber (air exposure <5 s). In some cases, solid samples or prespotted MALDI target plates were shipped

under N₂ in airtight stainless steel containers manufactured by Onyx and dip-sealed with paraffin wax.

MALDI mass spectra were collected without matrix signal suppression, using the following instruments: Bruker UltrafleXtreme (Figures 6.1, 6.4, 6.5a–d, 6.7, and 6.9c), Bruker Ultraflex II (6.9b), AB Sciex 5800 (6.3 and 6.5e), Applied Biosystems 4800 (6.2, 6.6, and 6.9a), and ThermoFisher MALDI LTQ Orbitrap XL (6.8). For further details, see Table 6.2. Pyrene was used as matrix, unless otherwise indicated. TOF spectra were collected in positive reflectron mode (unless otherwise indicated) with the accelerating voltage held at 20–25 kV for all experiments. Except in Figures 6.2 and 6.8, the laser energy was maintained at the threshold level required to observe a signal within a defined 100–800 shots. The number of shots was held constant for the spectra compared within each figure. MALDI LTQ Orbitrap spectra were collected in positive mode, using the Orbitrap as the mass filter. Mass spectrometers were calibrated externally before each use with RuCl₂(dppe)₂ ([M]⁺⁺ m/z 968.11; [M – Cl]⁺ m/z 933.14) or a standard peptide calibrant. Samples were analyzed immediately after inserting the target plate, to minimize premature matrix evaporation (20–60 min, depending on instrument).

Table 6.2. MALDI mass spectrometers used, and relevant instrument parameters.

Instrument	Location	Laser		Figure
		Type	Wavelength	
AB Sciex 5800 TOF/TOF	MALDI MS / Functional Proteomics Facility, London Regional Proteomics Centre, Western Univ.	Nd:YLF	349 nm	6.3, A43a
AB Sciex 5800 TOF/TOF	AB Sciex Framingham, MA	Nd:YLF	349 nm	6.5e
Applied Biosystems 4700 TOF/TOF	MALDI MS / Functional Proteomics Facility, London Regional Proteomics Centre, Western Univ.	Nd:YAG	355 nm	A44a ^a
Applied Biosystems 4800 TOF/TOF	Univ. Toronto Forestry Dept.	Nd:YAG	355 nm	6.2, 6.6, 6.9a
Bruker Microflex TOF	Bruker Daltonics Billerica MA	N ₂	337 nm	A43c
Bruker Omniflex TOF	Fogg Anaerobic MALDI-MS Facility, Univ. Ottawa	N ₂	337 nm	A43c
Bruker Reflex IV TOF	MALDI MS / Functional Proteomics Facility London Regional Proteomics Centre, Western	N ₂	337 nm	A44b ^a

Bruker Ultraflex II TOF/TOF	Univ. Bruker Daltonics Billerica, MA	N ₂	337 nm	6.9b
Bruker UltrafleXtreme TOF/TOF	Bruker Daltonics Billerica, MA	contoured Nd:YAG	355 nm	6.1, 6.4, 6.5a-d, 6.7, 6.9c, A41, A42
Shimadzu Performance TOF/TOF	Shimadzu Columbia MD	N ₂	337 nm	Figure A43c
ThermoFisher MALDI LTQ Orbitrap XL	Laboratory of Imaging Mass Spectrometry Univ. North Texas	N ₂	337 nm	6.8
Waters Micro MX TOF	Advanced Instrumental Mass Spectrometry Lab Univ. Toronto	N ₂	337 nm	Figure A43c
Waters Synapt G2-Si MALDI-QTOF	Waters Corp. Milford MA	Nd:YAG	355 nm	Figure A43b

^a At the time of use, these lasers were near the end of their operational lifetimes, and higher applied laser energies were therefore required. The impact on fragmentation is illustrated in Figure A44.

6.5.3 Solution Reactivity of **III** with Matrix Compounds

In a representative procedure, a stock solution of **III** (17.2 mg, 0.0275 mmol) and dimethyl terephthalate (DMT; ca. 1 mg, internal standard) was prepared in C₆D₆ (1400 µL) in the glovebox. Aliquot A (control, 650 µL) was removed, and a ¹H NMR spectrum was measured to establish the initial ratio of **III** to DMT. That aliquot was returned to the glovebox and transferred to a 4 mL screw-cap scintillation vial equipped with a magnetic stir bar. Aliquot B (650 µL) was transferred directly to an identical vial containing terthiophene (15.9 mg, 0.0638 mmol, 5 equiv). Both reaction mixtures were tightly capped and stirred in a 40 °C oil bath (thermocouple-equipped; ±1.5 °C) for 24 h. The proportion of **III** remaining was assessed at regular intervals by ¹H NMR analysis. Terthiophene: 3% loss of **III** at 24 h, identical with that in the control experiment. Dithranol (assessed identically, but in CD₂Cl₂, owing to its low solubility in C₆D₆): 15% loss at 24 h, vs 21% for the control experiment.

6.6 References

- (1) Yunker, L. P. E.; Stoddard, R. L.; McIndoe, J. S. *J. Mass Spectrom.* **2014**, *49*, 1–8.
- (2) Ingram, A. J.; Boeser, C. L.; Zare, R. N. *Chem. Sci.* **2016**, *7*, 39–55.
- (3) Wyatt, M. F. *J. Mass Spectrom.* **2011**, *46*, 712–719.

- (4) Henderson, W.; McIndoe, J. S., *Mass Spectrometry of Inorganic and Organometallic Compounds*. Wiley: Hoboken, N.J., 2005.
- (5) , (a) Chen, P. *Angew. Chem. Int. Ed.* **2003**, *42*, 2832–2847. (b) Adlhart, C.; Chen, P., Intrinsic Reactivity of Ruthenium Carbenes. In *Handbook of Metathesis*, Grubbs, R. H., Ed. Wiley-VCH: Weinheim, Germany, 2003; Vol. 1, p. 132–172.
- (6) Vikse, K. L.; Ahmadi, Z.; McIndoe, J. S. *Coord. Chem. Rev.* **2014**, *279*, 96–114.
- (7) Schroder, D. *Acc. Chem. Res.* **2012**, *45*, 1521–1532.
- (8) Vikse, K. L.; Ahmadi, Z.; Manning, C. C.; Harrington, D. A.; McIndoe, J. S. *Angew. Chem. Int. Ed.* **2011**, *50*, 8304–8306.
- (9) Limberger, J.; Leal, B. C.; Monteiro, A. L.; Dupont, J. *Chem. Sci.* **2015**, *6*, 77–94.
- (10) Iacobucci, C.; Reale, S.; De Angelis, F. *Angew. Chem. Int. Ed.* **2016**, *55*, 2980–2993.
- (11) Eelman, M. D.; Blacquiere, J. M.; Moriarty, M. M.; Fogg, D. E. *Angew. Chem. Int. Ed.* **2008**, *47*, 303–306.
- (12) McCarley, T. D.; McCarley, R. L.; Limbach, P. A. *Anal. Chem.* **1998**, *70*, 4376–4379.
- (13) Wang, H.; Zhao, Z.; Guo, Y. *Top. Curr. Chem.* **2013**, *331*, 165–192.
- (14) Blacquiere, J. M.; McDonald, R.; Fogg, D. E. *Angew. Chem. Int. Ed.* **2010**, *49*, 3807–3810.
- (15) Monfette, S.; Camm, K. D.; Gorelsky, S. I.; Fogg, D. E. *Organometallics* **2009**, *28*, 944–946.
- (16) Eelman, M. D.; Moriarty, M. M.; Fogg, D. E. *Educ. Adv. Chem.* **2006**, *10*, 213–234.
- (17) Chen, H.; Dawe, L. N.; Kozak, C. M. *Catal. Sci. Technol.* **2014**, *4*, 1547–1555.
- (18) Piche, L.; Daigle, J.-C.; Claverie, J. P. *Chem. Commun.* **2011**, *47*, 7836–7838.
- (19) Ikpo, N.; Butt, S. M.; Collins, K. L.; Kerton, F. M. *Organometallics* **2009**, *28*, 837–842.
- (20) Kozak, C. M.; Woods, A. M.; Bottaro, C. S.; Devaine-Pressing, K.; Ni, K. *Faraday Discuss.* **2015**, *183*, 31–46.
- (21) Grotevendt, A. G. D.; Lummiss, J. A. M.; Mastronardi, M. L.; Fogg, D. E. *J. Am. Chem. Soc.* **2011**, *133*, 15918–15921.
- (22) For work-arounds that limit such problems, see ref 1 and: Hesketh, A. V.; Nowicki, S.; Baxter, K.; Stoddard, R. L.; McIndoe, J. S. *Organometallics* **2015**, *34*, 3816–3819.
- (23) Brodbelt, J. S. *Chem. Soc. Rev.* **2014**, *43*, 2757–2783.
- (24) Brodbelt, J. S. *Anal. Chem.* **2016**, *88*, 30–51.
- (25) For a discussion of such methods, see refs 3, 4, and 11.
- (26) For MALDI-MS analysis of these and related alkylidene complexes using charge-transfer matrices, see refs 11, 14, 15, and 21, and: (a) 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. (b) Monfette, S.; Fogg, D. E. *Organometallics* **2006**, *25*, 1940–1944. (c) Zhu, W.; Wang, H.-Y.; Guo, Y.-L. *J. Mass Spectrom.* **2012**, *47*, 352–354.

- (27) Wang, Metzger and co-workers pointed out that the radical cations of **GII**, **III**, and the first-generation Grubbs catalyst $\text{RuCl}_2(\text{PCy}_3)_2(=\text{CHPh})$ **GI** can be observed by ESI-MS analysis in CH_2Cl_2 , although the dominant signals are due to $[\text{HPCy}_3]^+$ (for **GI**) or $[\text{H}_2\text{IMes}\cdot\text{H}]^+$ (for second-generation catalysts). See: (a) Wang, H.; Metzger, J. O. *Organometallics* **2008**, *27*, 2761–2766. (b) Wang, H.-Y.; Yim, W.-L.; Guo, Y.-L.; Metzger, J. O. *Organometallics* **2012**, *31*, 1627–1634. “Charge-tagging”, i.e. incorporation of a cationic site within a neutral ligand to convert neutral analytes to readily-observed cationic species, was developed to enable mechanistic studies of metathesis catalysts by ESI-MS. See: (c) Hinderling, C.; Adlhart, C.; Chen, P. *Angew. Chem. Int. Ed.* **1998**, *37*, 2685–2689. (d) Adlhart, C.; Hinderling, C.; Baumann, H.; Chen, P. *J. Am. Chem. Soc.* **2000**, *122*, 8204–8214, and refs 5a, 5b.
- (28) Higman, C. S.; Lummiss, J. A. M.; Fogg, D. E. *Angew. Chem., Int. Ed.* **2016**, *55*, 3552–3565.
- (29) Hillenkamp, F.; Jaskolla, T. W.; Karas, M., The MALDI Process and Method. In *MALDI MS: A Practical Guide to Instrumentation, Methods, and Applications*, 2nd ed.; Hillenkamp, F.; Peter-Katalinić, J., Eds. Wiley-VCH: Weinheim, Germany, 2013; pp 1–40.
- (30) For an authoritative discussion of the theory behind laser-induced dissociation, see ref 29. For the discovery of post-source decay in MALDI-MS and its spectroscopic consequences, see: (a) Kühlewind, H.; Neusser, H. J.; Schlag, E. W. *Int. J. Mass Spectrom. Ion Phys.* **1983**, *51*, 255–265. (b) Spengler, B.; Kirsch, D.; Kaufmann, R.; Cotter, R. J. *Rapid Commun. Mass Spectrom.* **1991**, *5*, 198–202.
- (31) For example, an ion of mass m that decays during flight to lower-mass fragments of mass m_1 and m_2 would be characterized by a momentum $p = mv = (m_1 + m_2)v$.
- (32) The instruments, laser wavelengths, and matrices used in these experiments are summarized in Table 6.2.
- (33) Dreisewerd, K. *Anal. Bioanal. Chem.* **2014**, *406*, 2261–2278.
- (34) As the core objective of the present work is to minimize decomposition, fragment assignment was not pursued. For assignment of fragments observed during ESI-MS analysis of **GII**, readers are directed to ref 27a and: Zhao, Z.-X.; Wang, H.-Y.; Guo, Y.-L. *Rapid Commun. Mass Spectrom.* **2011**, *25*, 3401–3410.
- (35) The lability of the PCy_3 ligand in **GIIIm** is 41,000 times lower than that of the first-generation Grubbs catalyst **GII**. For a tabulation of values for benzyldiene and methyldiene complexes, see: (a) Lummiss, J. A. M.; Perras, F. A.; Bryce, D. L.; Fogg, D. E. *Organometallics* **2016**, *35*, 691–698. For the greatly enhanced lability of **III**, see: (b) Bates, J. M.; Lummiss, J. A. M.; Bailey, G. A.; Fogg, D. E. *ACS Catal.* **2014**, *4*, 2387–2394. For experiments aimed at extracting the rate constants for PCy_3 loss, see ref 36.
- (36) Lummiss, J. A. M.; Higman, C. S.; Fyson, D. L.; McDonald, R.; Fogg, D. E. *Chem. Sci.* **2015**, *6*, 6739–6746.
- (37) Patiny, L.; Borel, A. *J. Chem. Inf. Model.* **2013**, *53*, 1223–1228.
- (38) Hong, S. H.; Wenzel, A. G.; Salguero, T. T.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2007**, *129*, 7961–7968.

- (39) Lummiss, J. A. M.; McClennan, W. L.; McDonald, R.; Fogg, D. E. *Organometallics* **2014**, *33*, 6738–6741.
- (40) Lummiss, J. A. M.; Ireland, B. J.; Sommers, J. M.; Fogg, D. E. *ChemCatChem* **2014**, *6*, 459–463.
- (41) The benzylphosphonium cation $[\text{PhCH}_2\text{PCy}_3]^+$ was likewise observed on collision-induced dissociation of **GII**. Monoruthenium fragments were observed under these conditions. See refs 27a, 27b.
- (42) In the MALDI process, the energy (E) absorbed per unit volume V is dependent on matrix absorptivity ϵ_M , and the laser energy H : that is, $E/V = \epsilon_M H$. See: ref 29.
- (43) Knochenmuss, R.; Zhigilei, L. V. *J. Phys. Chem. B* **2005**, *109*, 22947–22957.
- (44) Mowry, C. D.; Johnston, M. V. *J. Phys. Chem.* **1994**, *98*, 1904–1909.
- (45) Soltwisch, J.; Jaskolla, T. W.; Dreisewerd, K. *J. Am. Soc. Mass Spectrom.* **2013**, *24*, 1477–1488.
- (46) Soltwisch, J.; Jaskolla, T. W.; Hillenkamp, F.; Karas, M.; Dreisewerd, K. *Anal. Chem.* **2012**, *84*, 6567–6576.
- (47) The ϵ_M values shown were extracted from published spectra, where available (CHCA, DHB, DT, and TTP). See: (a) **CHCA**: Al Ghafly, H.; Siraj, N.; Das, S.; Regmi, B. P.; Magut, P. K. S.; Galpothdeniya, W. I. S.; Murray, K. K.; Warner, I. M. *Rapid Commun. Mass Spectrom.* **2014**, *28*, 2307–2314. (b) **DHB**: Strupat, K.; Karas, M.; Hillenkamp, F. *Int. J. Mass Spectrom. Ion Processes* **1991**, *111*, 89–102. (c) **DT**: Andersen, K. B.; Spanget-Larsen, J. *Spectrochim. Acta, Part A* **1997**, *53*, 2615–2625. (d) **TTP**: ref 12. (e) **DCTB**: Ulmer, L.; Mattay, J.; Torres-Garcia, H. G.; Luftmann, H. *Eur. J. Mass Spectrom.* **2000**, *6*, 49–52. For pyrene, anthracene, DCTB and SA, ϵ_M values were calculated from experimental spectra (Figure 6.10).
- (48) For reviews documenting the use of such Class A / B matrices for the analysis of transition-metal complexes and metal-containing polymers or supramolecular structures, see: refs 3, 4, 16. While most of the examples documented focus on analysis of a given compound of interest, Wyatt and co-workers have sought to identify sample preparation methods to enable polar matrices (in particular, DCTB) to be applied more broadly to the identification of inorganic and organometallic complexes. See: (a) Hughes, L.; Wyatt, M. F.; Stein, B. K.; Brenton, A. G. *Anal. Chem.* **2009**, *81*, 543–550. (b) Wyatt, M. F.; Stein, B. K.; Brenton, A. G. *Analyst* **2008**, *133*, 47–48. (c) Wyatt, M. F.; Stein, B. K.; Brenton, A. G. *J. Am. Soc. Mass Spectrom.* **2006**, *17*, 672–675. New developments focus on matrix-free analysis using nanostructured targets to ionize the analyte. For application of such “NALDI” methodologies to inorganic analytes, see: (d) Wyatt, M. F.; Ding, S.; Stein, B. K.; Brenton, A. G.; Daniels, R. H. *J. Am. Soc. Mass Spectrom.* **2010**, *21*, 1256–1259.
- (49) See: Siddiqi, M. A.; Siddiqui, R. A.; Atakan, B. *J. Chem. Eng. Data* **2009**, *54*, 2795–2802, and references therein.
- (50) Deacon, G. B.; Field, L. D.; Fisher, K.; Jaroschik, F.; Kay, D. L.; Maschmeyer, T.; Masters, A. F. *J. Organomet. Chem.* **2014**, *751*, 482–492.
- (51) A full spectrum of **GII** on a lower-resolution instrument (AB Sciex 5800; rated $R = 26,000$) appears in Figure 6.3. More extensive fragmentation results in the exclusive observation of

dimers in the molecular ion region, probably due to the use of a Gaussian Nd:YAG laser; see later.

(52) MALDI-TOF spectra adequate to verify the identity of insoluble Ru complexes have been obtained, albeit at the cost of resolution, on amorphous analyte-matrix samples prepared as Nujol mulls. See ref 11.

(53) Prentice, B. M.; Chumbley, C. W.; Caprioli, R. M. *J. Mass Spectrom.* **2015**, *50*, 703–710.

(54) Holle, A.; Haase, A.; Kayser, M.; Höhndorf, J. *J. Mass Spectrom.* **2006**, *41*, 705–716.

(55) Qiao, H.; Spicer, V.; Ens, W. *Rapid Commun. Mass Spectrom.* **2008**, *22*, 2779–2790.

(56) Lummiss, J. A. M.; Beach, N. J.; Smith, J. C.; Fogg, D. E. *Catal. Sci. Technol.* **2012**, *2*, 1630–1632.

(57) van Lierop, B. J.; Reckling, A. M.; Lummiss, J. A. M.; Fogg, D. E. *ChemCatChem* **2012**, *4*, 2020–2025.

(58) Seddon, E. A.; Seddon, K. R., *The Chemistry of Ruthenium*. Elsevier: Amsterdam, 1984.

Chapter 7. Conclusions and Future Directions

Sometimes, the most important innovations come from simple curiosity, the manifestation of a deep-rooted desire to understand and explore the world in elementary ways. This holds true in all of science, and the field of transition-metal catalysis is no exception. Powerful tools are born out of human ingenuity and perception. Fundamental research continues to leave its mark, often in unexpected ways. Research into the undesired chemistry associated with highly active, and yet highly *reactive* catalytic intermediates in metathesis is an under-explored field with potentially transformative insights to offer.

The findings in this thesis illustrate the insights and opportunities that can be unlocked through study of the “dark side” of catalysis. A fundamental incompatibility is revealed in Chapter 2 that has far-reaching consequences. While organic chemists would not think twice before proposing that a formed enolate would deprotonate (e.g.) an amine or alcohol substrate, the fact that catalysts are not immune, but can also be deprotonated, has gone widely unregarded. This is potentially game-changing. For metathesis catalysts, unlike many organic compounds, deprotonation can be *irreversible* and *deactivating*, and thus has profound consequences for catalyst productivity. This illustrates the delicate balance between performance and disaster in metathesis, a balance that is easily thrown off through the absence of knowledge required for informed choice. The potential generality of the “enolate paradigm” for nucleophilic functionalities on the substrate, catalyst, or contaminants constitutes a warning for the care that must be exercised in metathesis of electrophilic olefins.

The alarming *generality* of catalyst deprotonation by bases emerges in Chapter 3. Thus, the deprotonation by enolates observed in Chapter 2 is revealed to be no more than an extreme example of a widely general phenomenon. Unexpectedly, the MCB β -site is revealed as the target for deprotonation. Chapter 3 then begins to tackle an important, fundamental question: *what underlies the surprising acidity of the MCB?* Organic cyclobutanes are more acidic than *n*-butane, but their pK_a remains beyond the reach of (e.g.) NEt_3 . The C-C agostic interactions well-established for metathesis-active metallacyclobutanes are not the cause of the unexpected acidity. Indeed, the “non-agostic” MCB isomer investigated via DFT is even more acidic than the corresponding agostic isomer! As expected, the C-C agostic interactions appear to stabilize the MCB.

A closer examination of the DFT data reveals a number of potential factors that may contribute. One is the remarkable stability of the π -allyl intermediate, which is only ca. 9 kcal / mol higher in energy than the MCB. The steric accessibility of the β -site, which facilitates approach by the skinny enolate “arm” of the phosphonium enolate, undoubtedly also reduces the energy barrier to reaction (ca. 20 kcal / mol for NEt₃ and DBU; cf. 17 kcal / mol for the enolate; Scheme 3.6). The data also suggested a downstream cascade of subsequent events that ultimately drives irreversible deprotonation. Here, the susceptibility of the NHC ligand to facile C-H activation is potentially key. The cyclometallated allyl hydride and propene-ligated intermediates formed (see **Ru-I** and **Ru-P** in Scheme 3.6) are more stable than the MCB by 15 and 23 kcal / mol, respectively. A natural inference is that use of an activation-resistant NHC could potentially enhance catalyst performance, by enabling *reversibility* of the catalyst deprotonation step. Such an approach has been examined to a certain extent by our group and that of Grubbs, but clearly warrants further attention.

More generally, Chapter 3 exposes a clear gap in our understanding regarding metathesis-active MCB complexes. The electronic and steric factors that limit or impart stability to the MCB, vs. either base-induced or spontaneous decomposition processes, as well as the factors that promote desirable metathesis activity, are very poorly understood. A key opportunity here is the recent discovery that cyclic alkyl amino carbenes (CAACs) impart unprecedented activity and stability to the active intermediates in metathesis, even in ethylene metathesis. CAACs are more strongly σ -donating, but also more π -accepting than NHCs. Whether they, e.g.: (i) further stabilize the Ru(IV) MCBs via strong C-C agostic interactions (or through enhanced donicity), or (ii) destabilize the key π -allyl intermediates formed on both base-induced and spontaneous decomposition, is an interesting, worthwhile topic for investigation. More broadly, structure–activity studies aimed at correlating NHC/CAAC properties with MCB stability and decomposition are likely to be highly informative.

All of the insights and opportunities described above arose from curiosity-driven efforts to understand catalyst deprotonation at its most basic level. In that sense, Chapter 4 is the twin to Chapters 2 and 3, but instead of MCB deprotonation it examines *spontaneous* pathways that arise for the four-coordinate [Ru]=CHR intermediates. Such species are fascinating targets for study, in part because they are not directly observable; and hence, clever tactics must be devised to

enable their study. A further challenge, however, is the insatiable reactivity of the chief vulnerable species, four-coordinate methylidene intermediate $\text{RuCl}_2(\text{H}_2\text{IMes})(=\text{CH}_2)$. How to examine its behaviour—especially in the absence of olefin, donors, or other potentially perturbing agents—is a complex problem that will require a great deal of ingenuity and technical mastery to solve.

Chapter 4 presents some first attempts (and successes) at doing so. The donor-stabilized methylidenes isolated are in themselves highly worthwhile synthetic targets. They are the first known examples of phosphine-free, metathesis-active Ru-methylidenes, and they are stabilized only by weakly-donating ligands. As such, they are likely much closer in behaviour to “native” methylidene intermediates present during catalysis. In-depth study of their crystallographic / spectroscopic parameters and dynamic solution behaviour, in combination with DFT studies, could give valuable insight into structure and bonding. The isolated methylidenes are also a superior platform for investigation of deactivation pathways involving non-nucleophilic contaminants and methylidenes, as they avoid the competing abstraction pathways inherent to all PCy_3 -stabilized methylidenes. Finally, the potential generality of the synthetic strategy presented could open up new opportunities for catalyst synthesis, possibly from *any* metathesis-active metallacyclobutane. As noted in the introduction, installation of the alkylidene moiety is one of the key challenges in catalyst synthesis.

Moving beyond the synthetic context, the resurrection of bimolecular coupling pathways for the highly active Ru metathesis catalysts described in Chapter 4 is a key finding with potentially far-reaching implications. If bimolecular coupling pathways are indeed enhanced for fast-initiating catalysts, then this would motivate a move away from accelerated initiation as a design strategy in metathesis. It would also re-open critical dialog on how to prevent bimolecular coupling in the Ru systems. Bulky pseudohalides have already been examined with some success; they may therefore deserve closer reexamination. The labile stabilizing ligand may also play an important role, if both initiation and recapture of fragile metathesis intermediates are readily facilitated. The *o*-dianiline ligand examined in Chapter 4 offers a disguised opportunity in this regard. Efforts aimed at investigating the metathesis potential of *o*-dianiline-stabilized catalysts are already underway in our labs, with encouraging preliminary results (see: Higman, C. S.; Nascimento, D.; Ireland, B. J.; Audorsch, S.; Bailey, G. A.; Fogg, D. E. *J. Am. Chem. Soc.* **2018**, 1605–1607).

Finally, if bimolecular coupling pathways are operative in the forward direction, the possibility exists that they can be induced to occur in the reverse direction as well. Some of the preliminary findings presented in Chapter 4 have indeed already sparked followup research by our Norway collaborators, who have estimated that the reverse (alkylidene-forming) process is at least theoretically possible, with accessible energy barriers (DFT; Jensen, V. R. et al. *J. Am. Chem. Soc.* **2017**, *139*, 16609–16619). The question then becomes how to encourage the reverse process to occur, either in a synthetic process, or ideally, in situ during catalysis.

The last two chapters discuss solutions to some of the problems delineated above. Chapter 5 revealed the extraordinary ability of polyphenols to enable acrylate metathesis using the second-generation Grubbs catalyst. The key finding was that the resins upgrade the performance of **GII** to match *or exceed* that of the more costly phosphine-free derivative, **III**. The mechanistic basis for the improvement in activity over **III** is currently unclear, but it speaks to the strength of the approach, and a key, potentially general opportunity (not discussed in Chapter 5) for quenching basic contaminants, if a pK_a match can be achieved. Apparently, the polyphenol resins studied are fortuitously near-ideal for enolate quenching. The utility of the resins in quenching morpholine base (not discussed) was also investigated: this proved ineffective, likely because the polyphenol resin was insufficiently acidic to promote quenching. While highly acidic resins (such as the Amberlite CG50 resin discussed) would surely promote decomposition, there is undoubtedly a fine balance to be reached.

And lastly, regarding catalyst decomposition during MALDI-MS analysis: in some ways the least approachable chapter, Chapter 6 is likely also the most user-friendly. The strength in this work lies in the delineation of simple, generally applicable strategies for maximizing success during MALDI-MS analysis of a challenging class of analytes. The potential of MALDI-MS as a core tool for analysis of neutral metal catalysts and complexes is enormous, and yet its uptake remains extremely limited. Chapter 6 seeks to put the power of MALDI-MS methodologies for analysis of metal catalysts into the hands of the practicing organometallic (or synthetic) chemist. Broad uptake of MALDI MS in catalysis could lead to groundbreaking advances, via: (i) analysis of catalyst speciation and deactivation in situ during catalysis, under real catalytic conditions; (ii) the straightforward and routine analysis of synthesized complexes for elucidation of molecular identity; and (iii) analysis of isotopically labelled organic products and organometallic compounds (see *d*-labelling studies in Chapter 3). The latter opportunity involving analysis of *d*-

labelled organometallics is in fact a recent discovery. *d*-Label loss is a key problem for MALDI-MS analysis of *organic* compounds, probably owing to facile H/D scrambling pathways enabled by matrix. For organometallic complexes and charged phosphonium salts, such analysis could be facilitated using sulfur matrix (See also: Zhu, W.; Wang, H.-Y.; Guo, Y.-L. *J. Mass Spectrom.* **2012**, *47*, 352–354). This is an exciting new direction in analytical organometallic chemistry that is currently being investigated in our laboratories.

A. NMR Spectra

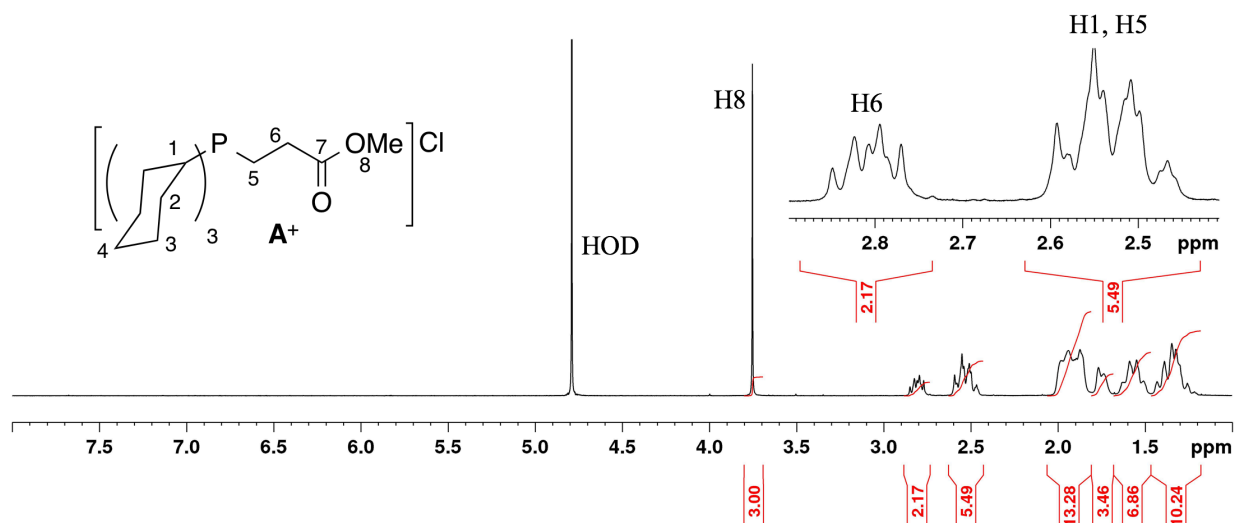


Figure A1. ^1H NMR spectrum of $[A]\text{Cl}$ (D_2O , 300.1 MHz).

