

**Ruthenium Catalysts for Olefin Metathesis: Understanding the Boomerang
Mechanism and Challenges Associated with Stereoselectivity**

Jennifer M. Bates

Thesis submitted to the
Faculty of Graduate and Postdoctoral Studies
In partial fulfillment of the requirements for the degree