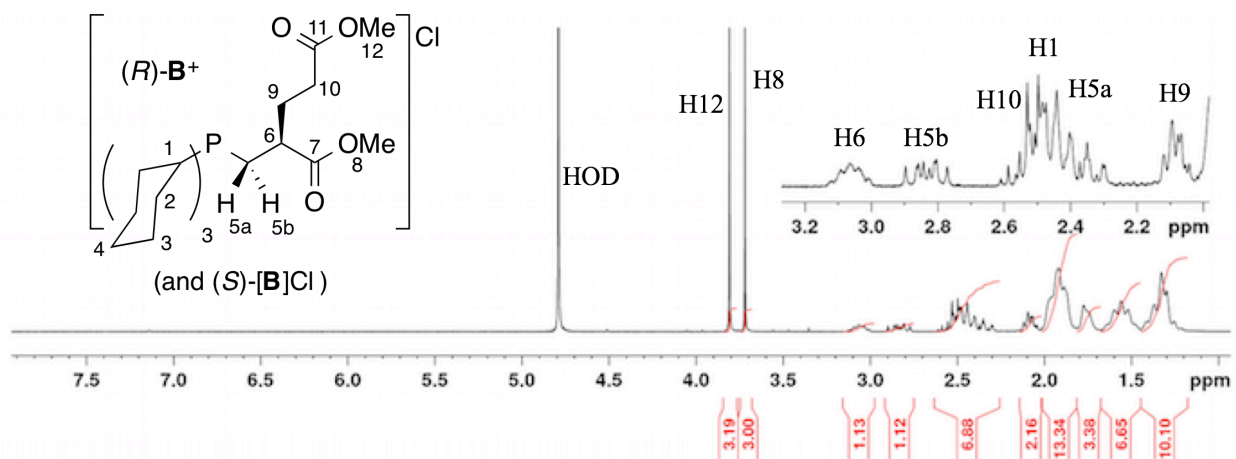


Figure A2. ^1H NMR spectrum of $[B]\text{Cl}$ (D_2O , 300.1 MHz).

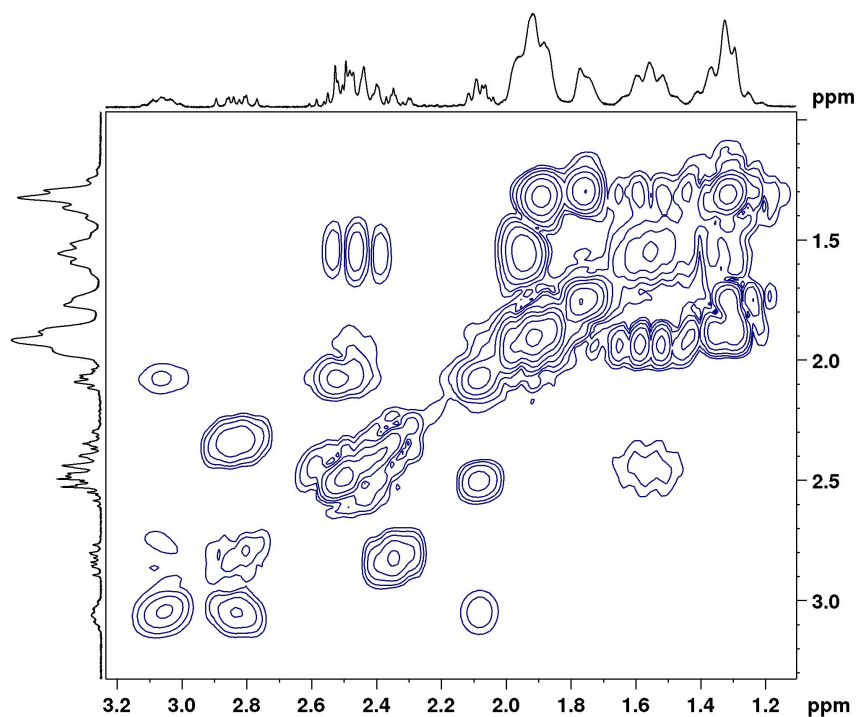


Figure A3. $^1\text{H} - ^1\text{H}$ COSY spectrum of $[\text{B}]\text{Cl}$ (D_2O). Cyclohexyl and carboxymethyl regions omitted for clarity.

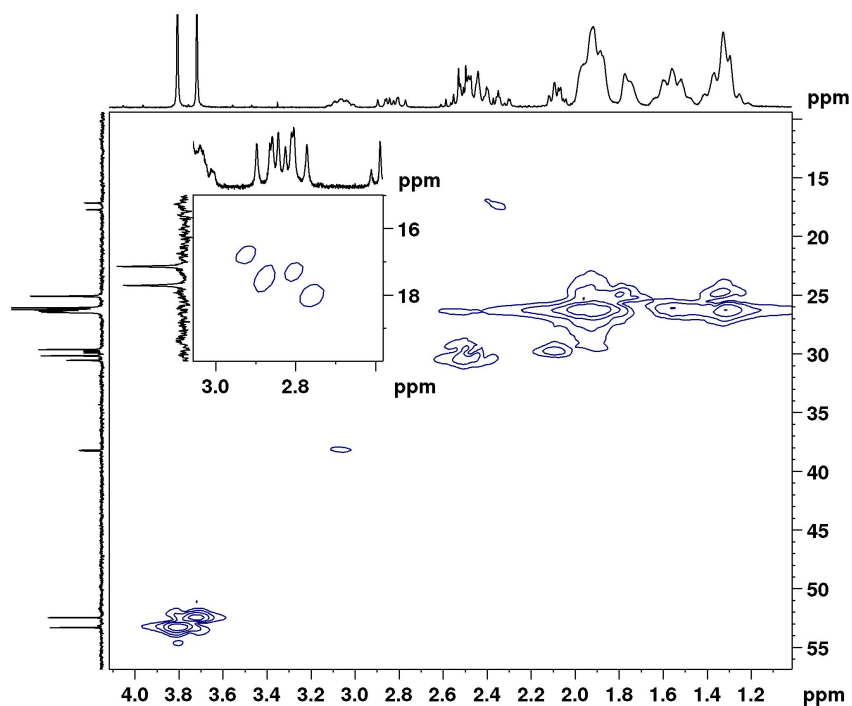


Figure A4. $^1\text{H} - ^{13}\text{C}$ HMQC spectrum of $[\text{B}]\text{Cl}$ (D_2O). Inset shows magnification of correlations between nuclei H5b and C5 .

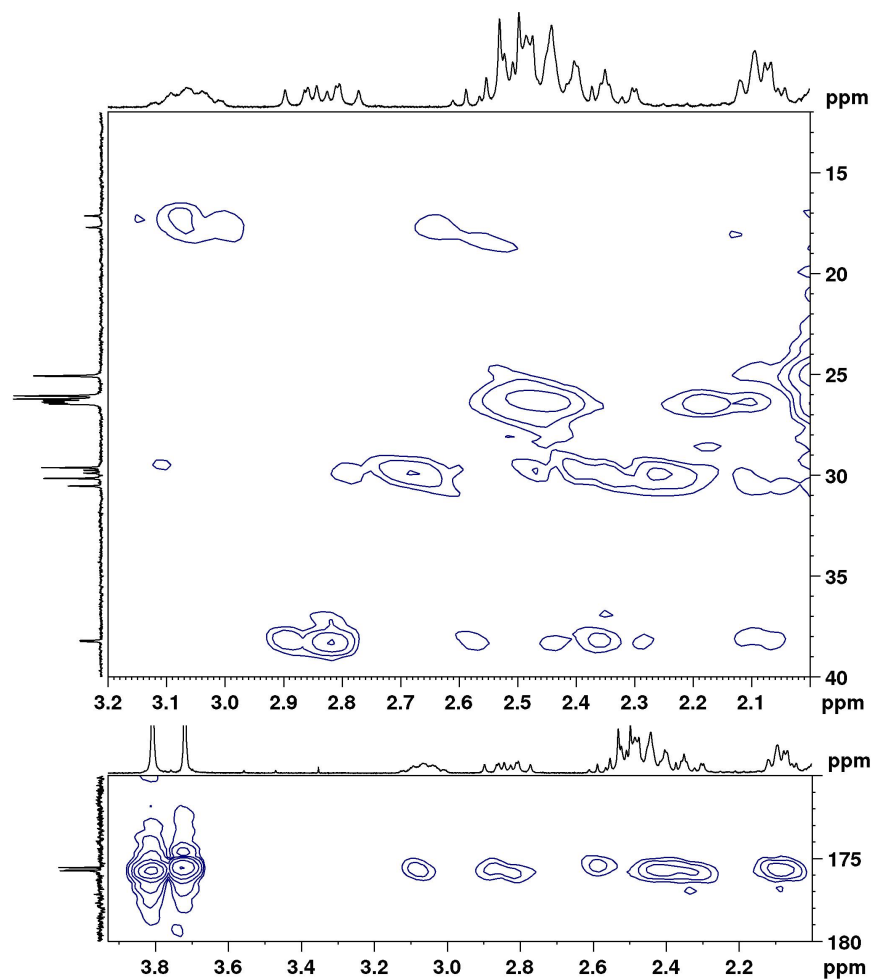


Figure A5. ^1H – ^{13}C HMBC spectrum of [B]Cl (D_2O). Inset shows correlations between carbonyl C7 / C11 and neighbouring protons. Cyclohexyl region omitted for clarity.

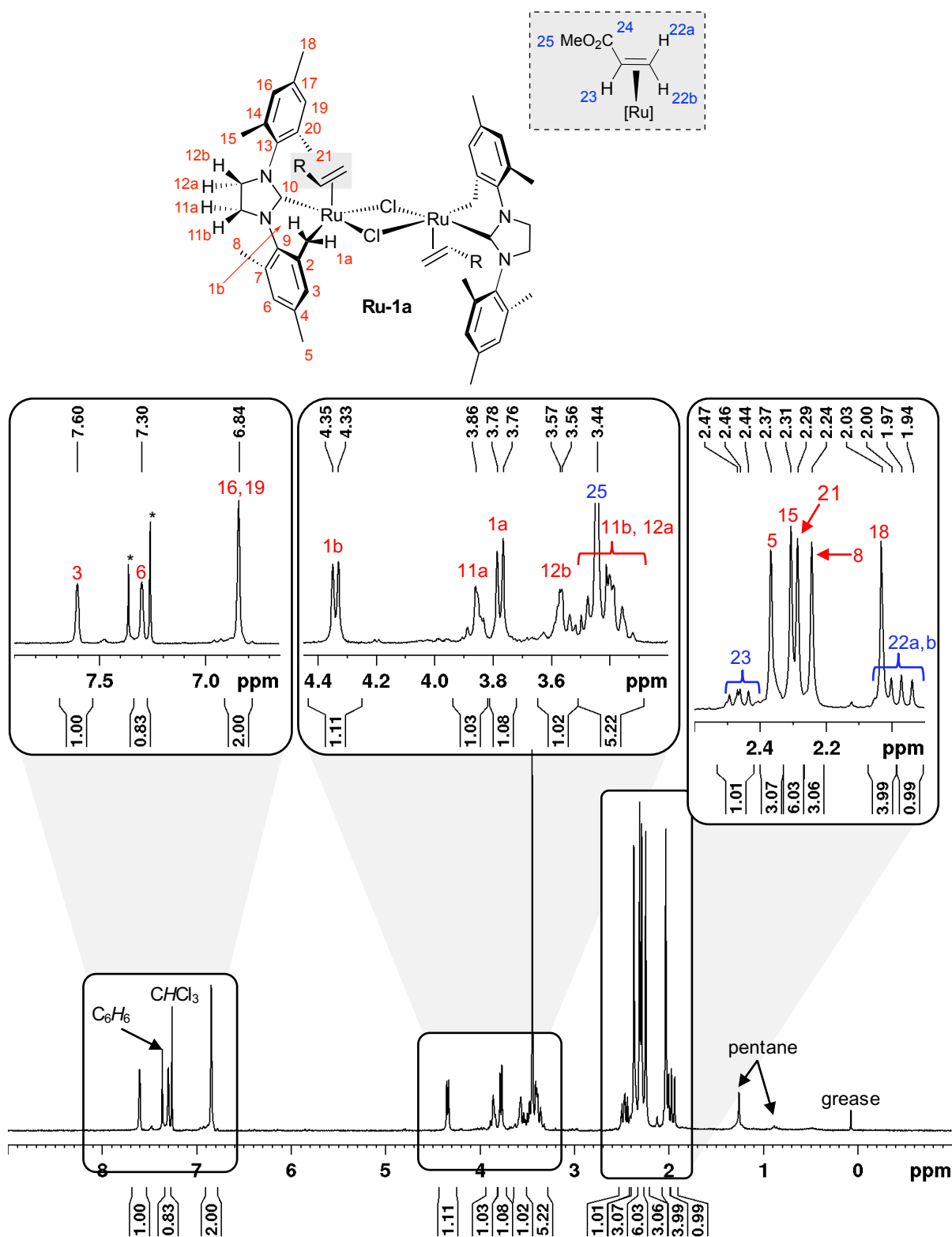


Figure A6. ^1H NMR spectrum for **Ru-1a**, $[\text{RuCl}(\kappa^2\text{-H}_2\text{IMes-H})(\eta^2\text{-H}_2\text{C=CHCO}_2\text{Me})]_2$ ($\text{R} = \text{CO}_2\text{Me}$; CDCl_3 , 300 MHz). (*) Denotes residual solvent: assigned in the full spectrum.

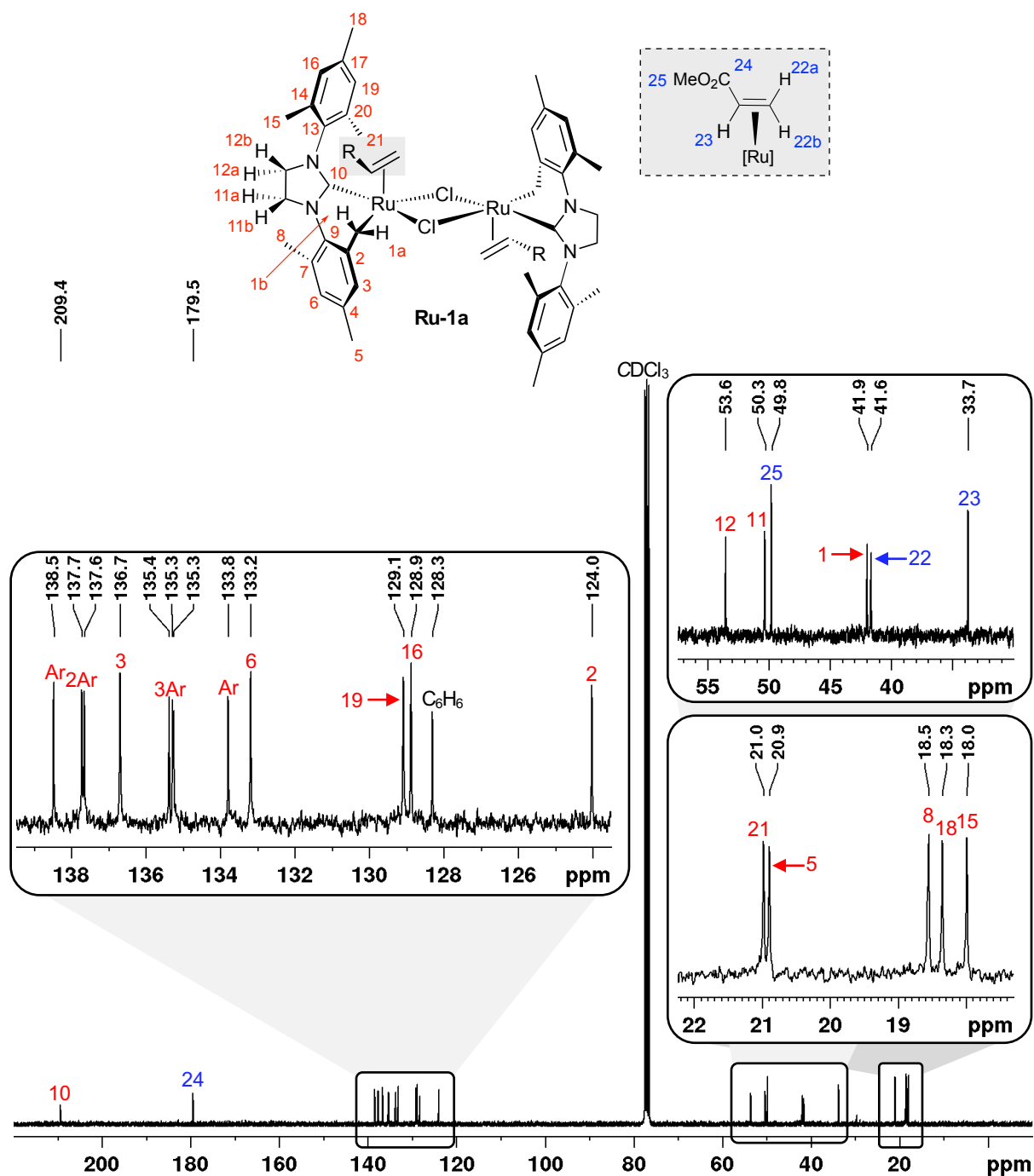


Figure A7. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum for **Ru-1a** (R = CO₂Me; CDCl₃, 77.5 MHz). “Ar” denotes carbon signals due to the aryl carbons of the mesityl rings.

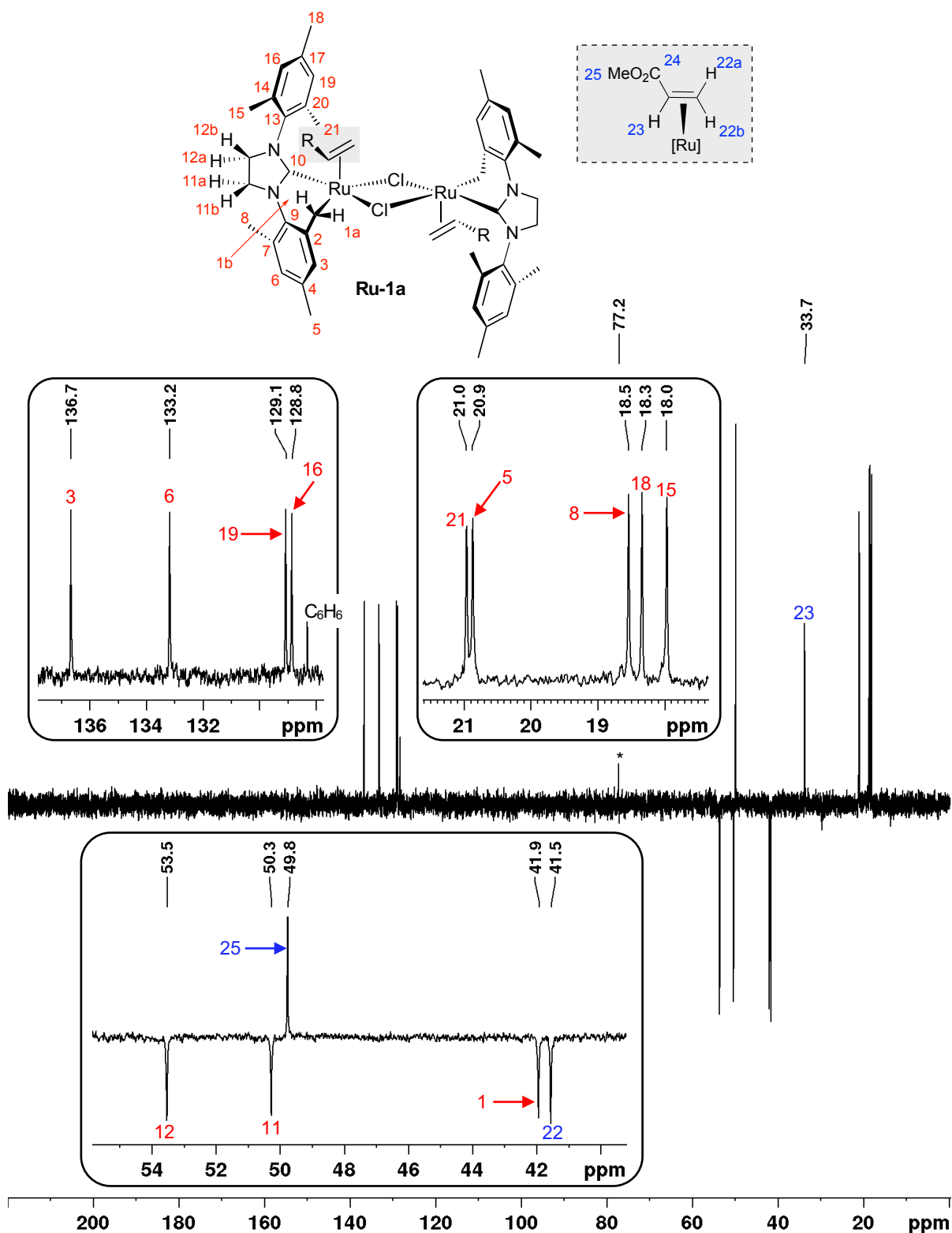


Figure A8. DEPT-135 spectrum for **Ru-1a** (R = CO₂Me; CDCl₃, 77.5 MHz). (*) Denotes residual CHCl₃.

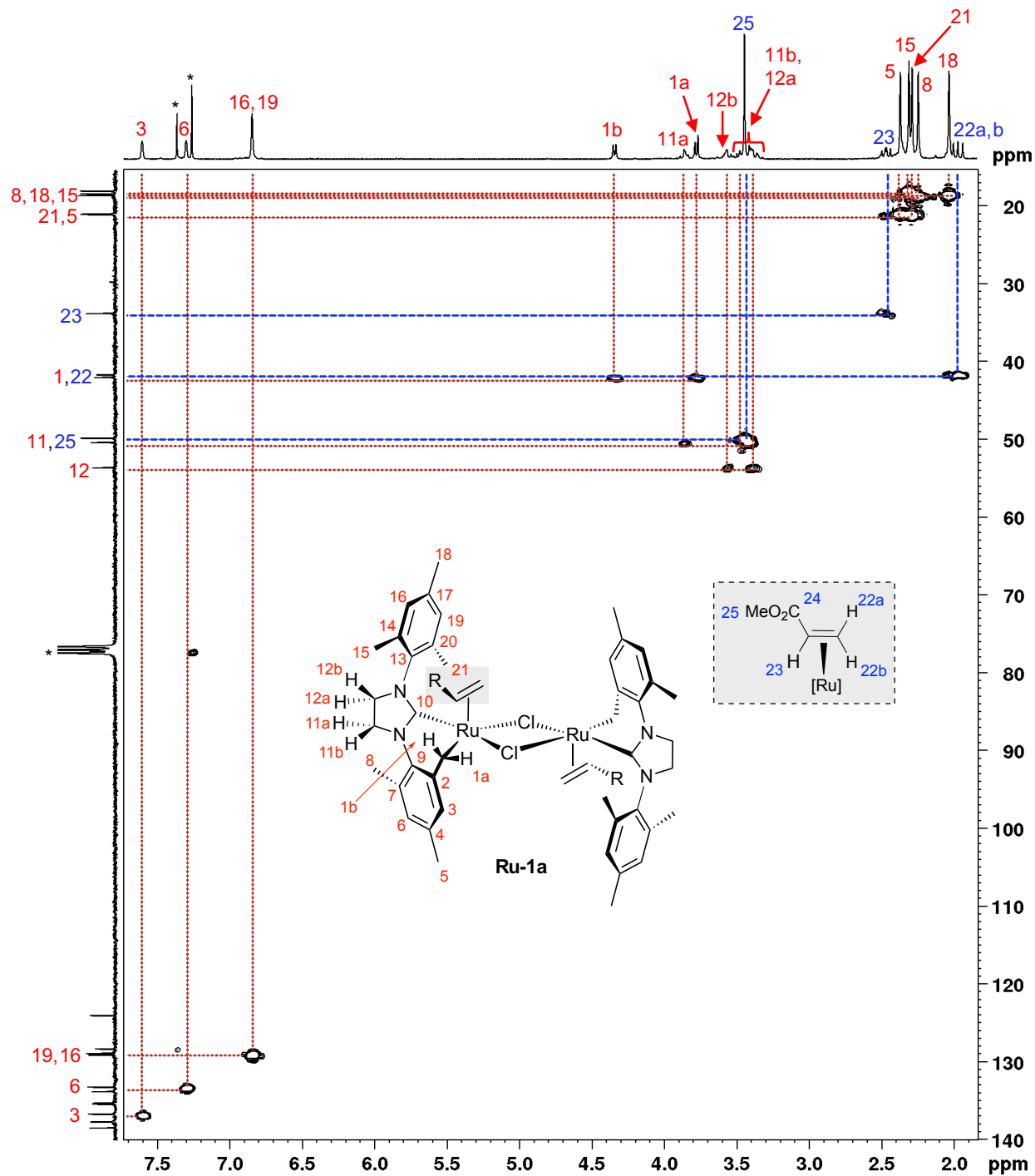


Figure A9. ^1H - ^{13}C HMQC spectrum for **Ru-1a** ($\text{R} = \text{CO}_2\text{Me}$; CDCl_3 , 300 MHz). (*) Denotes residual solvents (CDCl_3 , C_6H_6) as assigned in Figure A6 and Figure A7.

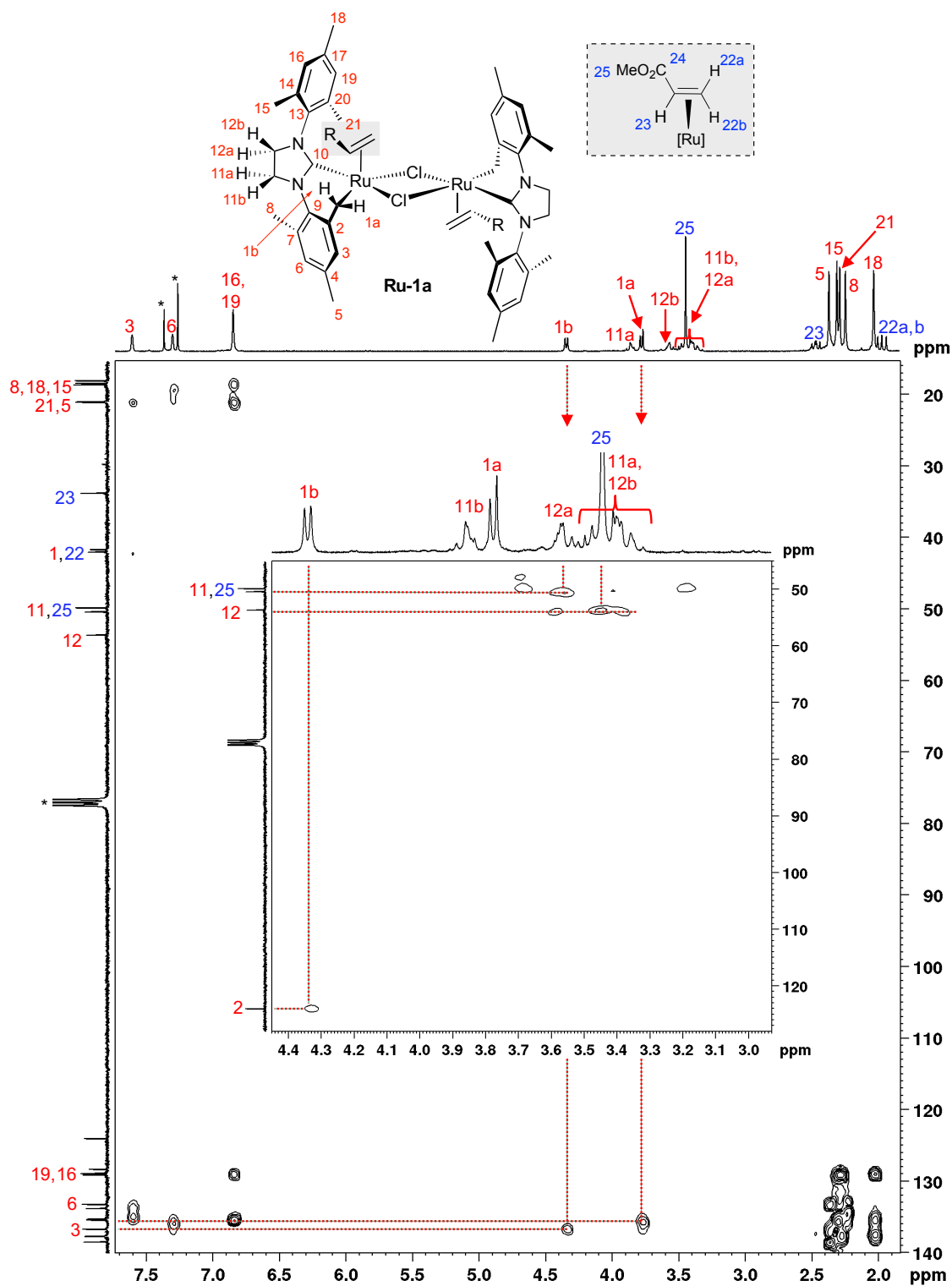


Figure A10. ^1H - ^{13}C HMBC spectrum for **Ru-1a** ($\text{R} = \text{CO}_2\text{Me}$; CDCl_3 , 300 MHz). (*) Denotes residual solvents as assigned in Figure A6 and Figure A7. Key correlations are highlighted using dashed lines.

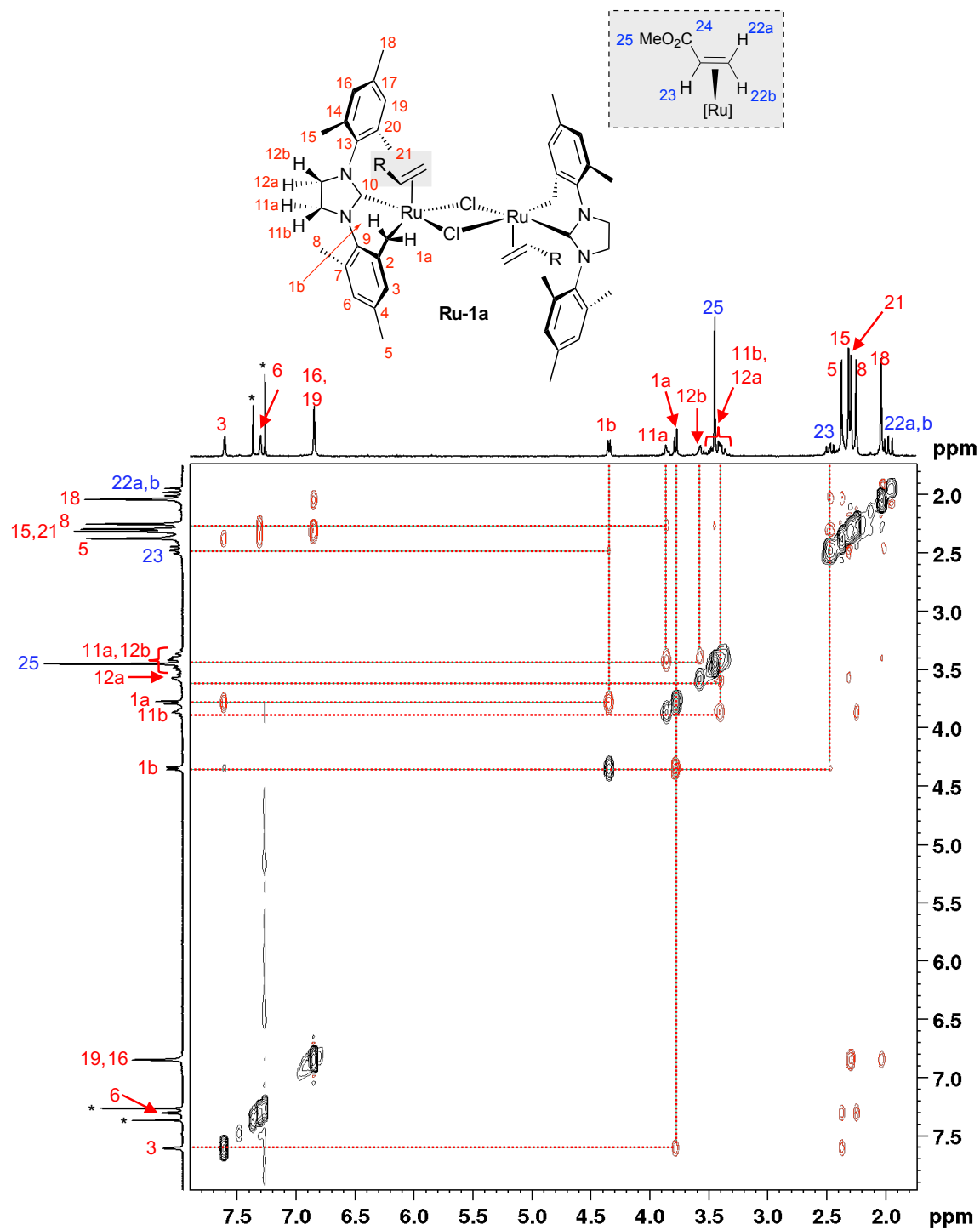


Figure A11. ^1H - ^1H NOESY spectrum for **Ru-1a** ($\text{R} = \text{CO}_2\text{Me}$; CDCl_3 , 300 MHz). (*) Denotes residual solvents (C_6H_6 and CHCl_3), as assigned in Figure A6.

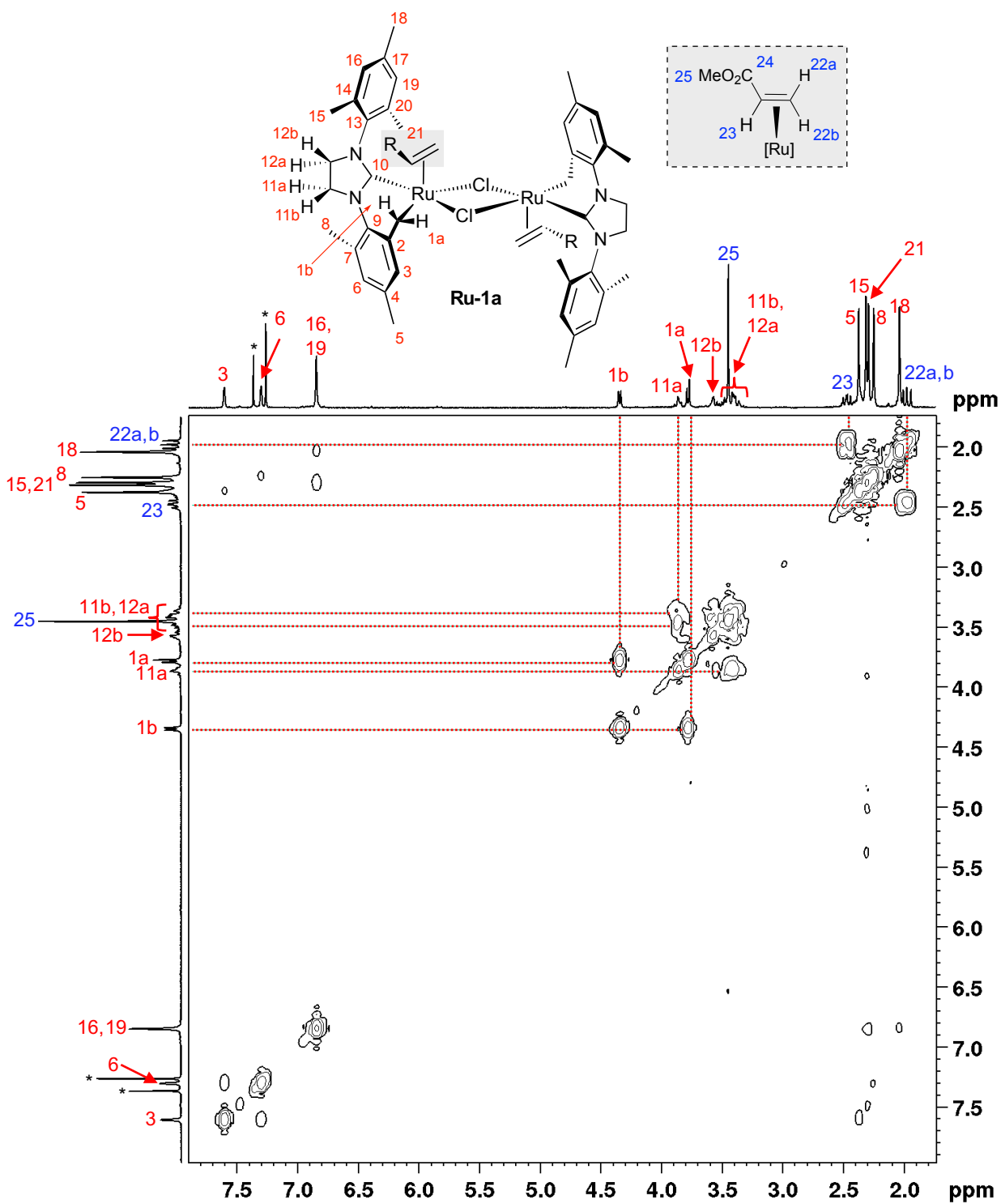


Figure A12. ^1H - ^1H COSY spectrum for **Ru-1a** ($\text{R} = \text{CO}_2\text{Me}$; CDCl_3 , 300 MHz). (*) Denotes residual solvents (C_6H_6 and CHCl_3), as assigned in Figure A6.

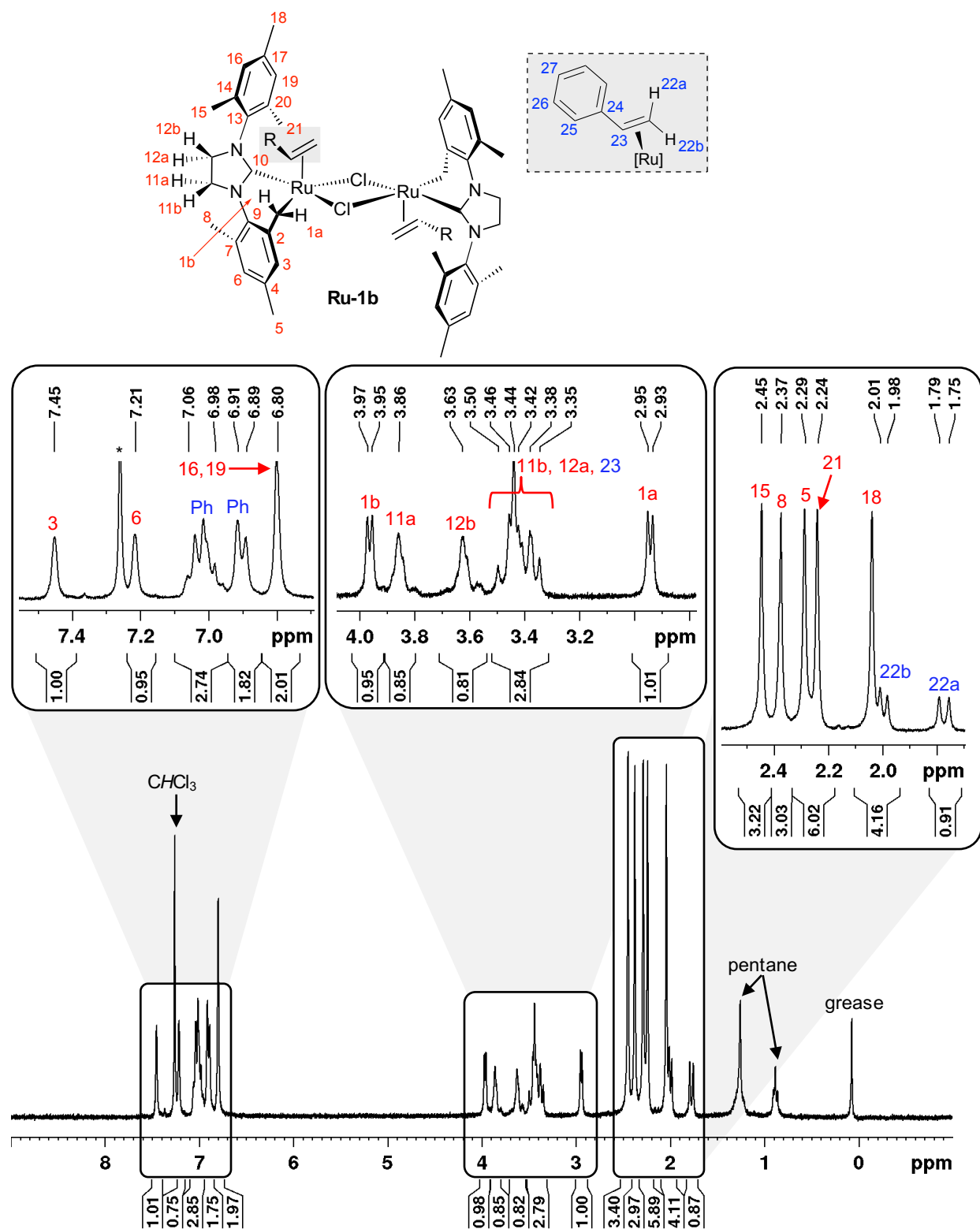


Figure A13. ¹H NMR spectrum for [RuCl(κ²-H₂IMes-H)(η²-H₂C=CHPh)]₂ **Ru-1b** (R = Ph; CDCl₃, 300 MHz). (*) Denotes residual CHCl₃.

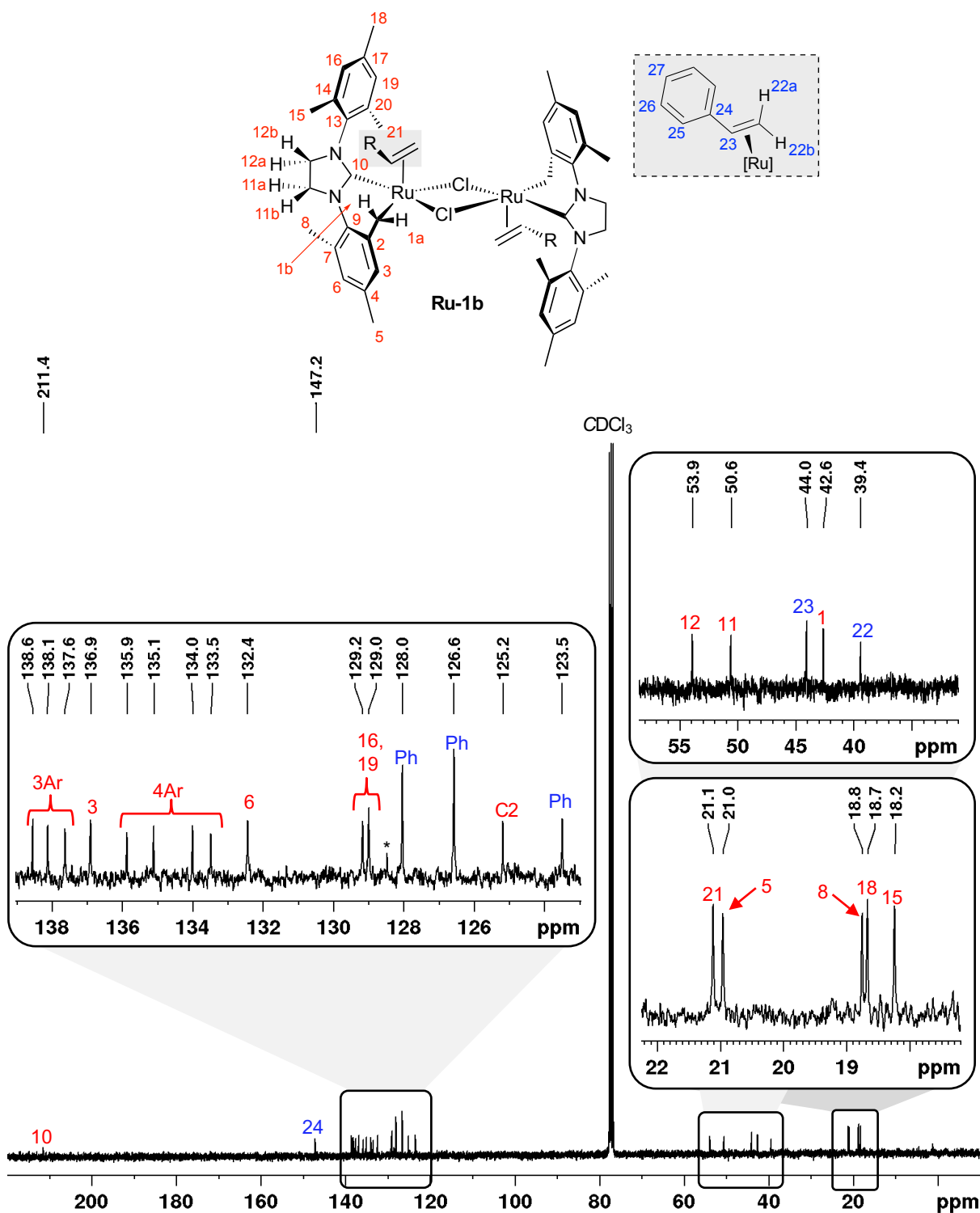


Figure A14. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum for **Ru-1b** (R = Ph; CDCl_3 , 77.5 MHz). “Ar” denotes Mes-ArC; “Ph” denotes styrene PhC signals, C25, C26, and C27. (*) Denotes residual C_6H_6 .

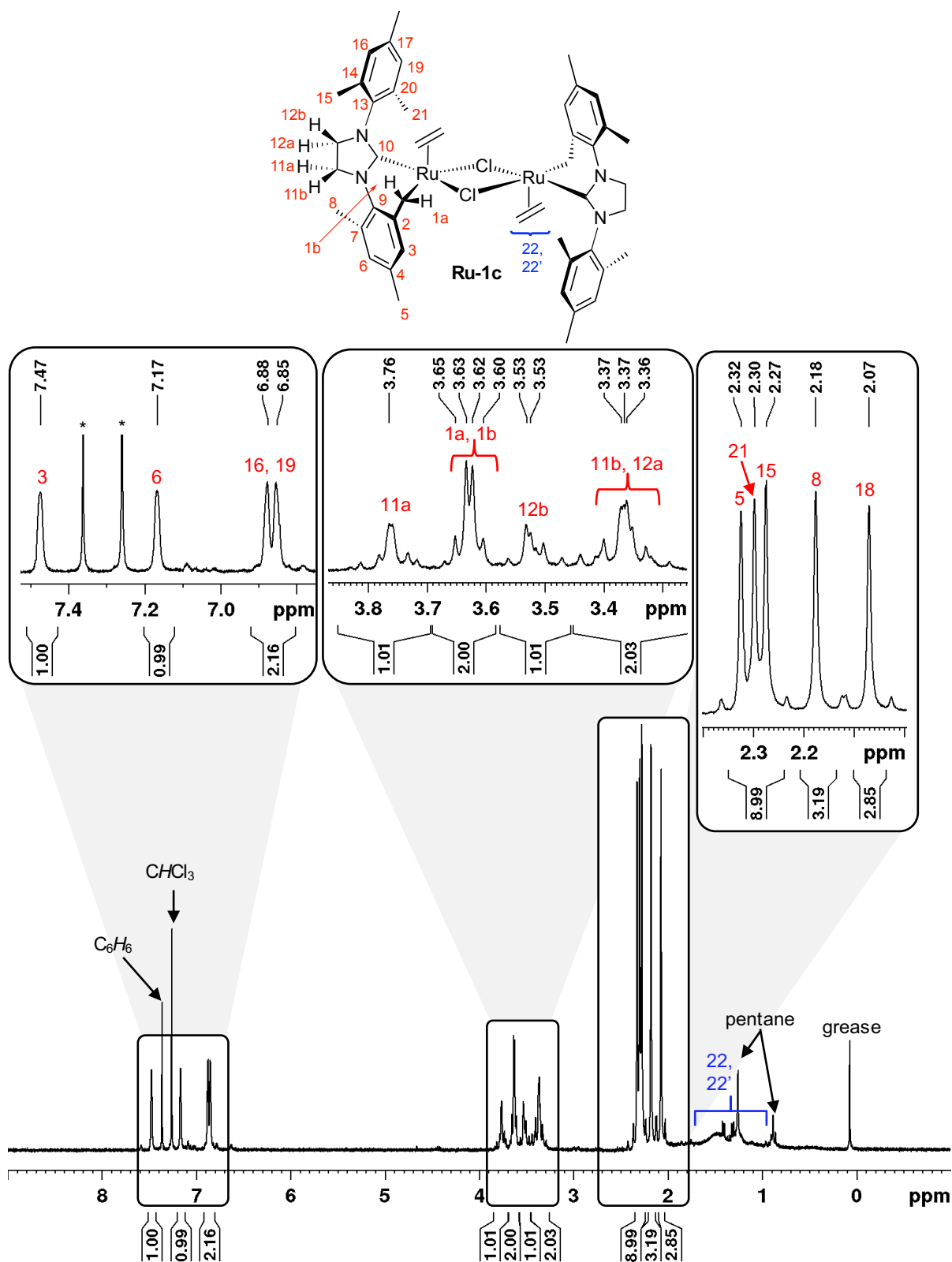


Figure A15. ¹H NMR spectrum for [RuCl(κ²-H₂IMes-H)(η²-H₂C=CH₂)₂ **Ru-1c** (CDCl₃, 300 MHz). (*) Denotes residual solvents, as assigned in the full spectrum.

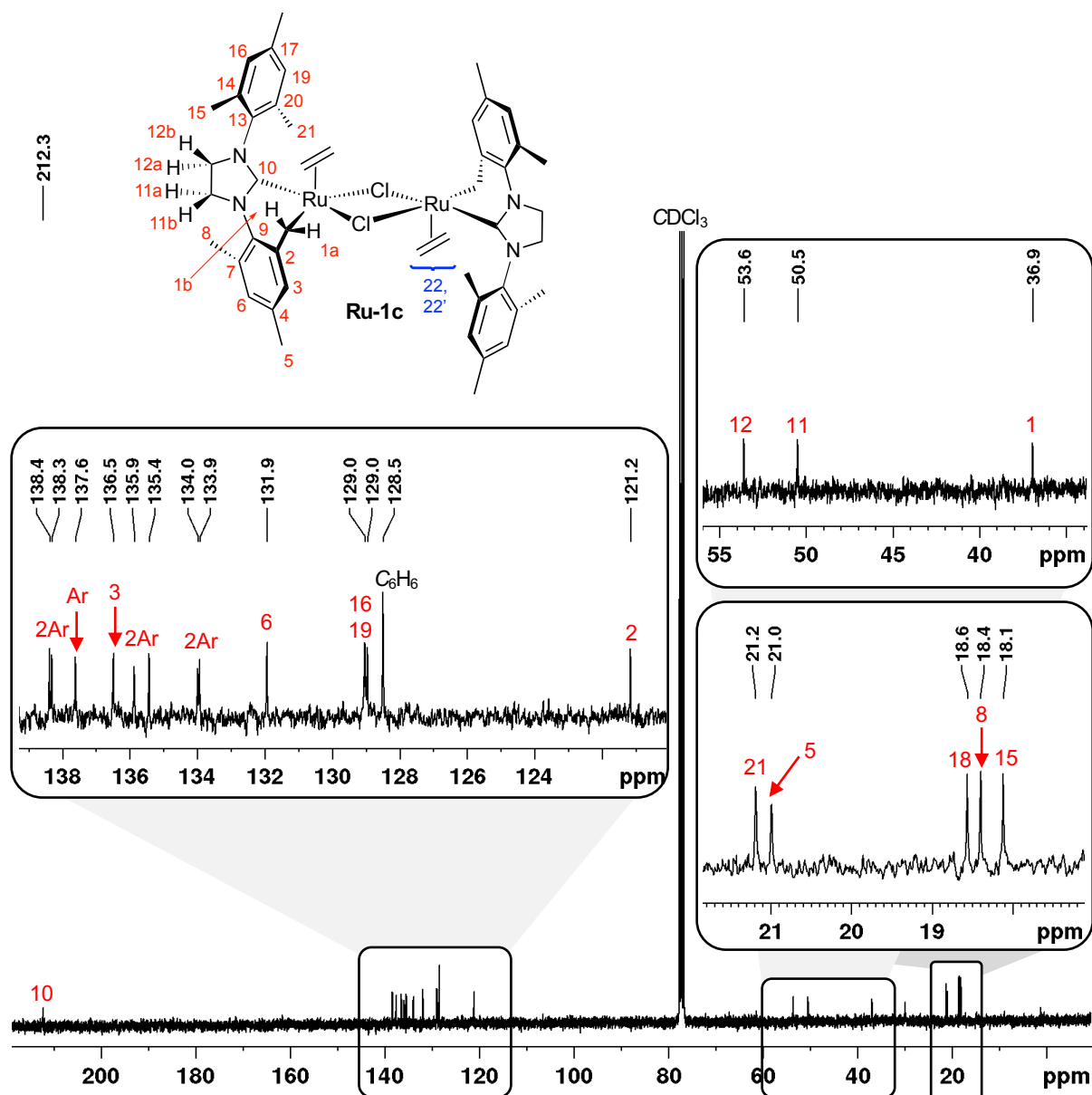


Figure A16. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum for **Ru-1c** (CDCl_3 , 77.5 MHz). “Ar” denotes carbon signals due to the aryl carbons of the mesityl rings.

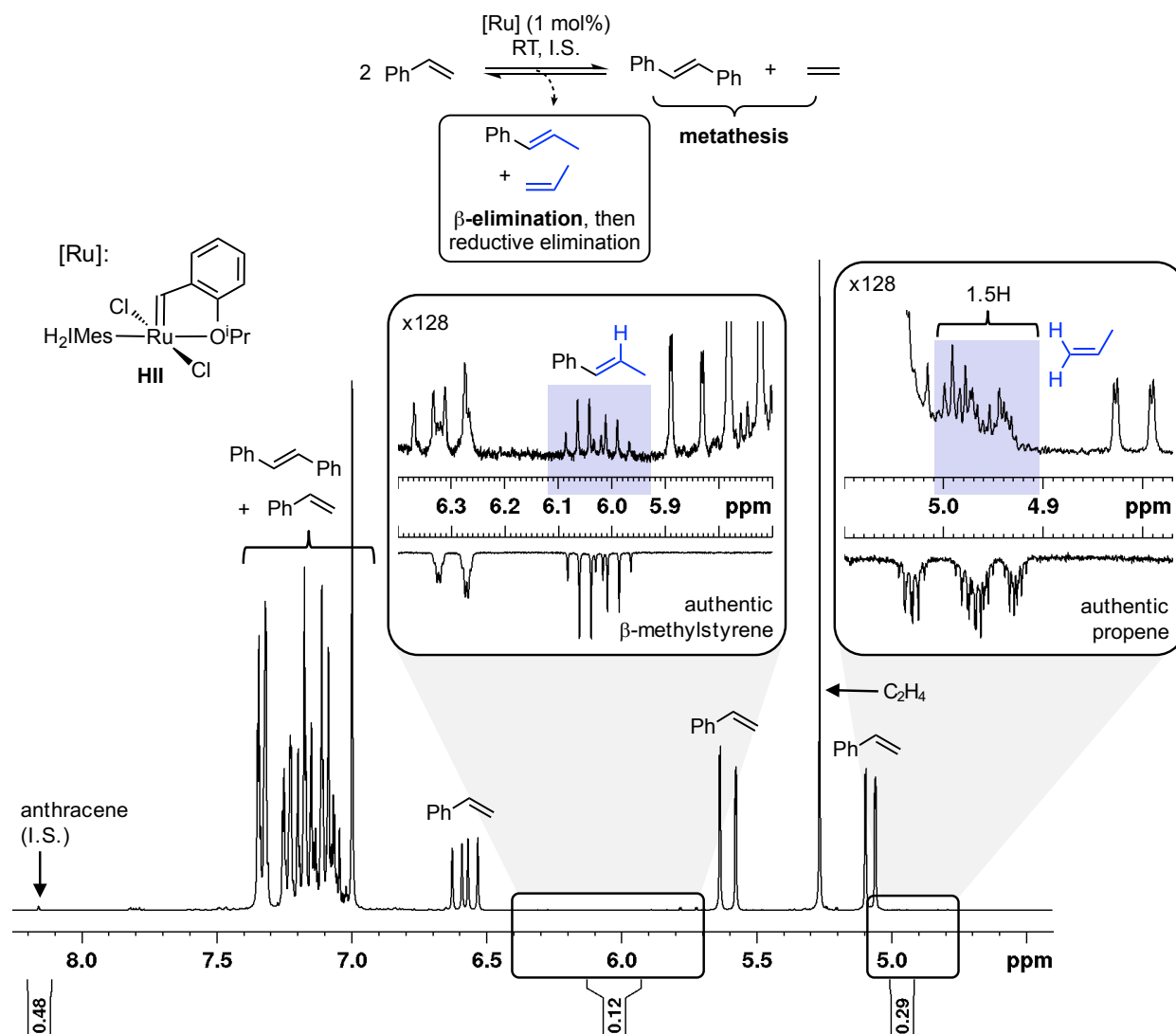


Figure A17. Representative ^1H NMR spectrum (C₆D₆, 300 MHz) showing quantification of propenyl products generated on metathesis of styrene by **HII**. Insets show (top) key regions for integration, along with (inverted) authentic samples of β -methylstyrene and propene. Blue shading indicates the specific signals used for integration relative to internal standard (anthracene). Integrations are normalized to starting **HII** $[\text{Ru}]=\text{CHPh}$ (δ_{H} 16.72, s, 1H).

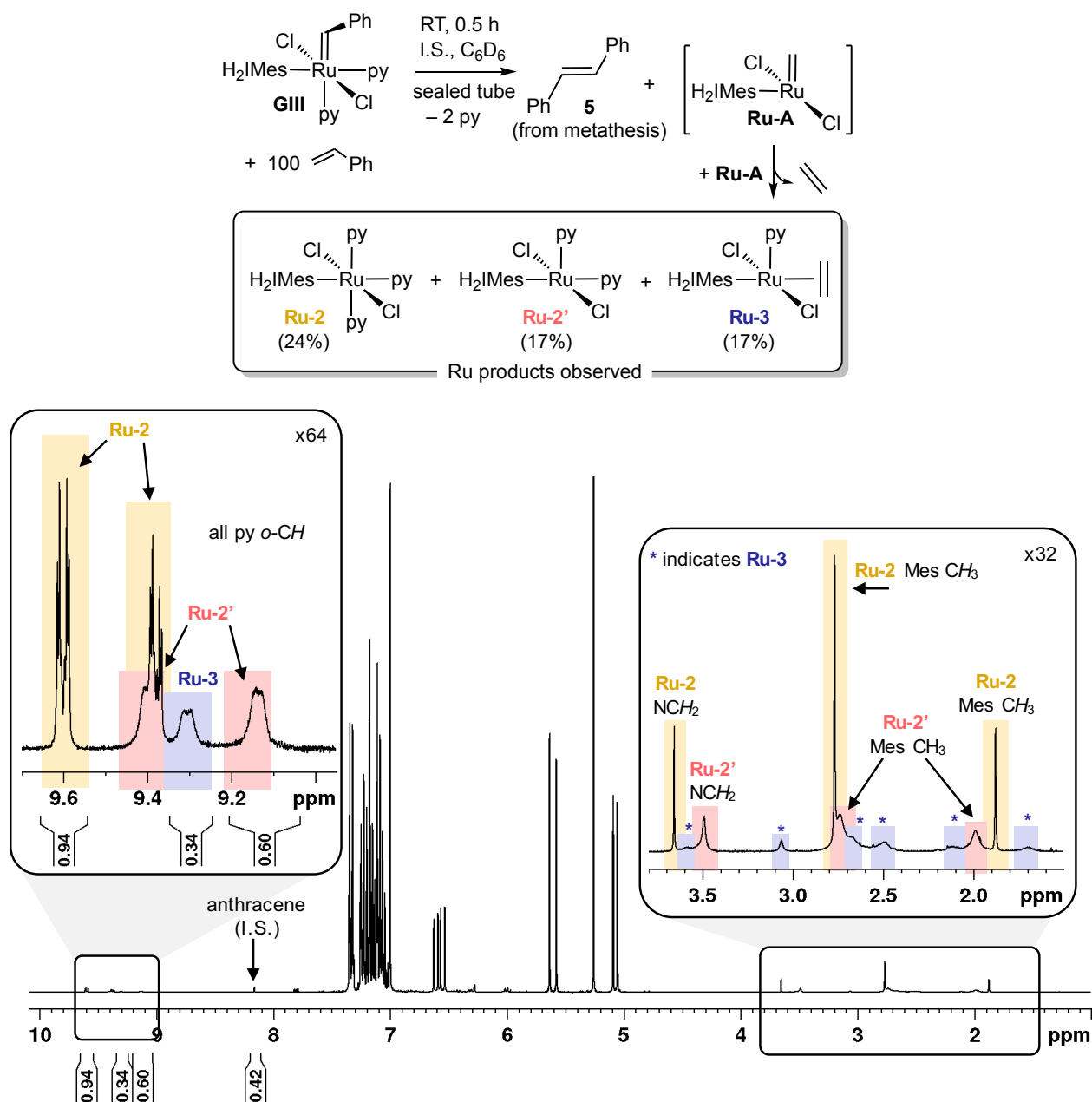


Figure A18. ^1H NMR spectrum (C_6D_6 , 300 MHz) of a representative sealed-tube reaction of **GIII** with styrene (100 equiv). For simplicity, the spectrum prior to addition of pyridine is shown: this affects the relative proportions of the Ru-py products (see text). The spectrum shows **Ru-2/2'/3** following complete loss of $[\text{Ru}]=\text{CHR}$ species. Insets: key py *o*-CH and aliphatic H_2IMes signals for **Ru-2/2'/3**. The Mes CH and py *m/p*-CH signals (obscured by those for styrene and stilbene) were located in experiments involving thermolysis of **GIII** (Figure A21; **Ru-2/2'**) or by ^1H - ^1H COSY/NOESY (**Ru-3**). Integrations are normalized to starting **GIII** $[\text{Ru}]=\text{CHPh}$ (δ_{H} 19.66, s, 1H).

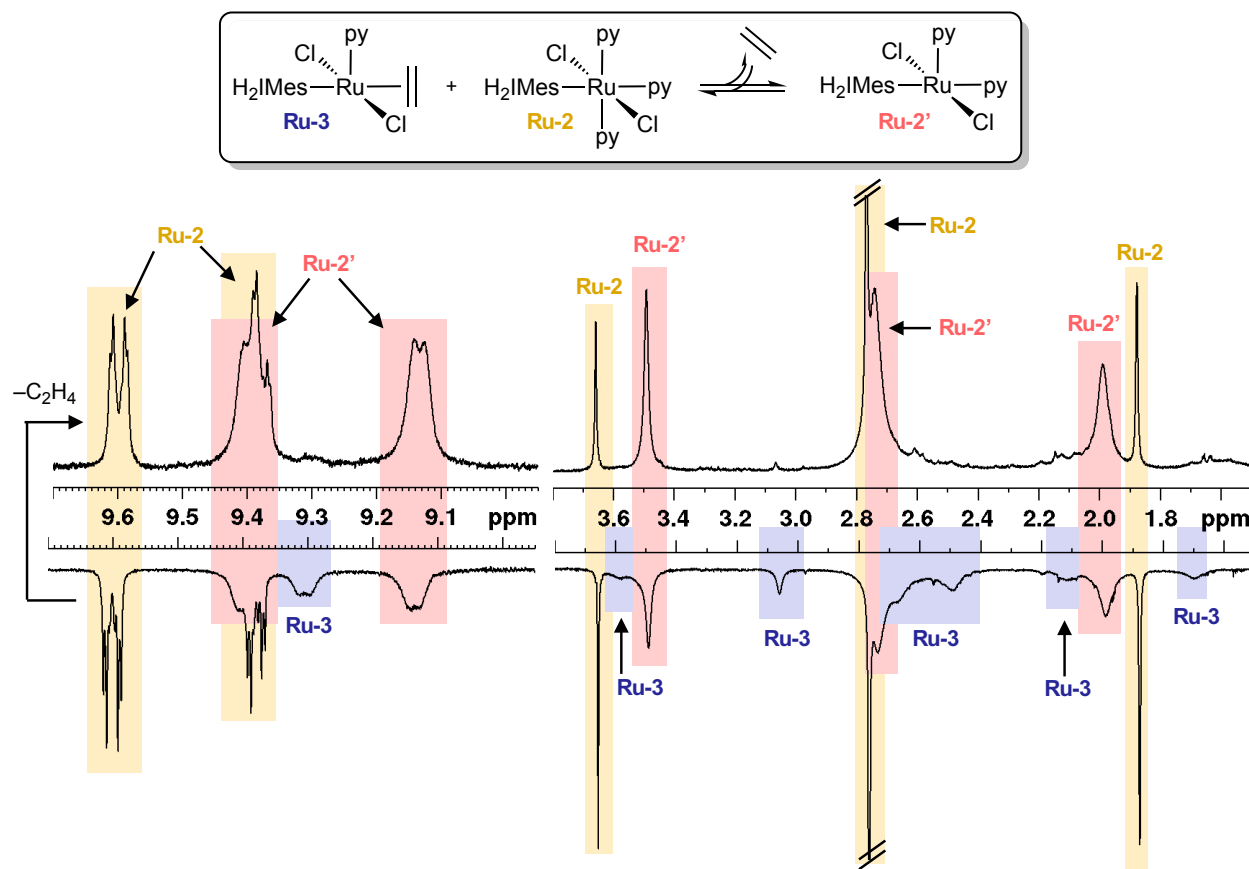


Figure A19. ¹H NMR spectra (C₆D₆, 300 MHz) showing loss of **Ru-3** on removal of ethylene. Upper trace: following volatilization of ethylene from (inverted trace; reproduced from Figure A18) mixture formed on full decomposition of **GIII** on reaction with styrene (100 equiv).

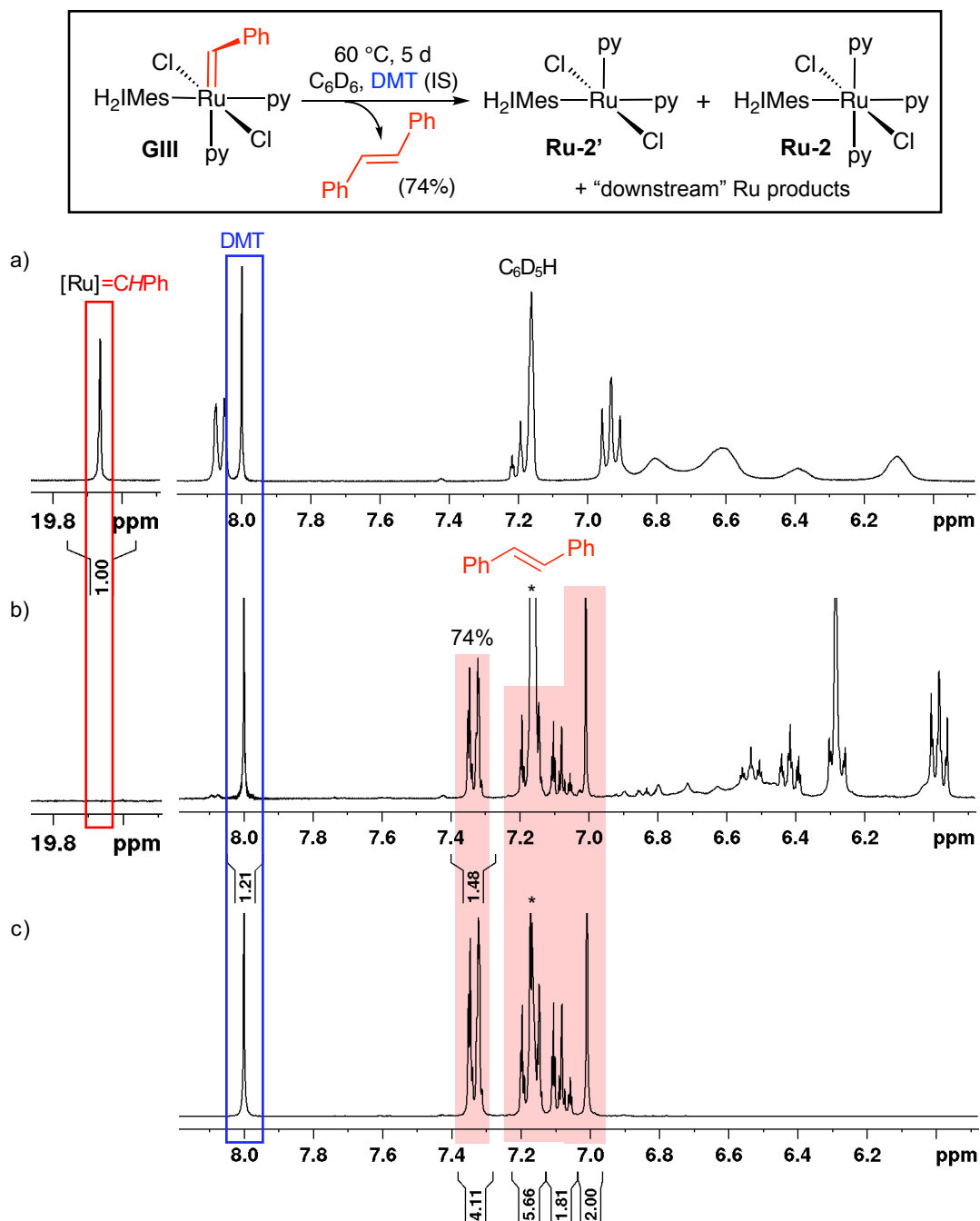


Figure A20. ¹H NMR spectra showing evolution of stilbene on thermolysis of **GIII** (C₆D₆, 300 MHz). (a) **GIII** and DMT before heating. (b) After 5 d at 60 °C. (c) Reference spectrum showing (*E*)-stilbene and DMT. (*) Denotes residual C₆D₅H. For assignment of the ¹H NMR signals for the Ru products of bimolecular decomposition, see Figure A21.

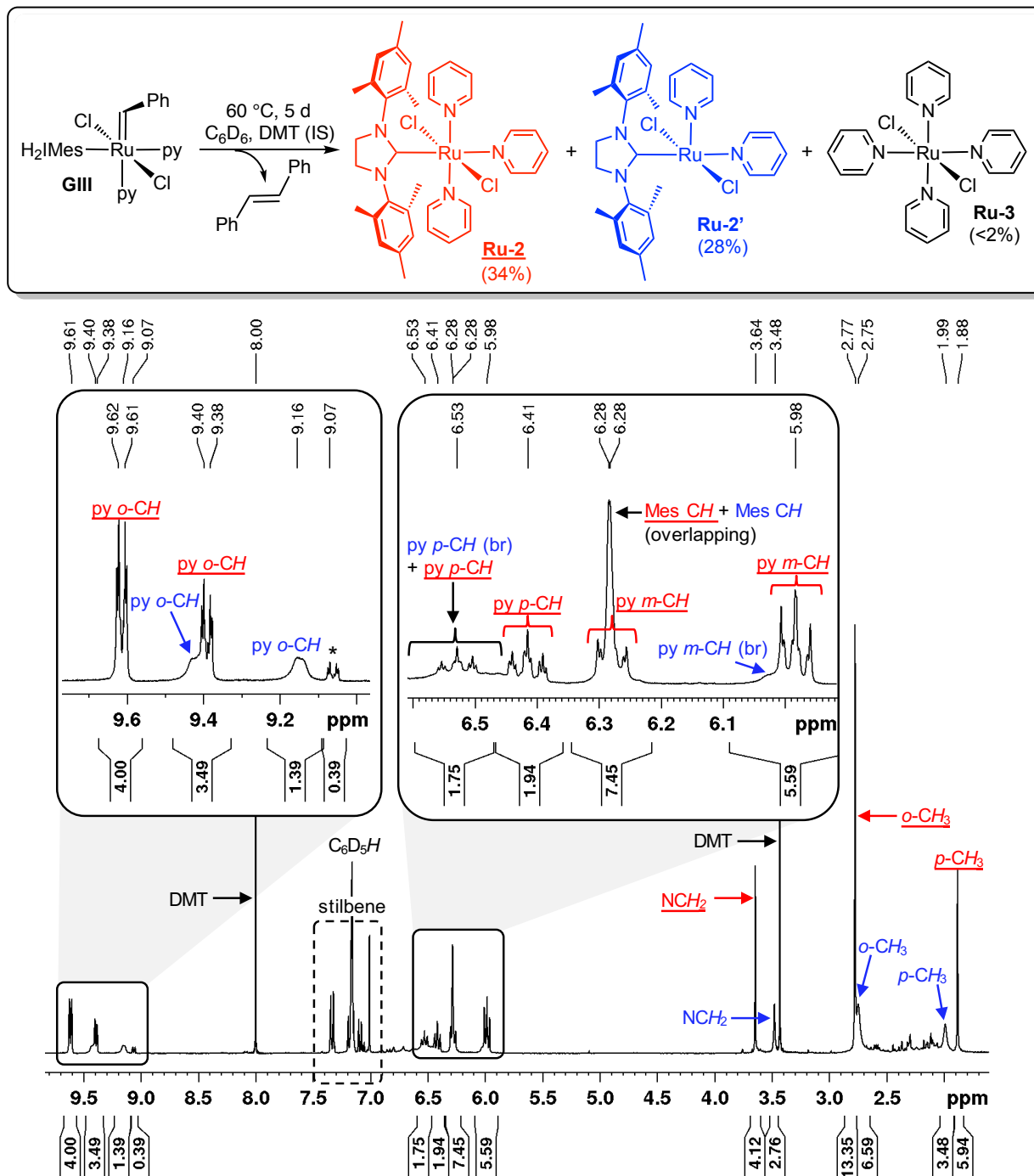


Figure A21. ¹H NMR spectra showing assignment of Ru products generated on thermolysis of **GIII** (5 d; C₆D₆, 300 MHz). Dashed box denotes signals assigned to (*E*)-stilbene. **Ru-2** is indicated by red font with underlining. (*) Denotes py *o*-CH signal for RuCl₂(py)₄.

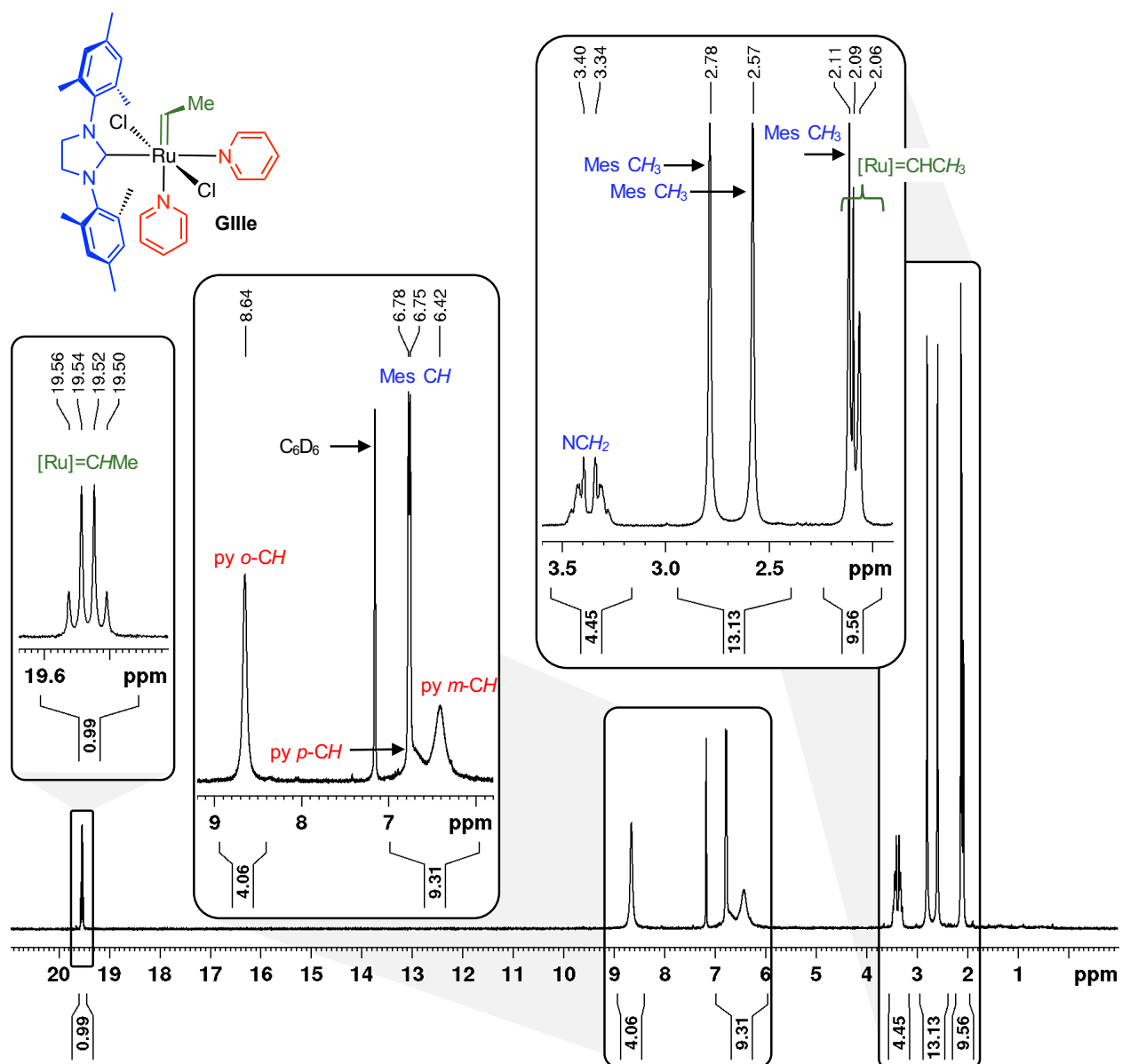


Figure A22. 1H NMR spectrum of ethylidene complex **GIIIe** (C₆D₆, 300 MHz).

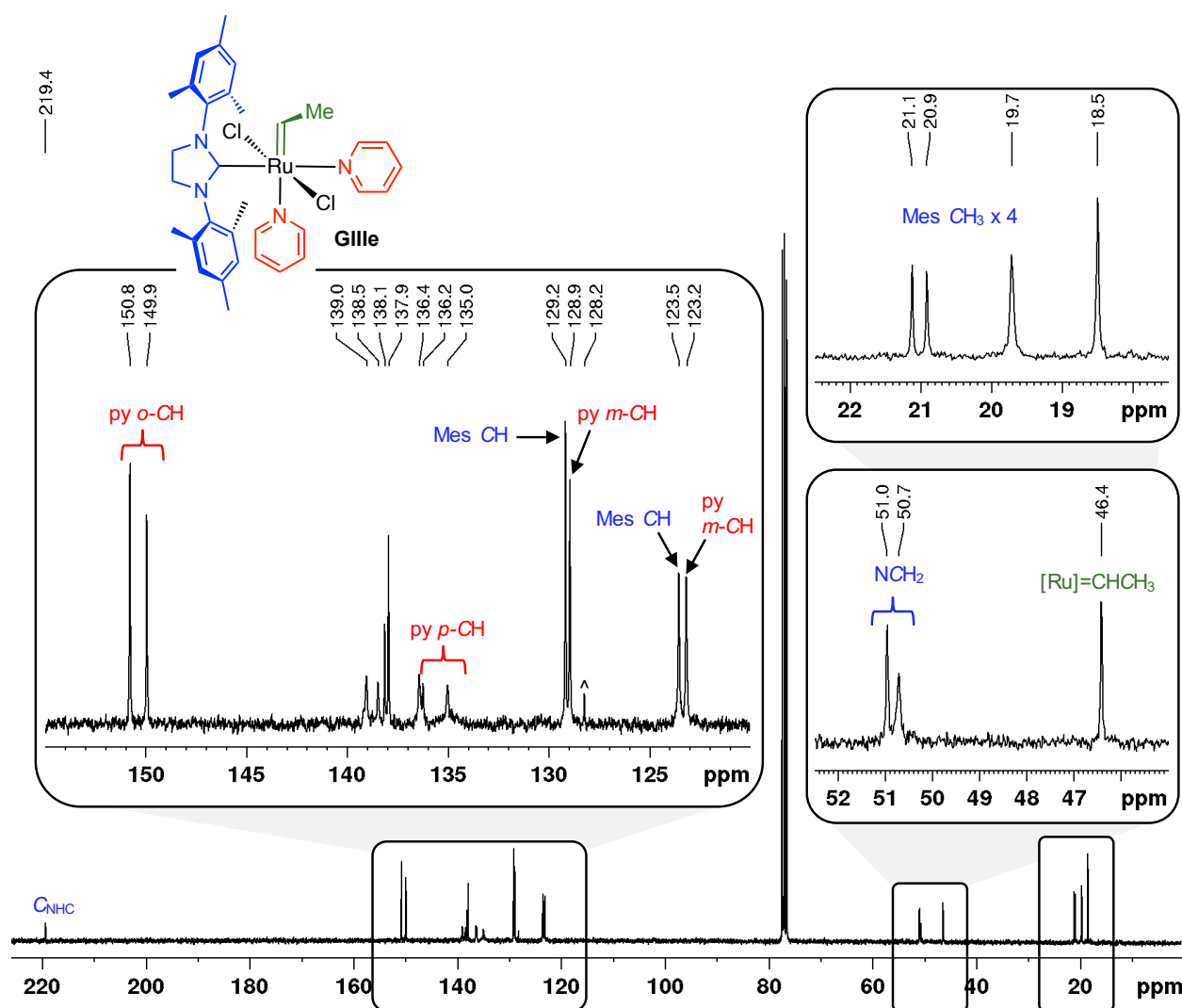


Figure A23. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of ethylidene **GIIIe** (CDCl_3 , -20°C , 77.5 MHz). The $[\text{Ru}]=\text{CHMe}$ signal was located at δ_{C} 330.1 by $^1\text{H}-^{13}\text{C}$ HMQC analysis. (^) Denotes residual C_6H_6 .

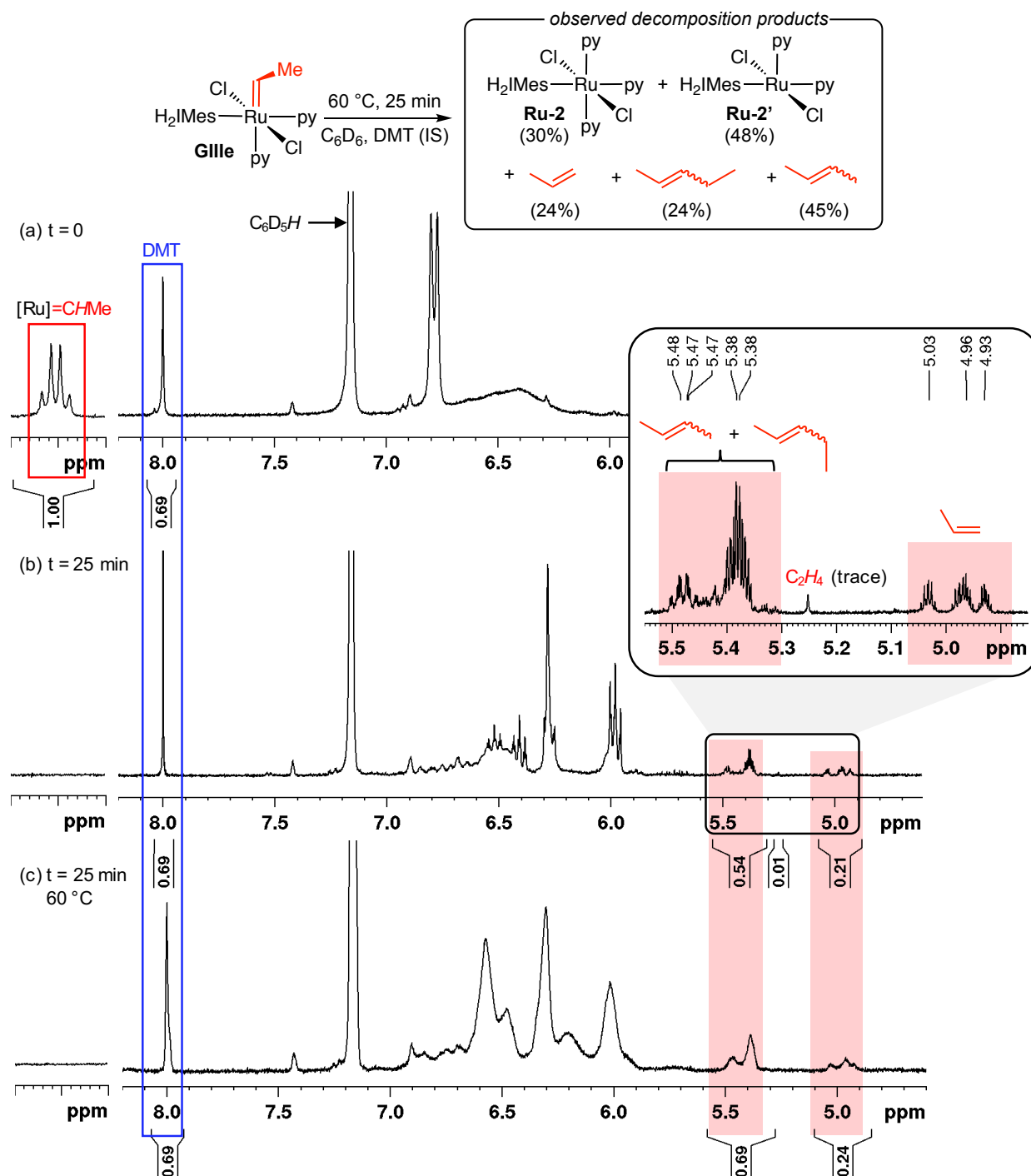


Figure A24. ^1H NMR spectra showing evolution of butene, pentene, and propylene on decomposition of **GIle** (C_6D_6 , 300 MHz). (a) **GIle** and DMT before heating. (b) After 25 min at 60°C ; spectrum collected at RT. (c) On heating the sample to 60°C in the probe.

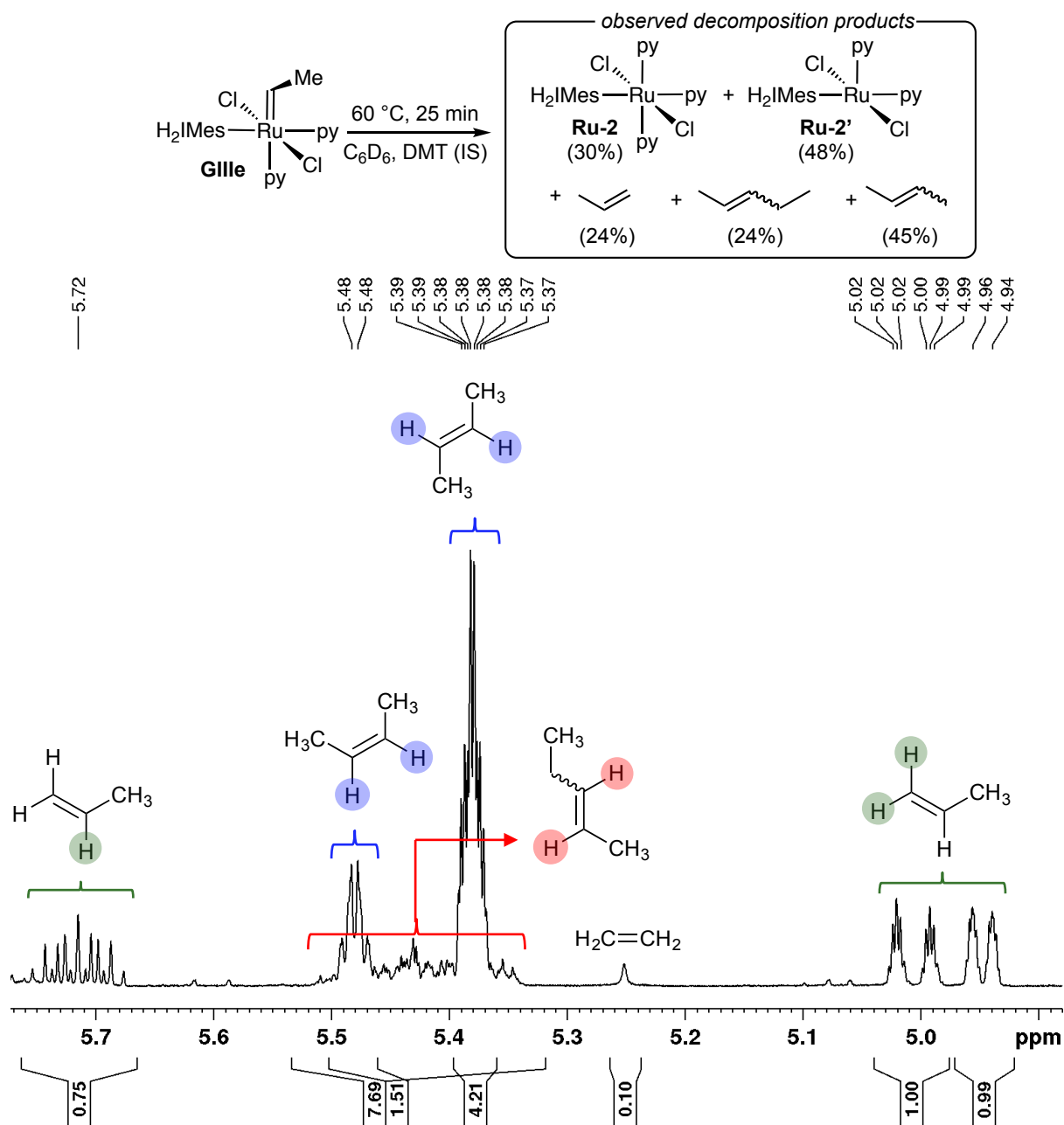


Figure A25. High-field ^1H NMR spectrum showing identification of olefinic products formed on decomposition of ethylidene **GIIIe** at 60°C (C_6D_6 , 600 MHz spectrometer with cryoprobe; spectrum collected at RT).

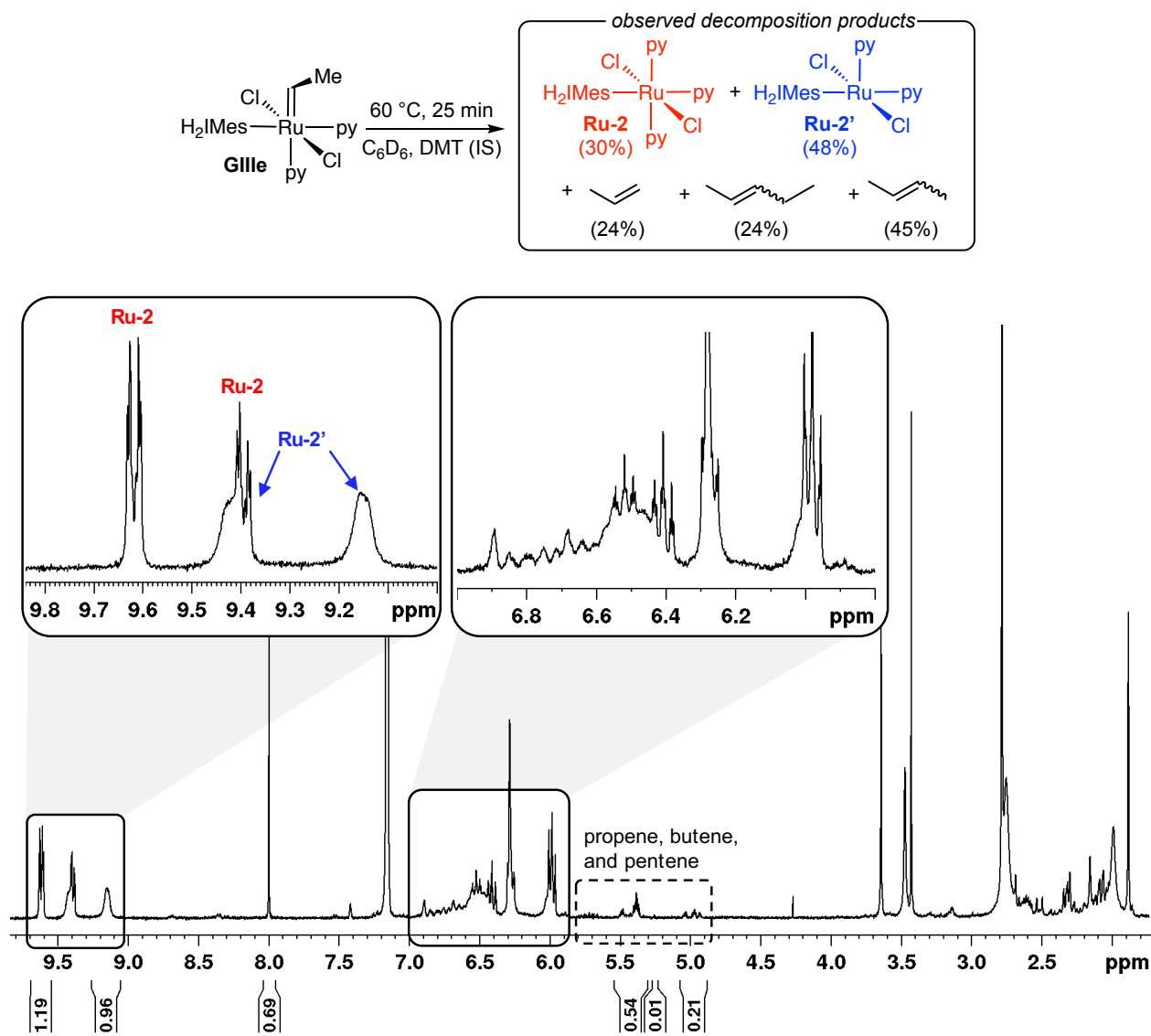


Figure A26. ^1H NMR spectrum (C_6D_6 , 300 MHz) showing Ru products formed on decomposition of ethylidene **GIIIe** at 60°C . Integrations are normalized to starting **GIIIe** $[\text{Ru}]=\text{CHPh}$ (δ_{H} 19.53, q, $^3J_{\text{HH}} = 5.9$ Hz).

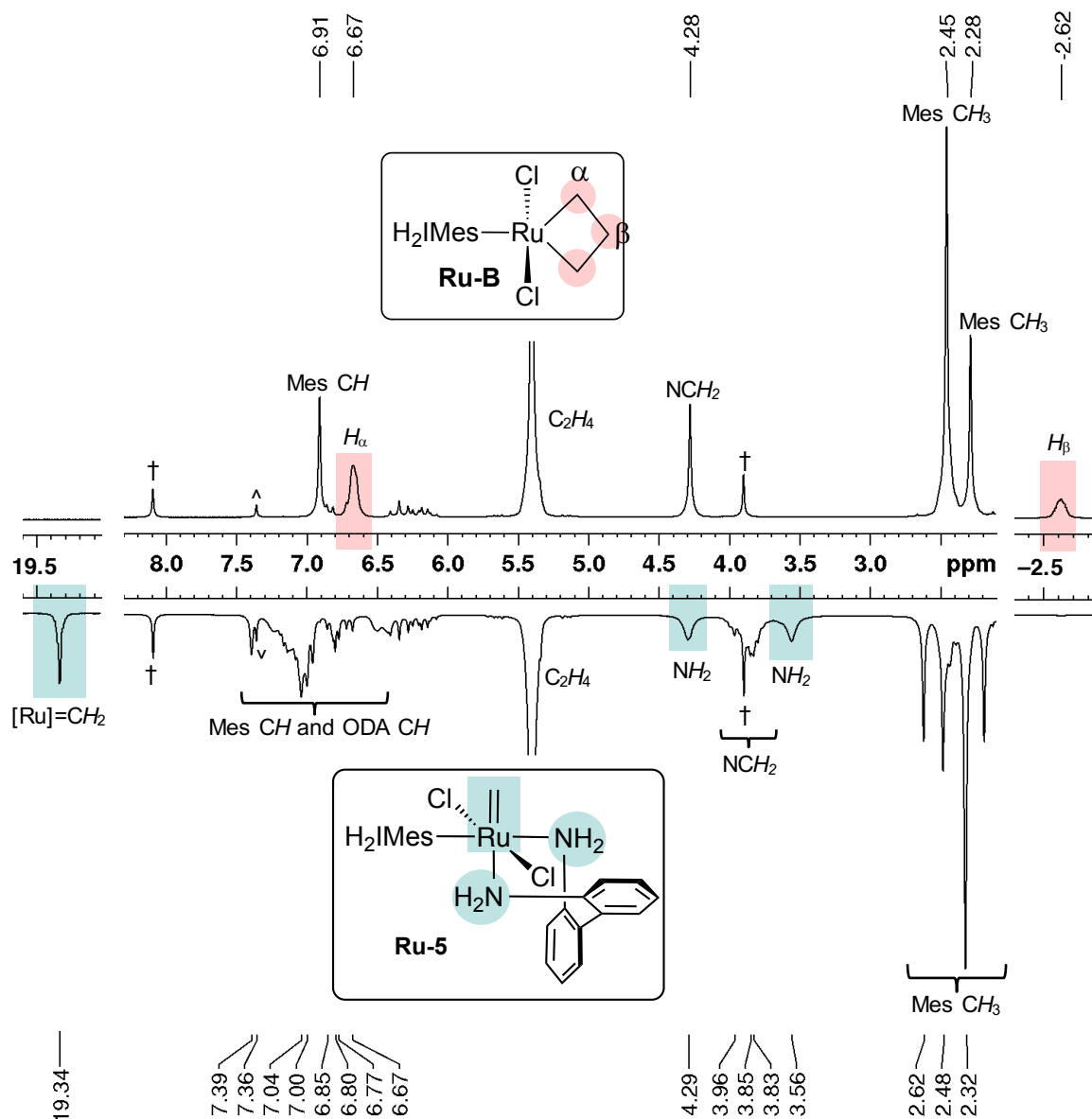


Figure A27. ¹H NMR spectra showing (top) **Ru-B**, and (inverted) its *o*-dianiline-stabilized derivative **Ru-5** (300 MHz, CD₂Cl₂, -50 °C). Diagnostic NMR signals for **Ru-B** and **Ru-5** are highlighted with bars that approximate the colours of the complexes. Reproduced from Figure 4.3 in chapter 4 above, with additional peak assignments and labels. †Denotes DMT (¹H internal standard); (^) denotes residual C₆H₆.

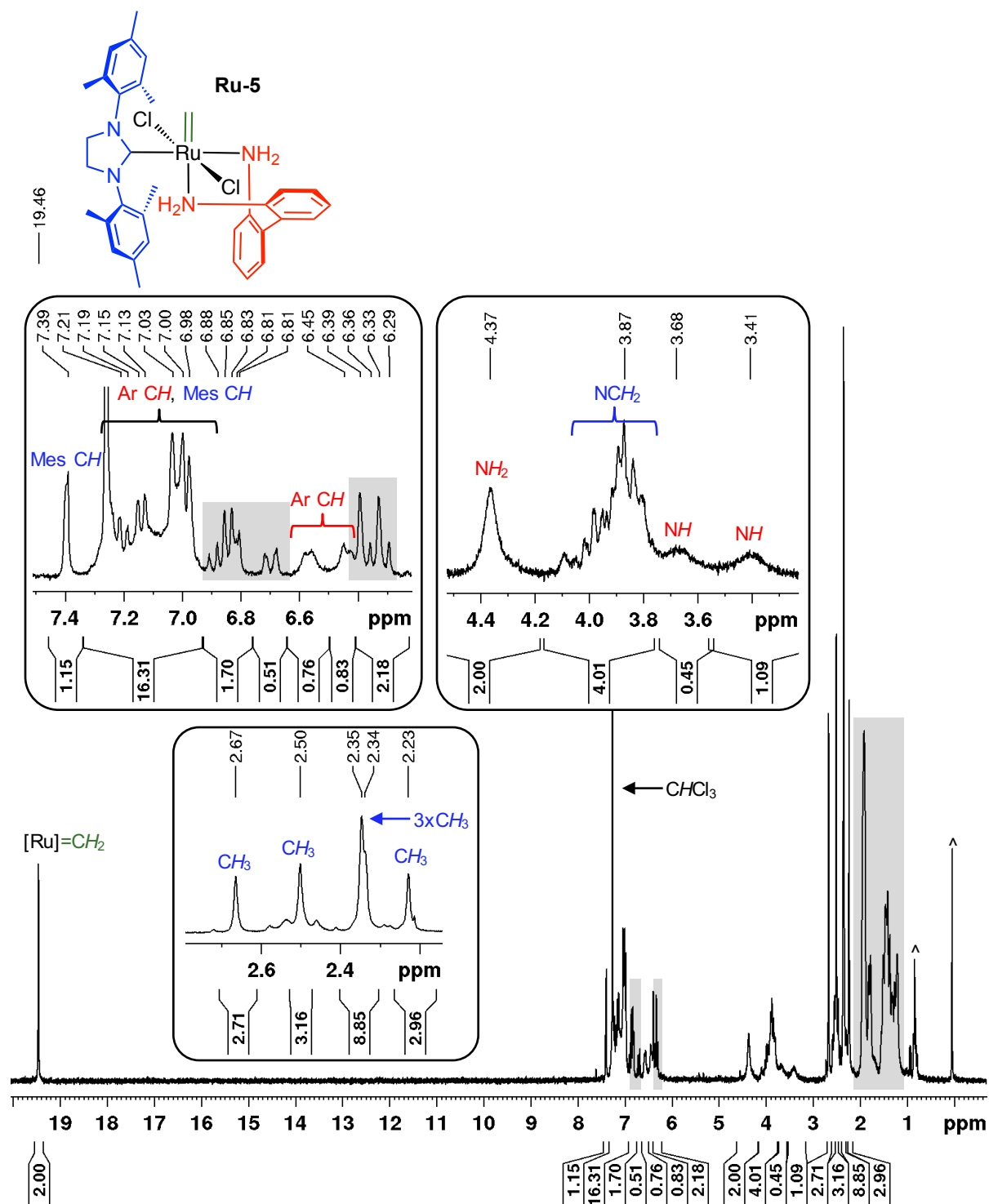


Figure A28. ¹H NMR spectrum of isolated **Ru-5** (CDCl₃, 300 MHz, -50 °C). Gray boxes denote [H₂C=CHPCy₃]OTf coproduct from initial reaction of **PII** with ethylene. (^) Denotes pentane or grease.

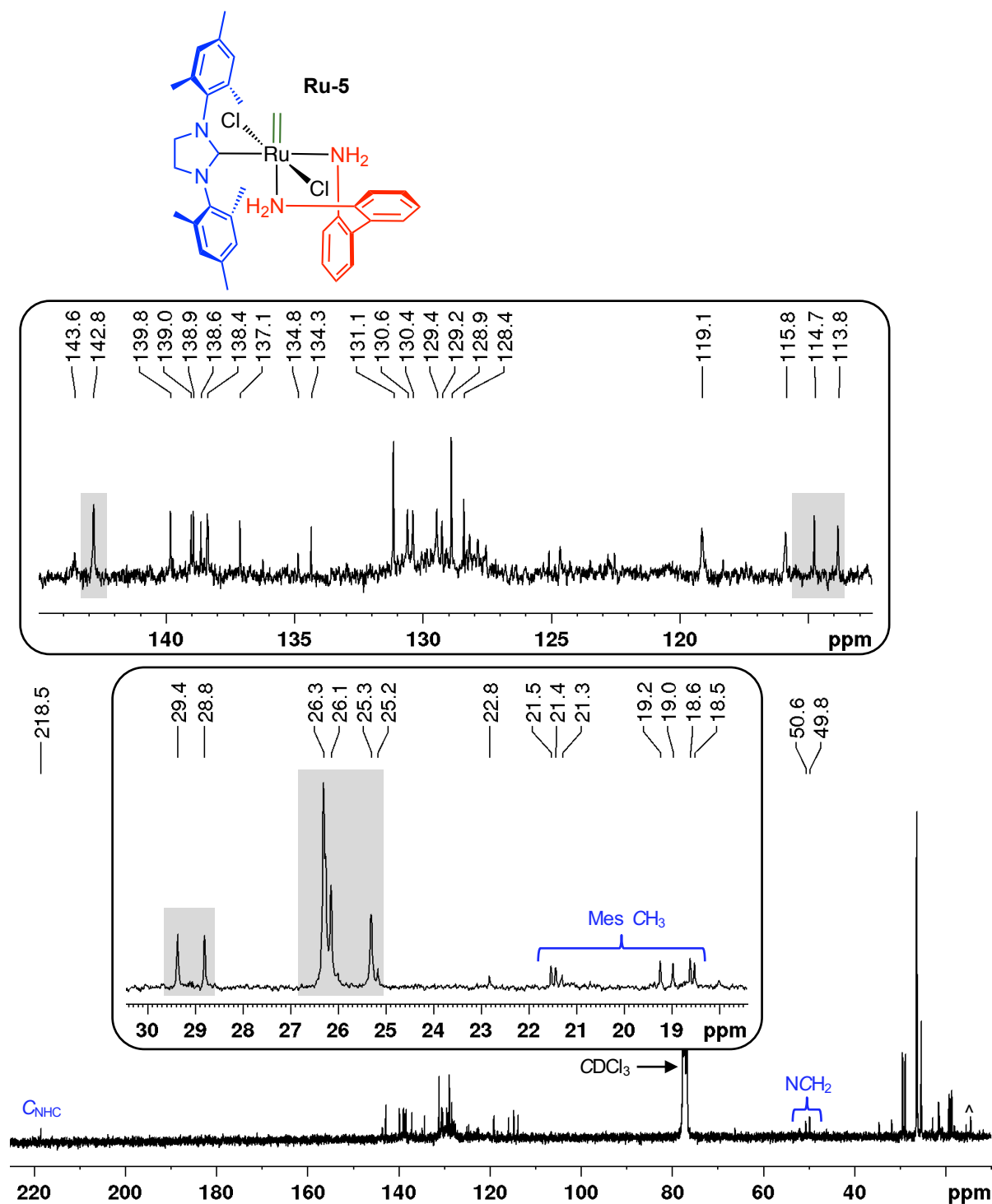


Figure A29. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of isolated **Ru-5** (CDCl_3 , 77.5 MHz, -50°C). Gray boxes denote [H₂C=CHPCy₃]OTf coproduct from the initial reaction of **P11** with ethylene. The [Ru]=CH₂ signal at δ_{C} 314.3 was located by ^1H - ^{13}C HMQC analysis. (^) Denotes trace pentane or grease.

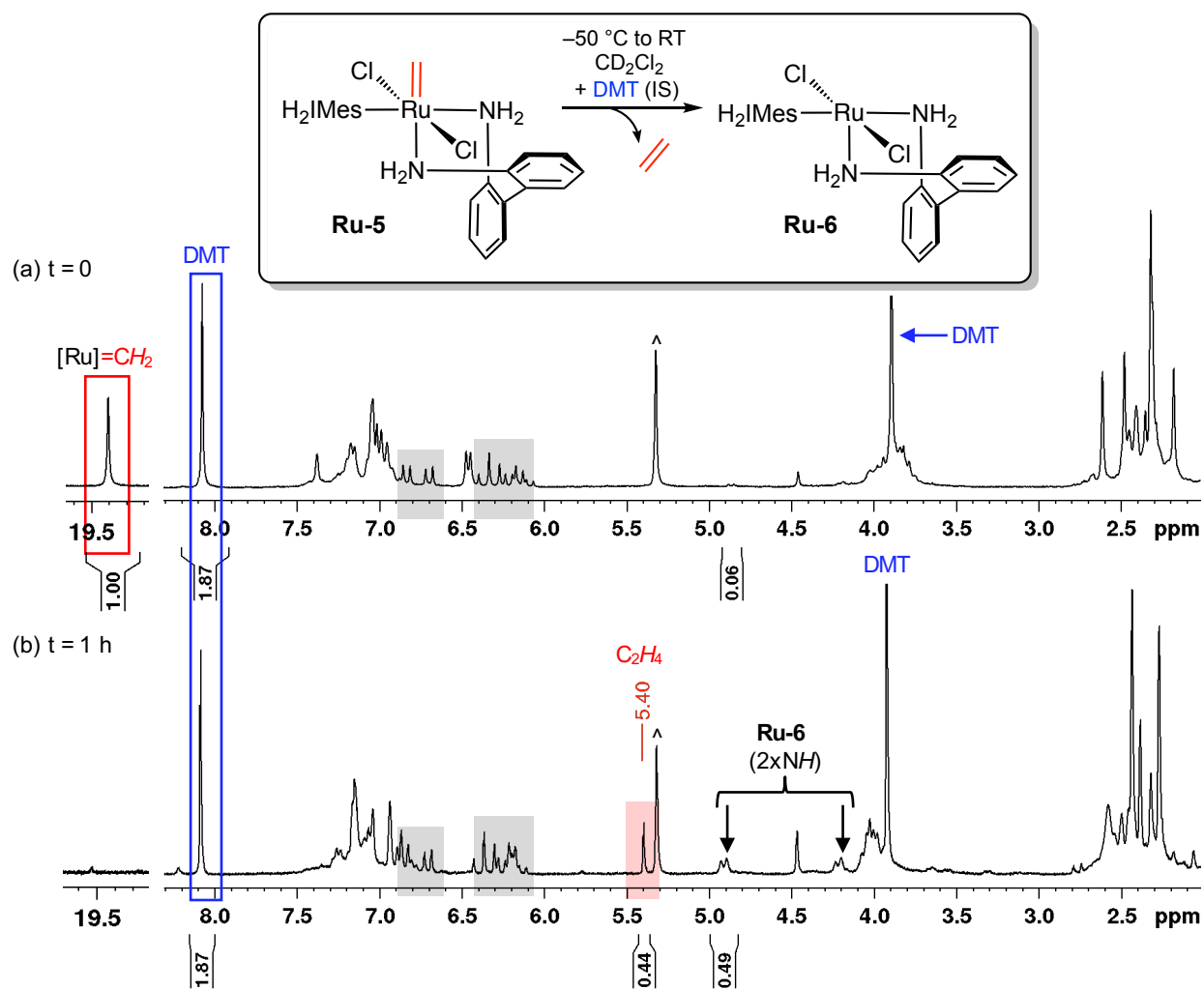


Figure A30. Representative ^1H NMR spectra showing decomposition of **Ru-5** to yield ethylene and **Ru-6** (CD_2Cl_2 , 300 MHz). (a) **Ru-5** and **DMT** at $-20\text{ }^\circ\text{C}$. (b) After 1 h at RT. For **Ru-6**, only the diagnostic NH_2 signals are indicated. Gray boxes denote the olefinic signals for the $[\text{H}_2\text{C}=\text{CHPCy}_3]\text{OTf}$ coproduct. ($\wedge$) Denotes residual CHDCl_2 .

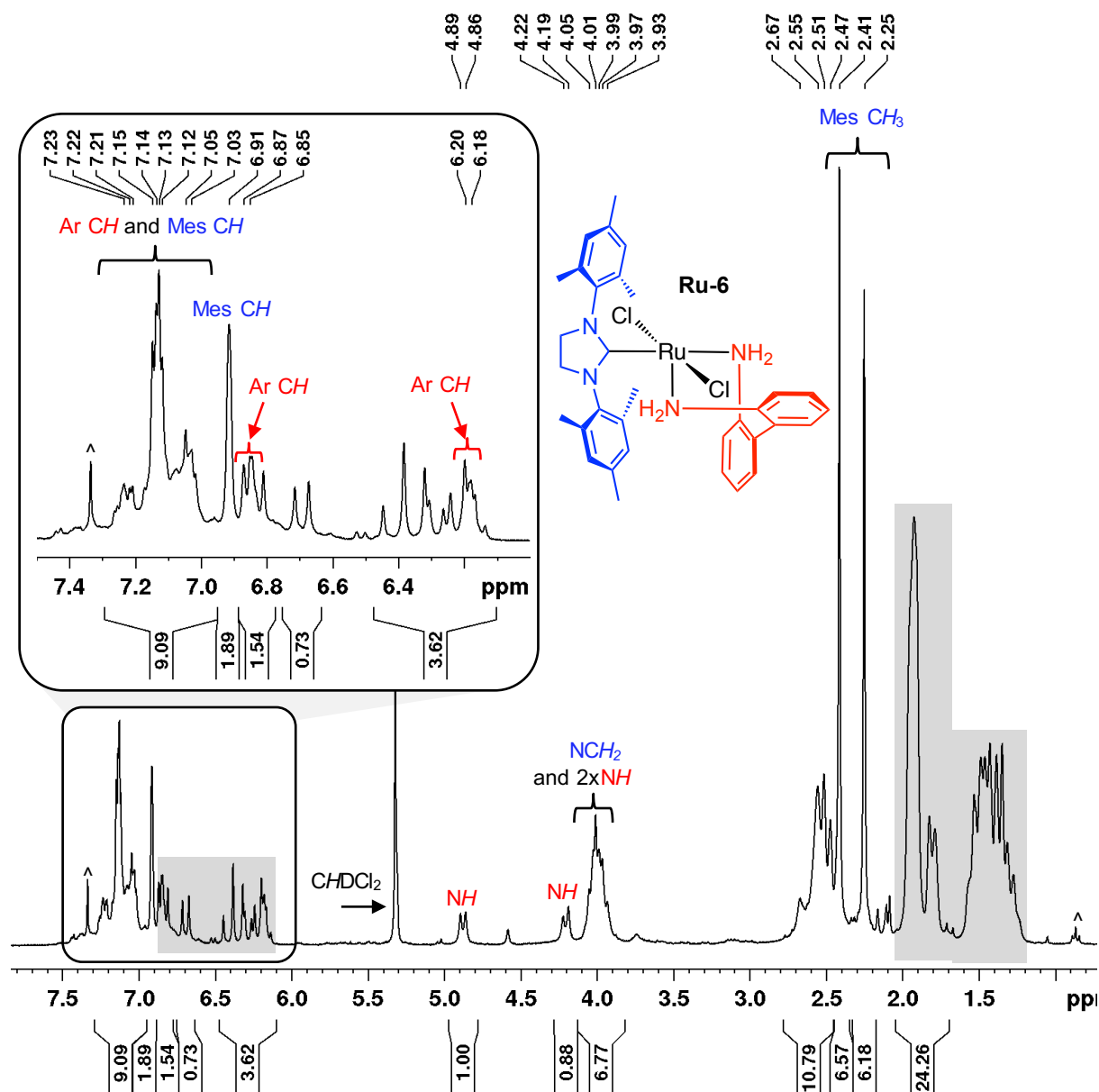


Figure A31. ¹H NMR spectrum of **Ru-6**, generated on decomposition of **Ru-5** (CD₂Cl₂, 300 MHz). Gray boxes denote [H₂C=CHPCy₃]OTf coproduct from initial ethenolysis of **PII**. (^) Denotes trace solvents (C₆H₆, hexanes).

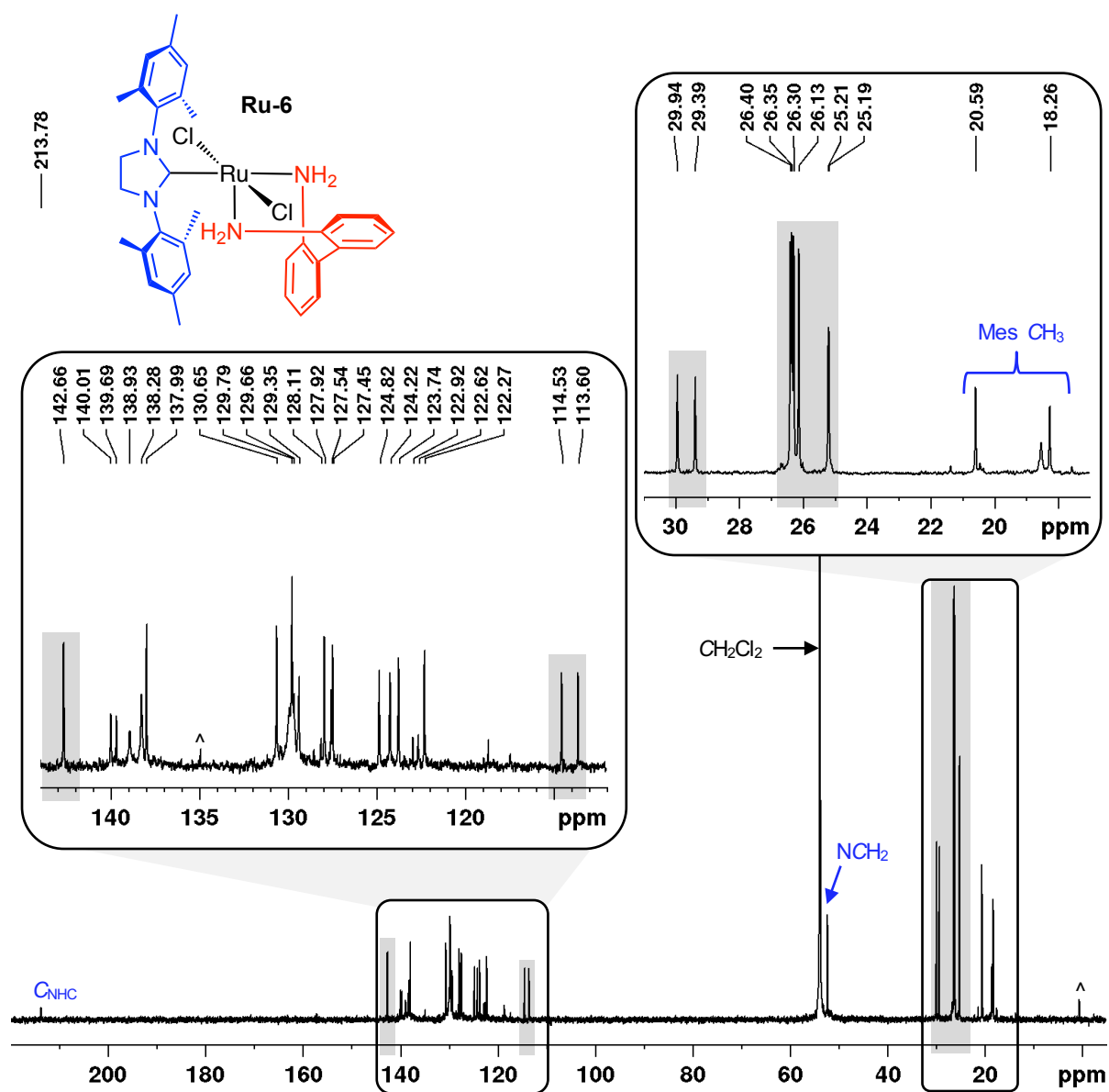


Figure A32. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of **Ru-6** (CH_2Cl_2 , 77.5 MHz). Gray boxes denote the $[\text{H}_2\text{C}=\text{CHPCy}_3]\text{OTf}$ coproduct from initial ethenolysis of **PII**. (^) Denotes residual benzene or trace silicone grease.

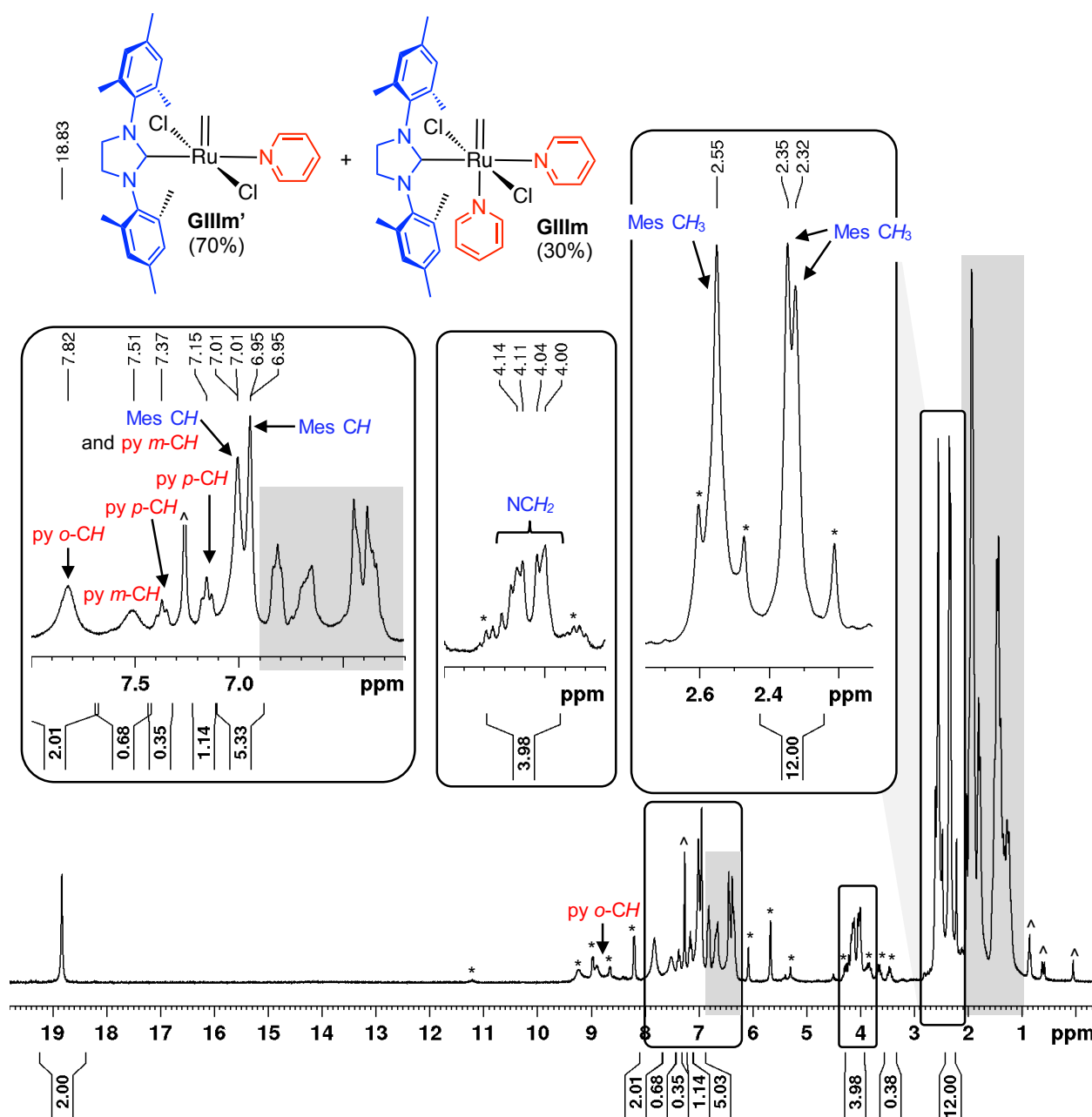


Figure A33. ^1H NMR spectrum of isolated $\text{RuCl}_2(\text{H}_2\text{IMes})(\text{py})_n(=\text{CH}_2)$ (**GIII'm'**: $n = 1$; **GIII'm**: $n = 2$; 70:30 mixture; CDCl₃, 300 MHz, 0 °C). Exchange averaging of the signals for **GIII'm/m'** is evident at this temperature, most notably in the observation of a single alkylidene peak: see text. Gray boxes denote $[\text{H}_2\text{C}=\text{CHPCy}_3]\text{OTf}$ coproduct from initial reaction of **PII** with ethylene. (*) Denotes unassigned Ru impurities; (^) denotes residual CHCl₃, and trace pentane or silicone grease.

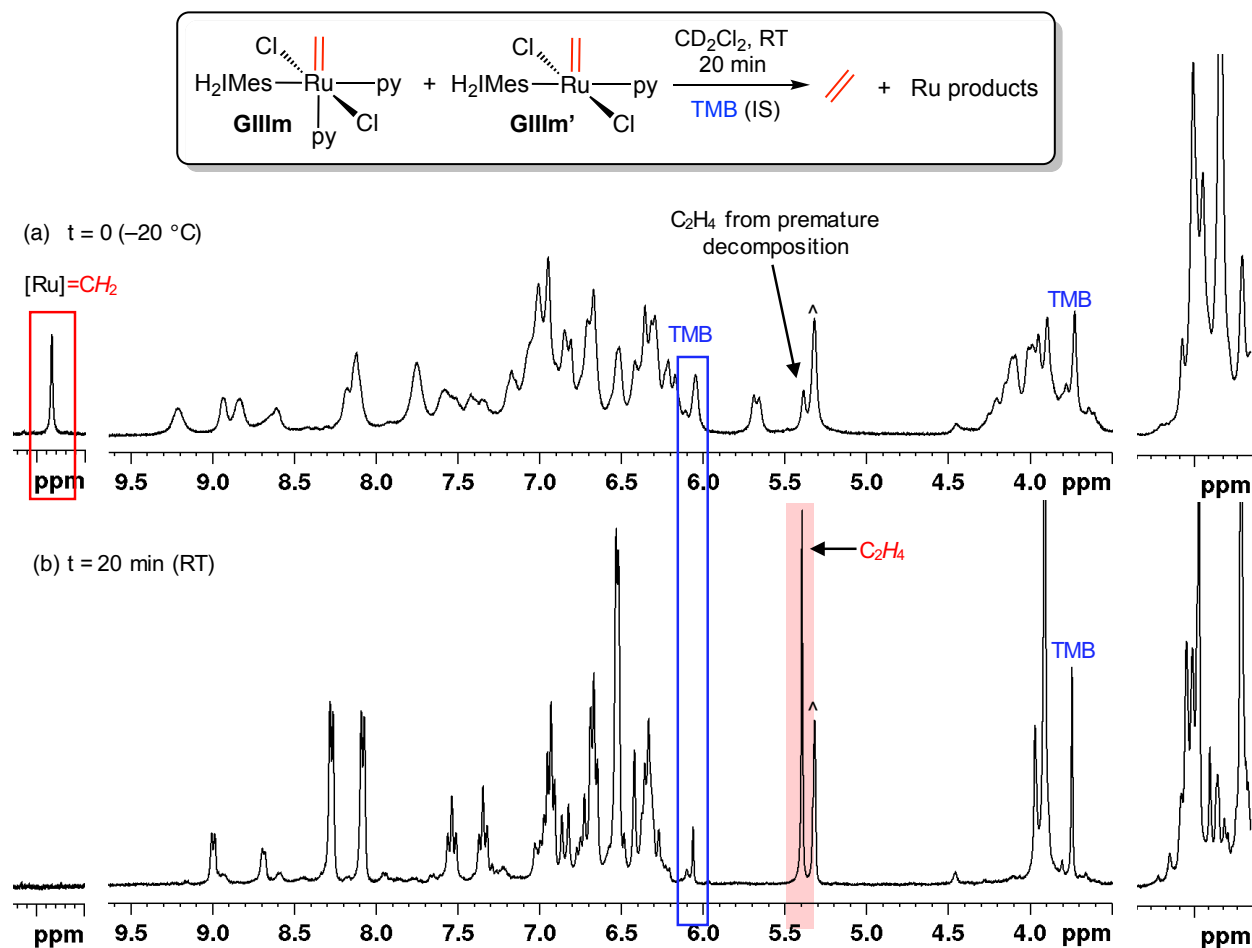


Figure A34. ^1H NMR spectra (CD_2Cl_2 , 300 MHz) showing evolution of ethylene on decomposition of **GIII m/m'**. (a) **GIII m/m'** and TMB at -20°C , before warming to RT. (b) After 20 min at RT. (^) Denotes residual CHDCl_2 .

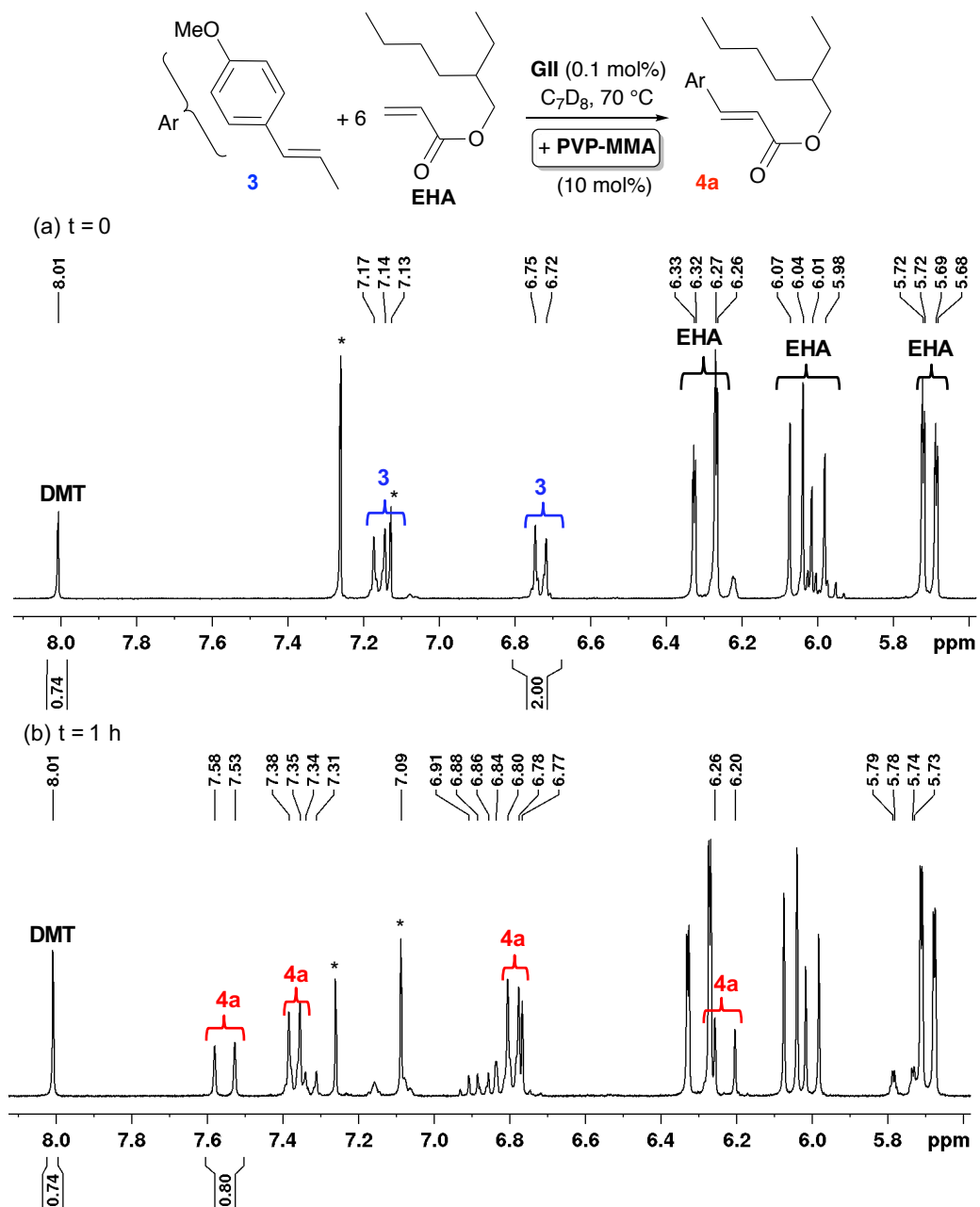


Figure A35. Exemplary ^1H NMR spectra showing quantification of 2-ethylhexyl cinnamate **4a**, relative to starting anethole **3** (300 MHz, CDCl_3). Spectra shown (a) at time zero, and (b) after 1 h. Quantification vs. DMT (internal standard); *denotes residual solvent (CDCl_3 , C_7D_8).

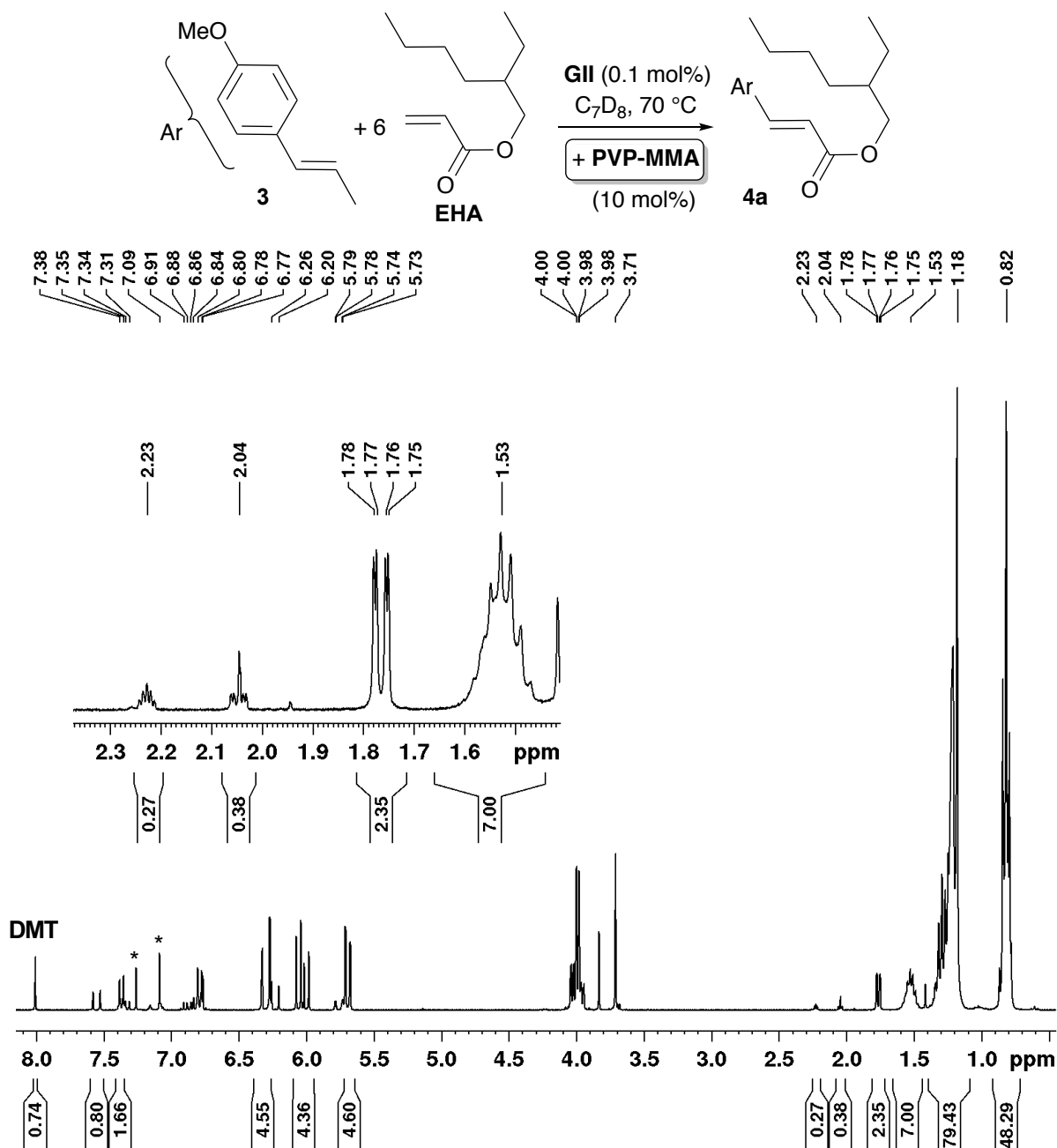


Figure A36. Exemplary 1H NMR spectrum (300 MHz, $CDCl_3$) showing the components present in cross-metathesis of anethole and EHA after 1 h. Integration shown relative to starting anethole **1** at t_0 , vs. DMT (internal standard). *denotes residual solvent ($CDCl_3$, C_7D_8).

B. Crystallographic Data

Crystal Structure of $[\text{RuCl}(\kappa^2\text{-H}_2\text{IMes-H})(\eta^2\text{-H}_2\text{C=CHCO}_2\text{Me})]_2$, Ru-1a

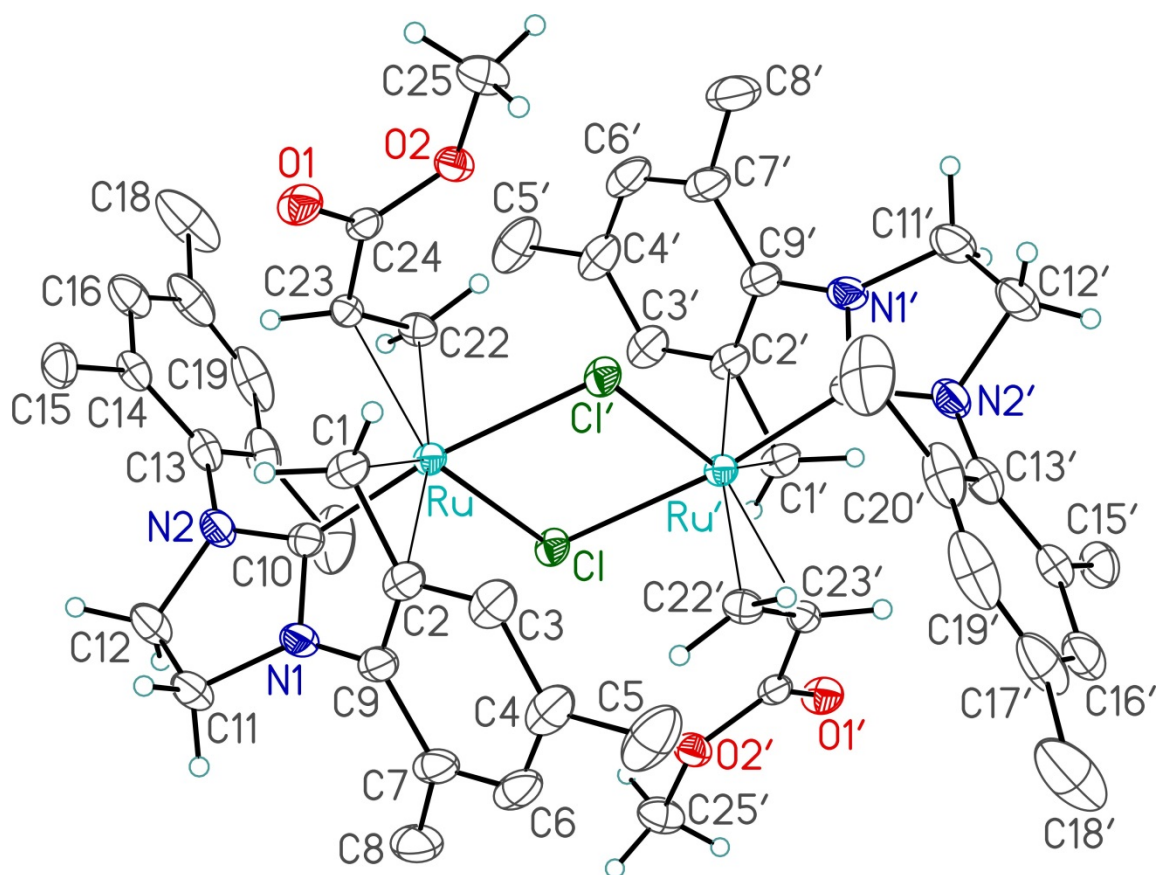


Figure A37. Perspective view of **Ru-1a** showing the atom labelling scheme. Non-hydrogen atoms are represented by Gaussian ellipsoids at the 30% probability level. Hydrogen atoms are shown with arbitrarily small thermal parameters, except for the aryl-ring and methyl hydrogens of the mesityl groups, which are not shown.

Table A1. Crystallographic Parameters for Ru-1a (CCDC number 1568999).

<i>A. Crystal Data</i>	
formula	C ₅₆ H ₆₈ Cl ₂ N ₄ O ₄ Ru ₂ (C ₅₀ H ₆₂ Cl ₂ N ₄ O ₄ Ru ₂ •C ₆ H ₆)
formula weight	1134.18
crystal dimensions (mm)	0.46 × 0.41 × 0.24
crystal system	triclinic
space group	<i>P</i> $\bar{1}$ (No. 2)
unit cell parameters ^a	
<i>a</i> (Å)	10.6206 (3)
<i>b</i> (Å)	11.5671 (3)
<i>c</i> (Å)	13.1397 (3)
α (deg)	98.4882 (7)
β (deg)	109.7667 (6)
γ (deg)	110.9004 (6)
<i>V</i> (Å ³)	1351.46 (6)
<i>Z</i>	1
ρ _{calcd} (g cm ⁻³)	1.394
μ (mm ⁻¹)	5.806
<i>B. Data Collection and Refinement Conditions</i>	
diffractometer	Bruker D8/APEX II CCD ^b
radiation (λ [Å])	Cu Kα (1.54178) (microfocus source)
temperature (°C)	−50 ^c
scan type	ω and φ scans (1.0°) (5 s exposures)
data collection 2θ limit (deg)	147.79
total data collected	9618 (−13 ≤ <i>h</i> ≤ 13, −14 ≤ <i>k</i> ≤ 14, −16 ≤ <i>l</i> ≤ 16)
independent reflections	5255 (<i>R</i> _{int} = 0.0199)
number of observed reflections (<i>NO</i>)	5185 [<i>F</i> _o ² ≥ 2σ(<i>F</i> _o ²)]
structure solution method	intrinsic phasing (<i>SHELXT-2014</i> ¹)
refinement method	full-matrix least-squares on <i>F</i> ² (<i>SHELXL-2014</i> ²)
absorption correction method	Gaussian integration (face-indexed)
range of transmission factors	0.5540–0.1924
data/restraints/parameters	5255 / 0 / 313
goodness-of-fit (<i>S</i>) ^d [all data]	1.068
final <i>R</i> indices ^e	
<i>R</i> ₁ [<i>F</i> _o ² ≥ 2σ(<i>F</i> _o ²)]	0.0250
<i>wR</i> ₂ [all data]	0.0669
largest difference peak and hole	0.377 and −1.274 e Å ⁻³

^aObtained from least-squares refinement of 9128 reflections with 13.04° < 2θ < 147.38°.

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

^cCrystals of this compound were observed to undergo a destructive phase change at lower temperatures.

^d*S* = [Σ*w*(*F*_o² − *F*_c²)/(*n* − *p*)]^{1/2} (*n* = number of data; *p* = number of parameters varied; *w* = [σ²(*F*_o²) + (0.0413*P*)² + 0.5115*P*]^{−1} where *P* = [Max(*F*_o², 0) + 2*F*_c²]/3).

^e*R*₁ = Σ||*F*_o| − |*F*_c||/Σ|*F*_o|; *wR*₂ = [Σ*w*(*F*_o² − *F*_c²)²/Σ*w*(*F*_o⁴)]^{1/2}.

Table A2. Selected Interatomic Distances (Å) for Ru-1a.

Atom1	Atom2	Distance	Atom1	Atom2	Distance
Ru	C1	2.4586(4)	C3	C4	1.380(3)
Ru	C1'	2.5210(5)	C4	C5	1.509(4)
Ru	C1	2.0896(18)	C4	C6	1.396(5)
Ru	C2	2.4471(18)	C6	C7	1.385(5)
Ru	C10	1.941(2)	C7	C8	1.498(4)
Ru	C22	2.0825(18)	C7	C9	1.412(3)
Ru	C23	2.1100(17)	C11	C12	1.510(4)
O1	C24	1.216(2)	C13	C14	1.391(3)
O2	C24	1.335(2)	C13	C20	1.403(3)
O2	C25	1.432(2)	C14	C15	1.506(3)
N1	C9	1.428(3)	C14	C16	1.387(3)
N1	C10	1.368(3)	C16	C17	1.386(4)
N1	C11	1.469(3)	C17	C18	1.507(4)
N2	C10	1.357(3)	C17	C19	1.375(5)
N2	C12	1.482(3)	C19	C20	1.400(5)
N2	C13	1.431(3)	C20	C21	1.502(5)
C1	C2	1.473(3)	C22	C23	1.426(3)
C2	C3	1.407(3)	C23	C24	1.479(2)
C2	C9	1.412(3)			

Table A3. Selected Interatomic Angles (°) for Ru-1a.^[a]

Atom1	Atom2	Atom 3	Angle	Atom1	Atom2	Atom3	Angle
Cl	Ru	Cl'	84.069(15)	C3	C4	C5	121.3(3)
Cl	Ru	C1	144.27(5)	C3	C4	C6	118.3(3)
Cl	Ru	C2	107.49(5)	C5	C4	C6	120.4(2)
Cl	Ru	C10	95.11(5)	C4	C6	C7	122.7(2)
Cl	Ru	C22	92.51(5)	C6	C7	C8	120.8(2)
Cl	Ru	C23	132.22(5)	C6	C7	C9	118.1(3)
Cl'	Ru	C1	92.81(6)	C8	C7	C9	121.0(3)
Cl'	Ru	C2	90.66(6)	N1	C9	C2	119.29(17)
Cl'	Ru	C10	170.38(6)	N1	C9	C7	120.1(2)
Cl'	Ru	C22	89.40(6)	C2	C9	C7	120.5(2)
Cl'	Ru	C23	95.05(5)	Ru	C10	N1	111.20(16)
C1	Ru	C2	36.83(7)	Ru	C10	N2	141.18(15)
C1	Ru	C10	82.24(8)	N1	C10	N2	107.09(18)
C1	Ru	C22	123.11(7)	N1	C11	C12	101.46(19)
C1	Ru	C23	83.50(7)	N2	C12	C11	103.2(2)
C2	Ru	C10	80.42(8)	N2	C13	C14	119.23(18)
C2	Ru	C22	159.90(7)	N2	C13	C20	119.9(2)
C2	Ru	C23	120.30(7)	C14	C13	C20	120.8(2)
C10	Ru	C22	100.22(8)	C13	C14	C15	121.2(2)
C10	Ru	C23	92.59(8)	C13	C14	C16	119.0(2)
C22	Ru	C23	39.76(7)	C15	C14	C16	119.8(2)
Ru	Cl	Ru'	95.931(15)	C14	C16	C17	121.9(3)
C24	O2	C25	116.75(17)	C16	C17	C18	120.9(4)
C9	N1	C10	116.02(18)	C16	C17	C19	117.7(3)
C9	N1	C11	126.93(19)	C18	C17	C19	121.5(3)
C10	N1	C11	112.7(2)	C17	C19	C20	123.1(2)
C10	N2	C12	111.6(2)	C13	C20	C19	117.2(3)
C10	N2	C13	124.92(17)	C13	C20	C21	121.0(3)
C12	N2	C13	121.3(2)	C19	C20	C21	121.8(3)
Ru	C1	C2	84.90(11)	Ru	C22	C23	71.16(10)
Ru	C2	C1	58.27(9)	Ru	C23	C22	69.08(10)
Ru	C2	C3	122.63(15)	Ru	C23	C24	117.09(12)
Ru	C2	C9	86.55(12)	C22	C23	C24	123.28(17)
C1	C2	C3	121.2(2)	O1	C24	O2	122.95(17)
C1	C2	C9	120.1(2)	O1	C24	C23	123.78(18)
C3	C2	C9	118.47(19)	O2	C24	C23	113.23(16)
C2	C3	C4	121.7(3)				

^a Primed atoms are related to unprimed ones via the crystallographic inversion center (0, 0, 0).

Crystal Structure of $[\text{RuCl}(\kappa^2\text{-H}_2\text{IMes-H})(\eta^2\text{-H}_2\text{C=CHPh})]_2$, Ru-1b

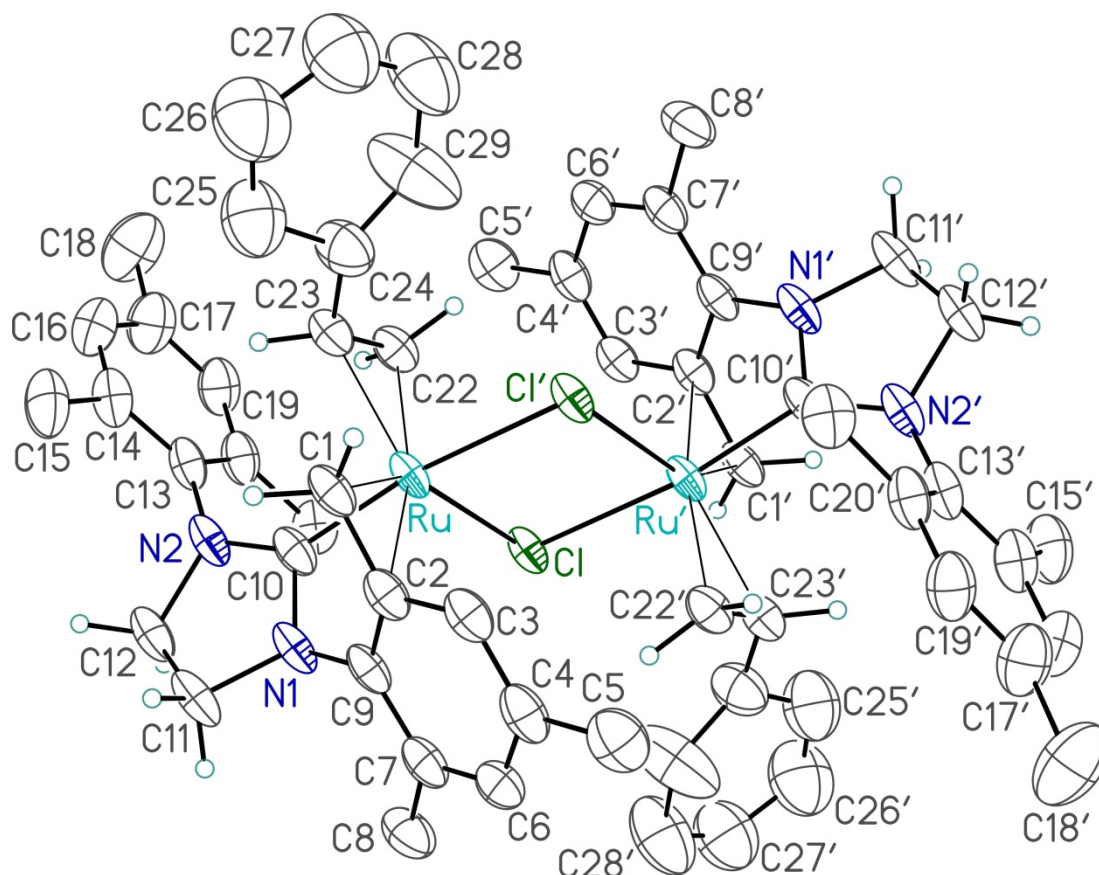


Figure A38. Perspective view of **Ru-1b** showing the atom labelling scheme. Non-hydrogen atoms are represented by Gaussian ellipsoids at the 30% probability level. Hydrogen atoms are shown with arbitrarily small thermal parameters, except for the aryl-ring and methyl hydrogens of the mesityl groups and the aromatic hydrogens of the styrene ligand, which are not shown. Primed atoms are related to unprimed ones via the crystallographic inversion center (1/4, 1/4, 0).

Table A4. Crystallographic Parameters for Ru-1b (CCDC number 1569000).

<i>A. Crystal Data</i>	
formula	C ₇₃ H ₈₁ Cl ₂ N ₄ Ru ₂ (C ₅₈ H ₆₆ Cl ₂ N ₄ Ru ₂ •2.5C ₆ H ₆)
formula weight	1287.45
crystal dimensions (mm)	0.34 × 0.20 × 0.09
crystal system	orthorhombic
space group	<i>Fddd</i> (No. 70)
unit cell parameters ^a	
<i>a</i> (Å)	11.4339 (3)
<i>b</i> (Å)	40.0510 (11)
<i>c</i> (Å)	54.661 (2)
<i>V</i> (Å ³)	1351.46 (6)
<i>Z</i>	16
ρ _{calcd} (g cm ⁻³)	1.367
μ (mm ⁻¹)	5.036
<i>B. Data Collection and Refinement Conditions</i>	
diffractometer	Bruker D8/APEX II CCD ^b
radiation (λ [Å])	Cu Kα (1.54178) (microfocus source)
temperature (°C)	–100 ^c
scan type	ω and φ scans (1.0°) (5 s exposures)
data collection 2θ limit (deg)	140.55
total data collected	39988 (–13 ≤ <i>h</i> ≤ 13, –48 ≤ <i>k</i> ≤ 48, –66 ≤ <i>l</i> ≤ 66)
independent reflections	5974 (<i>R</i> _{int} = 0.0454)
number of observed reflections (<i>NO</i>)	5033 [<i>F</i> _o ² ≥ 2σ(<i>F</i> _o ²)]
structure solution method	intrinsic phasing (<i>SHELXT-2014</i> ¹)
refinement method	full-matrix least-squares on <i>F</i> ² (<i>SHELXL-2014</i> ^{c,2})
absorption correction method	Gaussian integration (face-indexed)
range of transmission factors	0.9720–0.5719
data/restraints/parameters	5974 / 0 / 345
goodness-of-fit (<i>S</i>) ^d [all data]	1.190
final <i>R</i> indices ^e	
<i>R</i> ₁ [<i>F</i> _o ² ≥ 2σ(<i>F</i> _o ²)]	0.0652
<i>wR</i> ₂ [all data]	0.1898
largest difference peak and hole	0.860 and –0.674 e Å ⁻³

^aObtained from least-squares refinement of 9396 reflections with 5.48° < 2θ < 140.52°.

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

^cAttempts to refine peaks of residual electron density as disordered or partial-occupancy solvent benzene carbon atoms were unsuccessful. The data were corrected for disordered electron density through use of the SQUEEZE procedure as implemented in *PLATON* (Spek, A. L. *Acta Crystallogr.* **2015**, *C71*, 9–18. *PLATON* - a multipurpose crystallographic tool. Utrecht University, Utrecht, The Netherlands). A total solvent-accessible void volume of 3677 Å³ with a total electron count of 967 (consistent with 24 molecules of solvent benzene, or 1.5 molecules per formula unit of the diruthenium complex molecule) was found in the unit cell.

^d*S* = [Σ*w*(*F*_o² – *F*_c²)/(*n* – *p*)]^{1/2} (*n* = number of data; *p* = number of parameters varied; *w* = [σ²(*F*_o²) + (0.0657*P*)² + 403.8200*P*]⁻¹ where *P* = [Max(*F*_o², 0) + 2*F*_c²]/3).

^e*R*₁ = Σ||*F*_o| – |*F*_c||/Σ|*F*_o|; *wR*₂ = [Σ*w*(*F*_o² – *F*_c²)/Σ*w*(*F*_o⁴)]^{1/2}.

Table A5. Selected Interatomic Distances (Å) for Ru-1b.

Atom1	Atom2	Distance	Atom1	Atom2	Distance
Ru	Cl	2.4856(16)	C7	C8	1.513(10)
Ru	Cl'	2.5269(14)	C7	C9	1.403(10)
Ru	C1	2.083(6)	C11	C12	1.498(11)
Ru	C2	2.444(6)	C13	C14	1.393(11)
Ru	C10	1.942(7)	C13	C20	1.412(10)
Ru	C22	2.078(7)	C14	C15	1.531(12)
Ru	C23	2.137(8)	C14	C16	1.380(12)
N1	C9	1.425(8)	C16	C17	1.409(13)
N1	C10	1.370(9)	C17	C18	1.538(14)
N1	C11	1.464(8)	C17	C19	1.357(13)
N2	C10	1.340(9)	C19	C20	1.391(12)
N2	C12	1.485(8)	C20	C21	1.501(11)
N2	C13	1.430(10)	C22	C23	1.416(10)
C1	C2	1.470(10)	C23	C24	1.463(12)
C2	C3	1.397(9)	C24	C25	1.447(15)
C2	C9	1.410(9)	C24	C29	1.336(15)
C3	C4	1.378(10)	C25	C26	1.45(2)
C4	C5	1.509(11)	C26	C27	1.36(2)
C4	C6	1.394(11)	C27	C28	1.356(19)
C6	C7	1.366(10)	C28	C29	1.438(18)

Table A6. Selected Interatomic Angles (°) for Ru-1b.^[a]

Atom1	Atom2	Atom 3	Angle	Atom1	Atom2	Atom3	Angle
Cl	Ru	Cl'	83.35(5)	C4	C6	C7	122.2(8)
Cl	Ru	C1	145.2(2)	C6	C7	C8	120.9(8)
Cl	Ru	C2	108.46(17)	C6	C7	C9	118.6(7)
Cl	Ru	C10	95.6(2)	C8	C7	C9	120.4(7)
Cl	Ru	C22	92.6(2)	N1	C9	C2	119.9(7)
Cl	Ru	C23	131.8(2)	N1	C9	C7	119.6(6)
Cl'	Ru	C1	93.70(19)	C2	C9	C7	120.5(6)
Cl'	Ru	C2	91.00(16)	Ru	C10	N1	110.2(5)
Cl'	Ru	C10	170.3(2)	Ru	C10	N2	142.2(6)
Cl'	Ru	C22	89.2(2)	N1	C10	N2	106.8(6)
Cl'	Ru	C23	93.75(19)	N1	C11	C12	101.6(6)
C1	Ru	C2	36.8(2)	N2	C12	C11	102.4(5)
C1	Ru	C10	81.7(3)	N2	C13	C14	120.2(7)
C1	Ru	C22	122.0(3)	N2	C13	C20	119.4(7)
C1	Ru	C23	82.9(3)	C14	C13	C20	120.4(8)
C2	Ru	C10	80.2(3)	C13	C14	C15	120.1(8)
C2	Ru	C22	158.8(3)	C13	C14	C16	120.1(8)
C2	Ru	C23	119.7(3)	C15	C14	C16	119.8(9)
C10	Ru	C22	100.4(3)	C14	C16	C17	119.9(9)
C10	Ru	C23	94.1(3)	C16	C17	C18	119.1(10)
C22	Ru	C23	39.2(3)	C16	C17	C19	119.2(9)
Ru	Cl	Ru'	96.65(5)	C18	C17	C19	121.7(10)
C9	N1	C10	115.3(5)	C17	C19	C20	122.9(8)
C9	N1	C11	126.1(5)	C13	C20	C19	117.4(8)
C10	N1	C11	112.3(6)	C13	C20	C21	120.9(7)
C10	N2	C12	111.9(6)	C19	C20	C21	121.7(7)
C10	N2	C13	126.3(5)	Ru	C22	C23	72.6(4)
C12	N2	C13	119.3(6)	Ru	C23	C22	68.1(4)
Ru	C1	C2	85.1(4)	Ru	C23	C24	122.7(6)
Ru	C2	C1	58.1(3)	C22	C23	C24	123.7(7)
Ru	C2	C3	122.7(4)	C23	C24	C25	117.5(10)
Ru	C2	C9	85.1(4)	C23	C24	C29	126.7(10)
C1	C2	C3	120.5(6)	C25	C24	C29	112.1(12)
C1	C2	C9	120.4(6)	C24	C25	C26	122.1(14)
C3	C2	C9	118.7(7)	C25	C26	C27	117.5(17)
C2	C3	C4	120.7(7)	C26	C27	C28	123.3(17)
C3	C4	C5	120.3(7)	C27	C28	C29	115.7(14)
C3	C4	C6	119.2(7)	C24	C29	C28	127.8(14)
C5	C4	C6	120.4(8)				

^a Primed atoms are related to unprimed ones via the crystallographic inversion center (0, 0, 0).

C. MALDI-TOF Mass Spectra

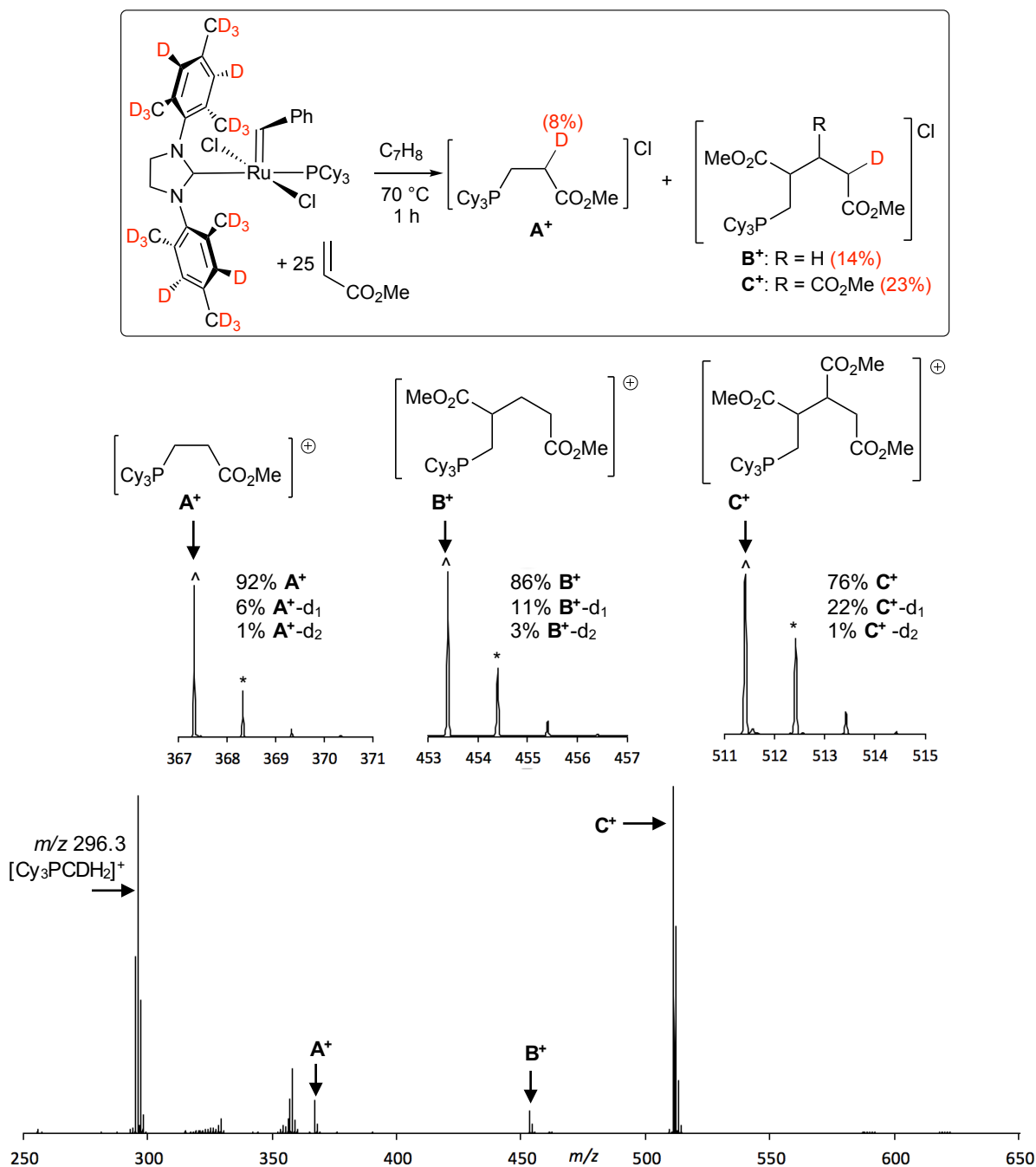


Figure A39. MALDI-TOF mass spectrum (sulfur matrix) showing minimal uptake of ²H into phosphonium salts [**A**]⁺–[**C**]⁺ on treatment of **GII-d₂₂** with methyl acrylate. Numbers in brackets refer to the extent of ²H incorporation at the designated positions. The symbols (^) and (*) denote peaks assigned to deprotonation at non-labelled (MCB) or labelled (*o*-Mes) sites, respectively. The relative proportions of key isotopologues (% values) are corrected for the natural ¹³C isotopic abundances for each species.

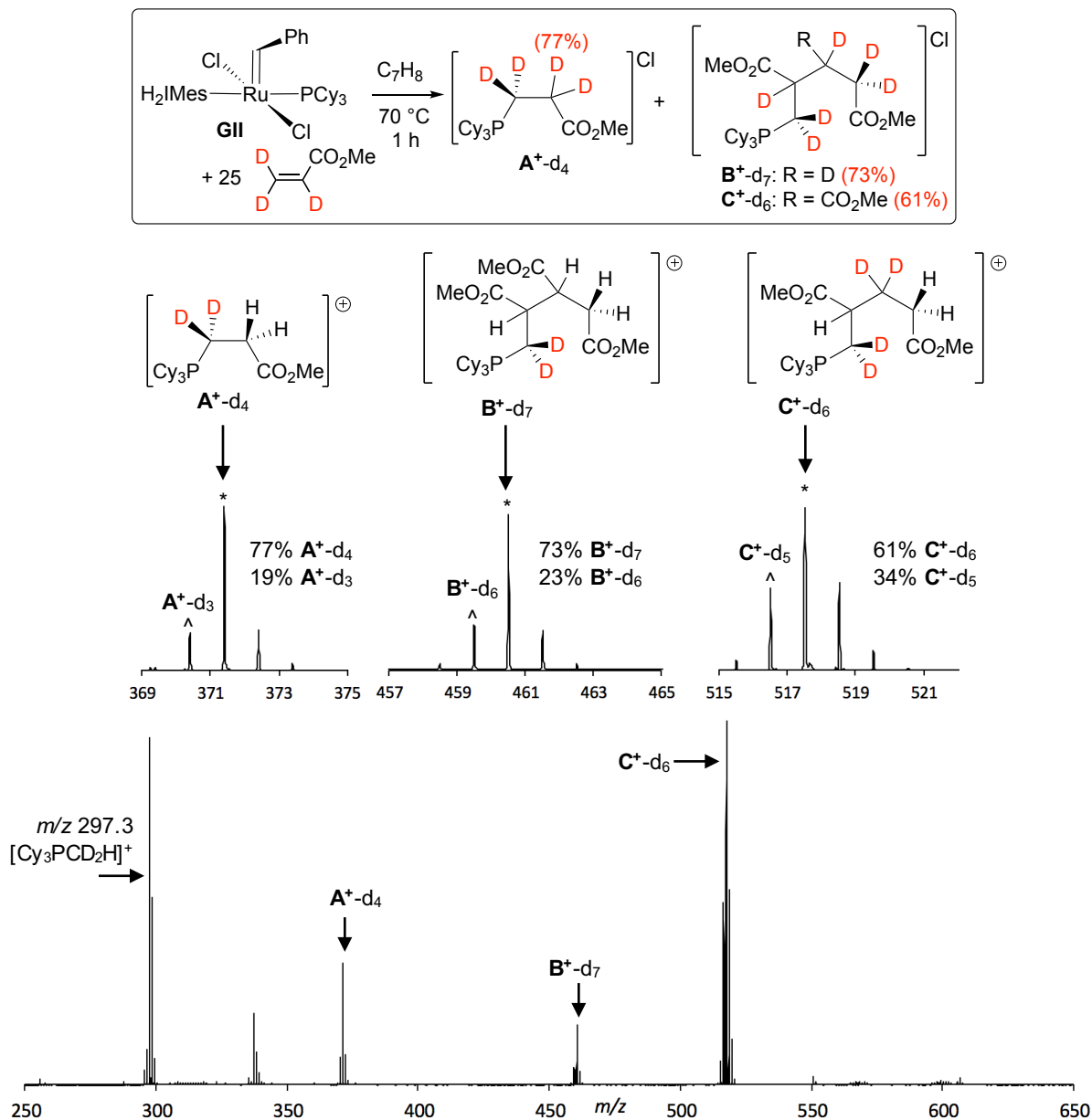


Figure A40. MALDI-TOF mass spectrum (sulfur matrix) showing extensive uptake of 2H into phosphonium salts **[A]Cl**–**[C]Cl** on treatment of **GII** with methyl acrylate- d_3 . The symbols (*) and (^) denote peaks assigned to deprotonation at labelled (MCB) or non-labelled (*o*-Mes) sites, respectively. The relative proportions of key isotopologues (% values) are corrected for the natural ^{13}C isotopic abundances for each species.

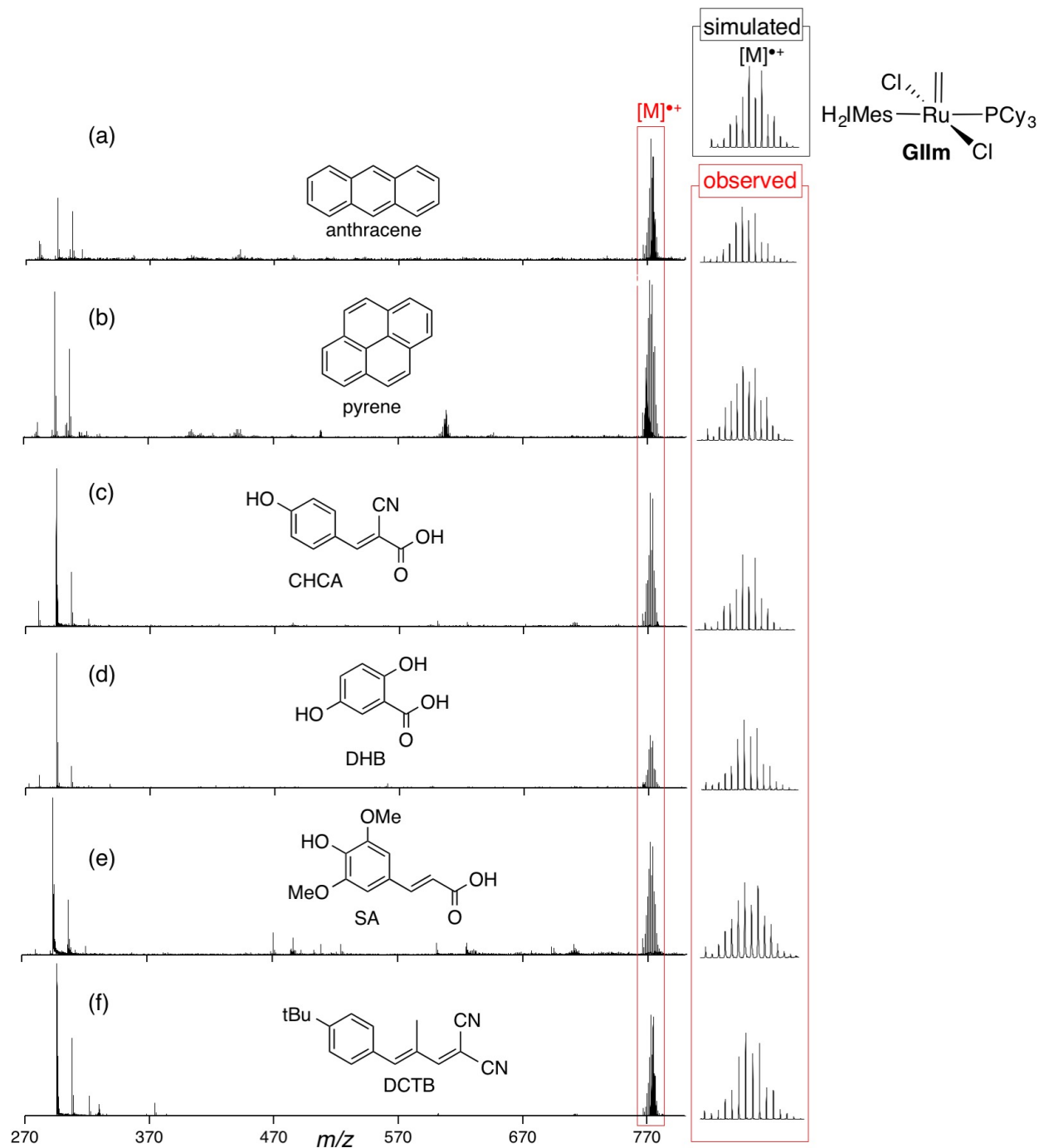


Figure A41. Impact of matrix ϵ_M on fragmentation, assessed in analysis of non-labile **GIIm**. MALDI mass spectra of **GIIm** with (a) anthracene; (b) pyrene; (c) CHCA; (d) DHB; (e) SA; (f) DCTB. These spectra supplement the two extremes shown in Figure 6.4.

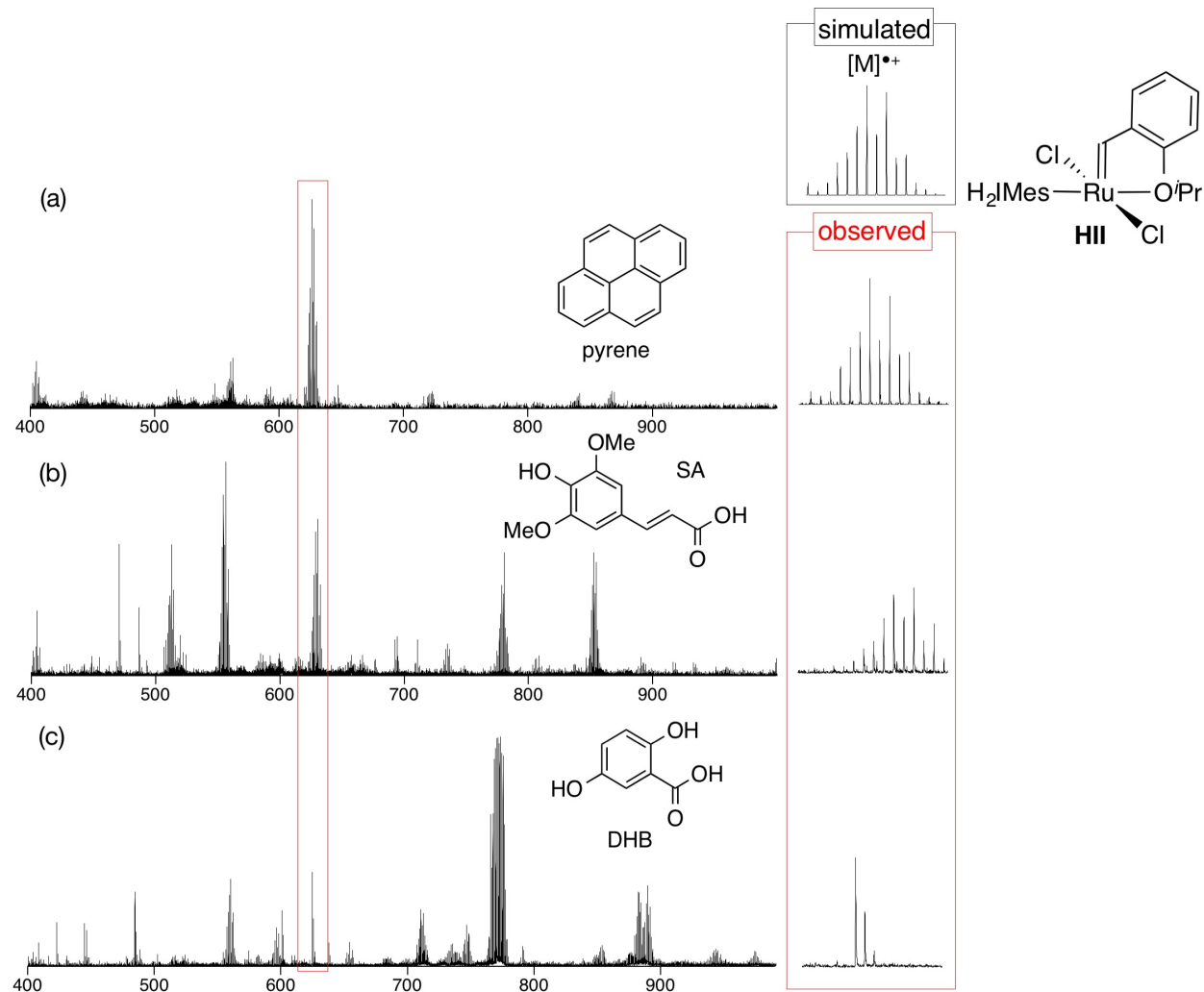


Figure A42. MALDI mass spectra showing gas-phase decomposition of **HII** by functionalized matrices, as compared to the benchmark pyrene. (a) Pyrene; (b) SA; (c) DHB. These spectra supplement those shown in Figure 6.5, which focus on the more widely-used matrices.

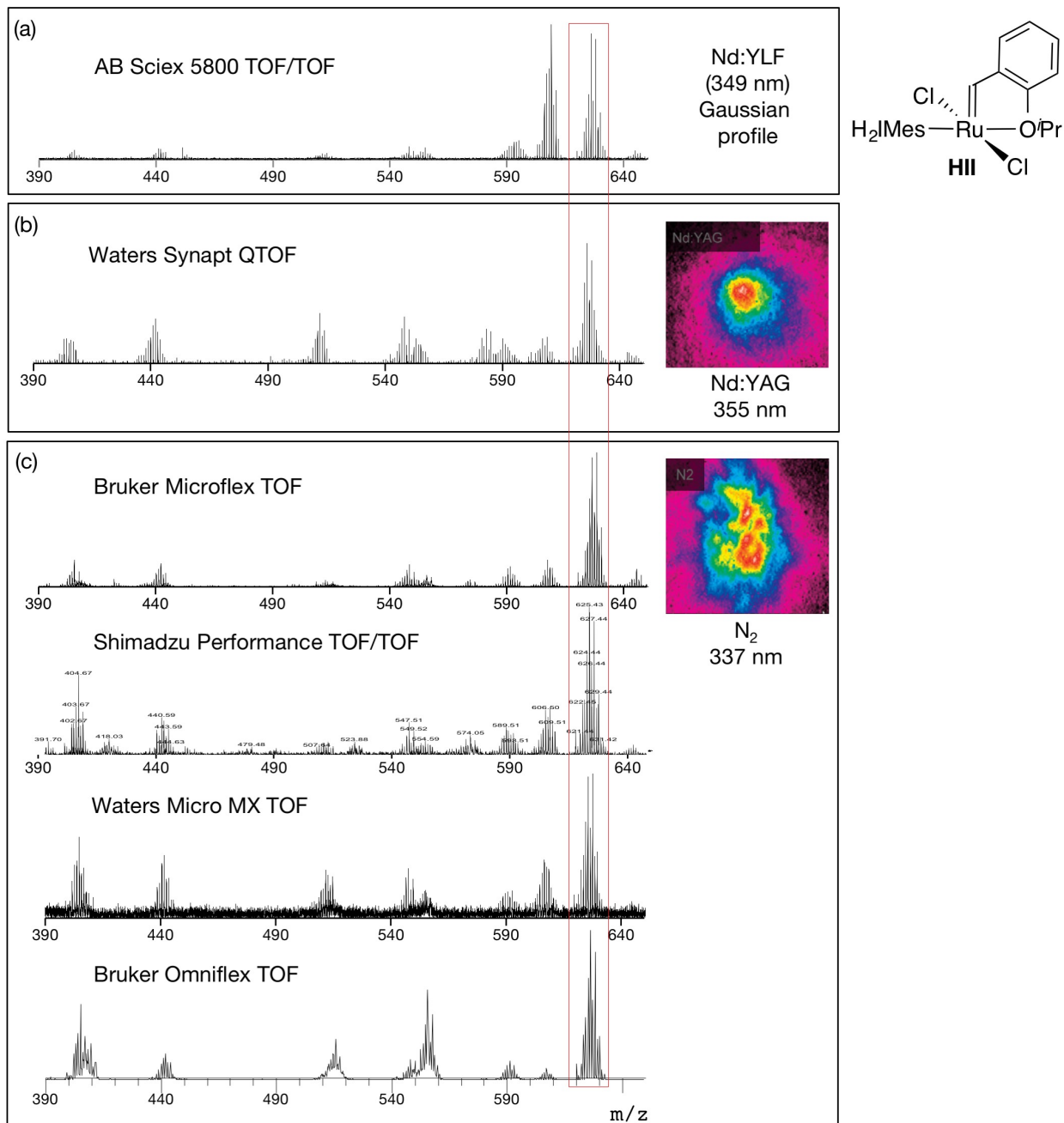


Figure A43. Impact of laser beam profile on fragmentation of **HII**. Spectra recorded using (a) a Nd:YLF laser; (b) a Nd:YAG laser; and (c) a N₂ laser. These examples supplement the spectra shown in Figure 6.9 (which were drawn from instruments matched as closely as possible, to facilitate comparison).

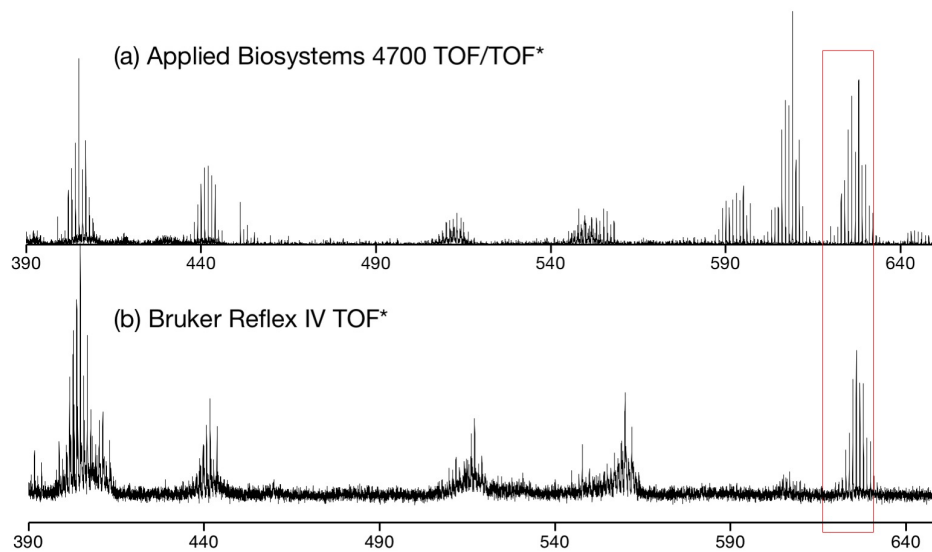


Figure A44. Negative impact of laser age on performance. MALDI mass spectra recorded for **III** on (a) Nd:YAG (Applied Biosystems 4700) and (b) N₂ (Bruker Reflex II) lasers that were nearing the end of their lifetime, necessitating use of higher applied laser energies.

D. GC Traces

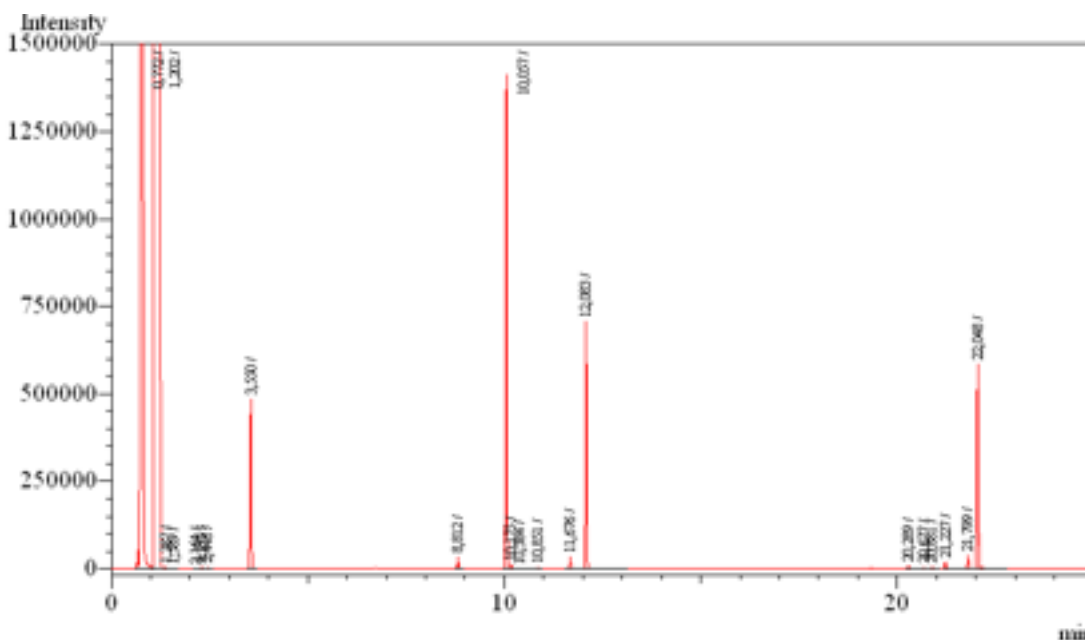


Figure A45. Representative GC trace for the cross-metathesis reaction between anethole and EHA (Shimadzu GC2010 Plus GC).

Table A7. Compounds analyzed by GC-FID on the Shimadzu GC2010 Plus GC.^a

Time (min)	Product	Identification ^b
3.5	<i>p</i> -xylene (internal standard)	Co-injection
8.8	4-vinylanisole (4)	¹ H NMR
10.0	2-ethylhexyl acrylate	Co-injection
10.3	<i>cis</i> -anethole	-
10.8	<i>trans</i> -anethole (1)	Co-injection
11.6	<i>cis</i> -2-ethylhexyl crotonoate	-
12.0	<i>trans</i> -2-ethylhexyl crotonoate	-
20.2	di(2-ethylhexyl) maleate	-
20.6	<i>cis</i> -4,4'-dimethoxystilbene (5)	-
20.8	<i>cis</i> -2-ethylhexyl methoxycinnamate (2a)	-
21.2	di(2-ethylhexyl) fumarate	-
21.7	<i>trans</i> -4,4'-dimethoxystilbene (5)	¹ H NMR
22.0	<i>trans</i> -2-ethylhexyl methoxycinnamate (2a)	¹ H NMR

^a For the corresponding GC trace, refer to Figure A45. Time = retention time. ^b All peaks were assigned by GC/MS, with additional characterization methods as indicated: co-injection of an authentic sample, or isolation and subsequent identification by ¹H NMR analysis.

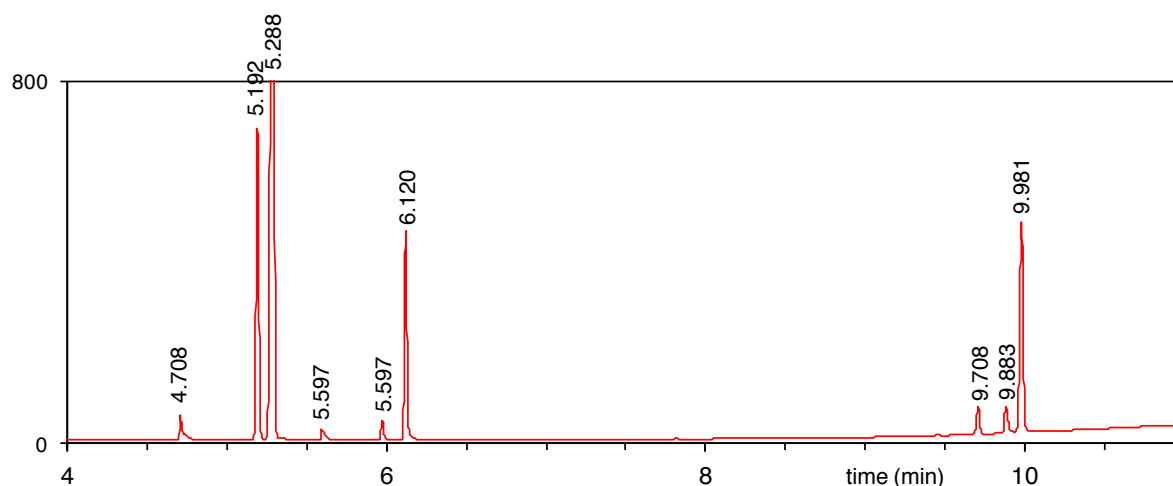


Figure A46. Representative GC trace for the cross-metathesis reaction between anethole and EHA (Agilent 7890A Series GC).

Table A8. Compounds analyzed by GC-FID on the Agilent 7890A Series GC.^a

Time (min)	Product	Identification ^b
4.7	4-vinylanisole (4)	Co-injection
5.2	dodecane (internal standard)	Co-injection
5.3	2-ethylhexyl acrylate	Co-injection
5.6	<i>trans</i> -anethole (1)	Co-injection
6.0	<i>cis</i> -2-ethylhexyl crotonate	-
6.1	<i>trans</i> -2-ethylhexyl crotonate	-
9.7	di(2-ethylhexyl) fumarate	-
9.9	<i>trans</i> -4,4'-dimethoxystilbene (5)	¹ H NMR
10.0	<i>trans</i> -2-ethylhexyl methoxycinnamate (2a)	¹ H NMR

^a For the corresponding GC trace, refer to Figure A46. Time = retention time. ^b All peaks were identified using GC/MS, and the additional characterization methods as indicated: co-injection of an authentic sample, or isolation and subsequent identification by ¹H NMR analysis.

E. NMR Tubes Employed to Exclude Oxygen and Moisture

See section 4.5 (page 99)

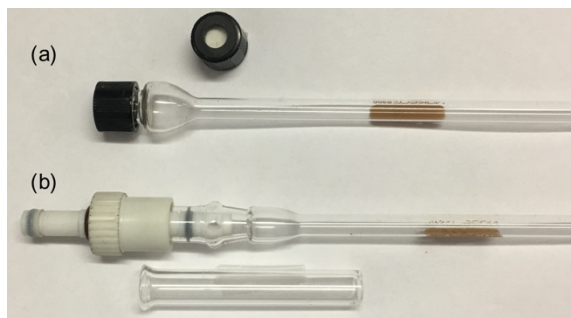


Figure A47. NMR tubes employed to exclude oxygen and moisture: (a) Screw-capped NMR tubes (Norrell, #S-5-300-SC). (b) J. Young NMR tubes (Norrell, #S-5-300-VT; 3.40 or 4.20 mm inner diameter; 2.15 or 2.80 mL capacity). Also shown in (b) is the glass adapter provided to connect the tube to a vacuum line.

F. Pressure Calculations for Sealed-Tube Experiments

Calculated below is the minimum headspace volume required to accommodate pressure buildup on thermal expansion of the solvent, as well as evolution of gaseous byproducts, during bimolecular coupling of **GIIIe** or **Ru-5** in sealed NMR tubes filled to the maximum safe volume.

(a) *Bimolecular coupling of ethylidene **GIIIe***. Butenes are highly soluble in aromatic solvents, including benzene. The mole fraction solubility (x_g) of 1-butene in benzene at 1 atm and 298 K is 0.245, which translates to a solution concentration of >1 M.³ As the solubility of butenes scales with their boiling point,³ and 2-butenes are slightly higher-boiling than 1-butene, minimal pressure buildup is anticipated on generating <0.01 M of 2-butene in a filled tube.

To estimate the pressure buildup associated with thermal expansion of benzene, the volume increase on warming from $+23$ °C to 60 °C was calculated from the reported temperature-dependent density of benzene (Table A9, Figure A48).⁴ Based on these data, a thermal expansion of $0.8758/0.8370 = 104.5\%$ (i.e. a 4.5% increase) is anticipated. Tripling to 15% as a safety margin translates into a headspace of ≥ 0.32 mL for a J. Young tube of total volume 2.15 mL (or ≥ 0.42 mL if the total volume is 2.80 mL).

Table A9. Temperature-dependent density of C_6H_6 between $+23$ and $+63$ °C.⁴

Temperature (°C)	Density (g/mL)
23	0.8758
29	0.8700
34	0.8641
40	0.8581
46	0.8581
52	0.8460
57	0.8398
60	0.8370 (interpolated)
63	0.8336

^a Values extrapolated from the reported data between -12.2 and $+23$ °C.

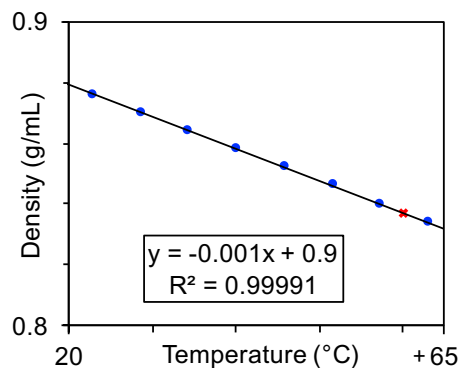


Figure A48. Temperature-dependent density of benzene plotted between +23 and +65 °C.⁴ • literature values; x interpolated.

The pressure buildup in the headspace on thermal expansion of benzene and warming of the tube is calculated using the ideal gas law:

$$V_i = 0.43 \text{ mL} \quad T_i = 296 \text{ K} \quad P_i V_i = nRT_i$$

$$V_f = 0.35 \text{ mL} \quad T_f = 336 \text{ K} \quad P_f V_f = nRT_f$$

$$\frac{P_i V_i}{P_f V_f} = \frac{T_i}{T_f} \quad \text{or} \quad P_f = \frac{P_i V_i T_f}{V_f T_i}$$

$$P_f = \frac{(1 \text{ atm})(0.32 \text{ mL})(336 \text{ K})}{(296 \text{ K})(0.24 \text{ mL})} = 1.5 \text{ atm}$$

The anticipated pressure buildup on warming to 60 °C is 1.5 atm, well within the 5 atm pressure rating of the J. Young NMR tube.

(b) *Bimolecular coupling of methyldiene Ru-5*. These calculations were conducted as for the ethylidene **IIIe** above, but with CD₂Cl₂ as solvent, predicated on temperature range of –20 to +23 °C.

To limit pressure buildup associated with ethylene evolution, filled-tube experiments were carried out at concentrations ≤20 mM Ru, such that the maximum anticipated ethylene concentration (10 mM) remains well below the solubility limit of ethylene in CD₂Cl₂ under the experimental conditions chosen. These are based on a solubility of ≥32 mM under 1 atm ethylene at RT.⁵

To assess the pressure buildup due to thermal expansion of CD₂Cl₂, the volume increase on warming from –20 °C to +23 °C was calculated from the reported temperature-dependent density

of CH₂Cl₂ (Table A10; Figure A49).⁴ From this, a thermal expansion of (1.392)/(1.318)*100% = 105.6% (i.e. a 5.6% increase) is expected. Tripling to ca. 20% as a safety margin translates into a headspace of ≥0.56 mL for a J. Young NMR tube of total volume 2.80 mL (≥0.43 mL, if the total volume is 2.15 mL).

Table A10. Temperature-dependent density of CH₂Cl₂ between –20 and +23 °C.⁴

Temperature (°C)	Density (g/mL)
–20 ^a	1.392 ^a
–12.2	1.378
–10	1.375
0	1.358
+10	1.341
+20	1.324
+23	1.318

^a Values extrapolated from the reported data between –12.2 and +23 °C.

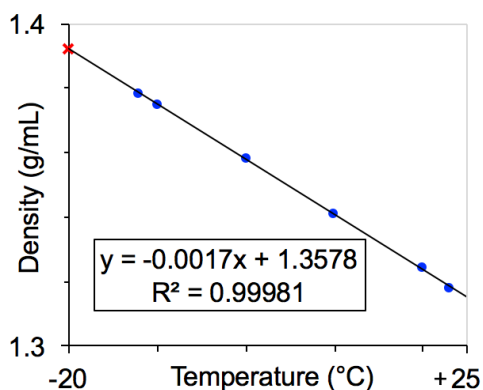


Figure A49. Temperature-dependent density of CH₂Cl₂ plotted between –20 and +23 °C.⁴ • literature values; x extrapolated.

Finally, the pressure buildup in the headspace from thermal expansion of CD₂Cl₂ on warming from –20 °C to RT was calculated for a 2.80 mL J. Young NMR tube filled with 2.25 mL CD₂Cl₂, as an exemplar. Using the ideal gas law as before, and assuming a 5.6% increase in volume on warming:

$$V_i = 0.55 \text{ mL} \quad T_i = 253 \text{ K} \quad P_i V_i = nRT_i$$

$$V_f = 0.42 \text{ mL} \quad T_f = 296 \text{ K} \quad P_f V_f = nRT_f$$

$$P_f = \frac{(1 \text{ atm})(0.55 \text{ mL})(296 \text{ K})}{(253 \text{ K})(0.42 \text{ mL})} = 1.5 \text{ atm}$$

The calculated pressure buildup is ca. 1.5 atm, well within the 5 atm pressure rating of the J. Young NMR tube.

G. Prices of Metathesis Catalysts

Chart A1. Dominant Ru-NHC catalysts in current academic use.

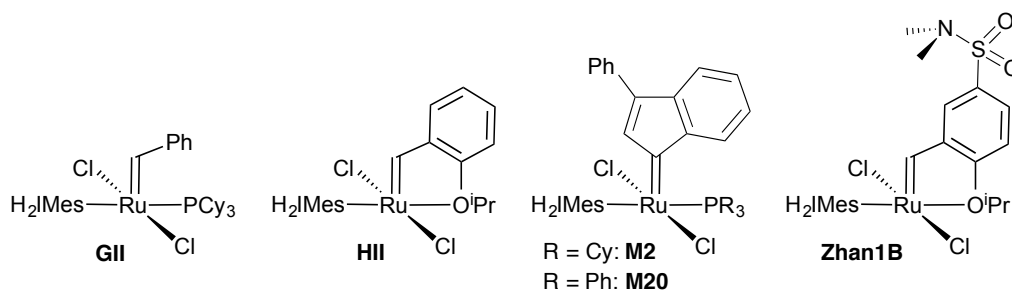


Table A11. Dominant metathesis catalysts in current academic use, sorted by price.

Catalyst	Supplier	Catalogue number - unit size	Price (USD) ^a	Price per gram
GI	Sigma	569747-100MG	\$67	\$670
		569747-500MG	\$207	\$414
		569747-2G	\$585	\$293
		569747-10G	\$1,640	\$164
HI	Sigma	569755-100MG	\$70	\$700
		569755-500MG	\$284	\$568
		569755-2G	\$791	\$396
		569755-25G	\$6,680	\$268
M2	Sigma	775258-100MG	\$67	\$670
		775258-500MG	\$263	\$526
	Strem	44-7777-100MG	\$57	\$570
		44-7777-500MG	\$229	\$458
M20	Sigma	775266-100MG	\$51	\$510
Zhan 1B	Strem	44-0082-100MG	\$39	\$390
		44-0082-500MG	\$156	\$312
		44-0082-2G	\$498	\$249

^a Prices rounded to nearest US dollar, as of Mar 17, 2017.

H. Calculated H₂O Concentrations in Water-Saturated Toluene

Solubility of H₂O in toluene:⁶ 0.033 wt%

0.033 g H₂O / 100 g toluene

= 1.83 mmol H₂O / 115.3 mL toluene

= 15.9 mM H₂O

GII 0.1 mol% 0.72 nmol / 3.6 mL = 0.20 mM

15.9 mM H₂O / 0.20 mM **GII** = 79 equiv H₂O vs. **GII**

I. References

- (1) Sheldrick, G. M. *Acta Crystallogr. A*, **2015**, 71, 3-8.
- (2) Sheldrick, G. M. *Acta Crystallogr. C*, **2015**, 71, 3-8.
- (3) Miyano, Y.; Nakanishi, K. *J. Chem. Thermodyn.* **2003**, 35, 519–528.
- (4) For temperature-dependent solvent densities, see: (a) Benzene. Dortmund Data Bank: Saturated Liquid Density for Benzene. <http://ddbonline.ddbst.de/DIPPR105DensityCalculation/DIPPR105CalculationCGI.exe?component=Benzene> (accessed 2018-03-07). (b) Methylene chloride. Occidental Petroleum: Methylene Chloride Temperature vs. Density Table. http://www.oxy.com/OurBusinesses/Chemicals/Products/Documents/methylenechloride/tech-methylene_chloride_temp-density_table.pdf (accessed 2017-06-10).
- (5) Reported values for the solubility of ethylene in CD₂Cl₂ vary widely. In one recent study, our group reported a concentration of 54 ± 3 mM at 23 ± 1.5 °C, on the basis of NMR experiments in which the solvent was saturated in ethylene by carrying out five freeze-pump-thaw cycles of degassing, then thawing under 1 atm ethylene. See: (a) Lummiss, J. A. M.; Botti, A. G. G.; Fogg, D. E. *Catal. Sci. Technol.* **2014**, 4, 4210–4218. A value of 32 mM was reported by Diver and coworkers under balloon pressure at RT. See: (b) Smulik, J. A.; Diver, S. T. *J. Org. Chem.* **2000**, 65, 1788–1792. In the present calculations, the lower value is assumed as a safety margin. At 10 mM **Ru-4**, the maximum pressure of evolved ethylene, assuming a solubility of 32 mM at 1 atm, is 10/32, or ca. 0.3 atm. Taking into account the rated pressure limit of 5 atm for the glass J. Young NMR tubes, and the solubility of ethylene in this solvent, the pressure buildup due to evolution of ethylene is negligible.
- (6) László, K.; Demé, B.; Czakkel, O.; Geissler, E. *J. Phys. Chem. C*. **2014**, 118, 23723–23727.

J. List of Contributions

Articles published or accepted in refereed journals (*F* = full paper; *C* = communication)

11F. Bailey, G.A., Foscatto, M., Higman, C.S., Day, C.S., Jensen, V.R., and Fogg, D.E. (2018) Bimolecular Coupling as a Vector for Decomposition of Fast-Initiating Metathesis Catalysts. *J. Am. Chem. Soc.*, Accepted.

10C. Higman, C.S., do Nascimento, D.L., Ireland, B.J., Audörsch, S., **Bailey, G.A.**, McDonald, R., Fogg, D.E. (2018) Chelate-Assisted Ring-Closing Metathesis: A Strategy for Accelerated Macrocyclization at Ambient Temperatures. *J. Am. Chem. Soc.*, 1604–1607.

9C. Bailey, G.A., Lummiss, J.A.M., Foscatto, M., Occhipinti, G., McDonald, R., Jensen, V.R., Fogg, D.E. (2017) Decomposition of Metathesis Catalysts by Brønsted Base: Metallacyclobutane Deprotonation as a Primary Deactivating Event. *J. Am. Chem. Soc.* **2017**, 16446–16449.

8F. Santos, A.G.[†], **Bailey, G.A.**[†], dos Santos, E.N., and Fogg, D.E. (2017) Overcoming Catalyst Decomposition in Acrylate Metathesis: Polyphenol Resins as Enabling Agents for PCy₃-Stabilized Metathesis Catalysts. *ACS Catal.* **7**: 3181–3189. (ACS Editor's Choice; selected for ACS virtual issue on "Hot Materials in a Cool Country") [†]Equal contributions

7F. Bailey, G.A. and Fogg, D.E. (2016) Confronting Neutrality: Maximizing Success in the Analysis of Transition-Metal Catalysts by MALDI Mass Spectrometry. *ACS Catal.* **6**: 4962–4971.

6C. Bailey, G.A. and Fogg, D.E. (2015) Acrylate Metathesis via the Second-Generation Grubbs Catalyst: Unexpected Pathways Enabled via a PCy₃-Generated Enolate. *J. Am. Chem. Soc.* **107**: 7318–7321.

5F. Rodríguez-Rodríguez, C., Telpoukhovskaia, M.A., Alí-Torres, J., Rodríguez-Santiago, L., Manso, Y., **Bailey, G.A.**, Hidalgo, J., Sodupe, M., and Orvig, C. Thioflavin-Based Molecular Probes for Application in Alzheimer's Disease. (2015) *Metallomics*. **7**: 78–87.

4F. Telpoukhovskaia, M. A., Rodríguez-Rodríguez, C., Cawthray, J. F., Scott, L. E., Page, B. D. G., Alí-Torres, J., Sodupe, M., **Bailey, G.A.**, Patrick, B.O., and Orvig, C. (2014) 3-Hydroxy-4-pyridinones as Metal Ion and Amyloid Binding Agents. *Metallomics*, **6**: 249–262.

3F. Bates, J.M., Lummiss, J.A.M., **Bailey, G.A.**, and Fogg, D.E. (2014) Operation of the Boomerang Mechanism in Olefin Metathesis Reactions Promoted by the Second-Generation Hoveyda Catalyst. *ACS Catalysis* **4**: 2387–2394. (highlighted on "All Things Metathesis")

2F. Bailey, G.A.[†], Price, E.W.[†], Zeglis, B.M., Ferreira, C.L., Boros, E., Lacasse, M.J., Patrick, B.O., Lewis, J.S., Adam, M.J., and Orvig, C. (2012) H₂azapa: A Versatile Multifunctional Chelator for ⁶⁷Ga, ⁶⁴Cu, ¹¹¹In, and ¹⁷⁷Lu. *Inorg. Chem.* **51**: 12575–12589. [†]Equal contributions

1F. Price, E.W., Cawthray, J.C., **Bailey, G.A.**, Ferreira, C.L., Boros, E., Adam, M.J., Orvig, C. (2012) An Acyclic Chelator for ¹¹¹In Radiopharmaceuticals. *J. Am. Chem. Soc.* **134**, 8670–8683.

Manuscripts in preparation (*R = review; C = communication*)

13C. Bailey, G.A.; Jensen, V.R.; Fogg, D.E. (2018) “Fundamental Processes in Olefin Metathesis: Impact of the Alkylidene on Olefin Binding.” (In preparation)

12R. Bailey, G.A.; Nascimento, D.L.; Fogg, D.E. (2018) “Decomposition of Highly-Active Ruthenium Olefin Metathesis.” *Acc. Chem. Res.* (Invited review in preparation)

Presentations (*P = poster, O = oral; *indicates presenting author*)

O18. Bailey, G.A.*, Higman, C.S., and Fogg, D.E. (2017) Student symposium for 2017 Leibniz prize winner, Prof. Holger Braunschweig, Ottawa: May 2. (Institutional)

O17. Bailey, G.A.*, Higman, C.S., and Fogg, D.E. (2017) Gordon Research Conference in Inorganic Reaction Mechanisms, Galveston, TX: Mar 5–10. (International; *1 of 3 student lectures selected*)

P16. Bailey, G.A.*, Higman, C.S., and Fogg, D.E. (2017) Gordon Research Conference in Inorganic Reaction Mechanisms, Galveston, TX: Mar 5–10. (International)

O15. Bailey, G.A.*, Higman, C.S., and Fogg, D.E. (2017) Gordon Research Seminar in Inorganic Reaction Mechanisms, Galveston, TX: Mar 4–5. (International; *1 of 8 selected lectures*)

O14. Bailey, G.A.*, Higman, C.S., and Fogg, D.E. (2016) Centre for Catalysis Research & Innovation lunchtime seminars, Ottawa: Dec 8. (Institutional)

P13. Bailey, G.A.* and Fogg, D.E. (2016) Gordon Research Conference in Inorganic Chemistry, Biddeford, ME: June 19–24. (International)

O12. Bailey, G.A.* and Fogg, D.E. (2016) Ottawa–Carleton Chemistry Institute Meeting, Ottawa: June 3. (Institutional)

O11. Bailey, G.A.* and Fogg, D.E. (2016) 24th Canadian Symposium on Catalysis, Ottawa: May 8–11. (National; **Oral Presentation Award**)

O10. Bailey, G.A.* and Fogg, D.E. (2015) 48th Inorganic Discussion Weekend, Kingston: Nov 6–8. (Regional; **Oral Presentation Award**)

P9. Bailey, G.A.* and Fogg, D.E. (2015) 21st International Symposium on Olefin Metathesis, Graz, Austria: July 11–16. (International)

P8. Bailey, G.A.* and Fogg, D.E. (2015) 98th Canadian Chemistry Conference & Exhibition, Ottawa: June 13–17. (National)

P7. Bailey, G.A.* and Fogg, D.E. (2014) 47th Inorganic Discussion Weekend, Montreal: Nov 16–18. (Regional)

P6. Bailey, G.A.* and Fogg, D.E. (2014) 19th International Symposium on Homogeneous Catalysis, Ottawa: July 6–11. (International)

P5. Bailey, G.A.* and Fogg, D.E. (2013) 96th Canadian Chemistry Conference & Exhibition, Quebec City: May 26–30, 2013. (National)

Appendices

O4. Bailey, G.A.*, Price, E.W., Zeglis, B.M., Ferreira, C.L., Boros, E., Lacasse, M.J., Patrick, B.O., Lewis, J.S., Adam, M.J., and Orvig, C. **(2012)** Western Canadian Undergraduate Chemistry Conference, Edmonton: May 3–5. (Regional; **Oral Presentation Award**)

O3. Bailey, G.A.*, Price, E.W., and Orvig, C. **(2012)** Chemistry Undergraduate Research Conference, University of British Columbia, Vancouver: Apr 3, 2012. (Institutional)

P2. Yang, Z.*, **Bailey, G.A.***, Gray, M.R., and Chou, K.C. **(2010)** Centre for Oil Sands Innovation Stewardship Meeting, Edmonton: May 4–5. (Institutional)

O1. Bailey, G.A.* and Heuft, M.A. **(2010)** Xerox Research Center Canada R&D Meeting, Mississauga, Ontario, Dec 10. (Institutional).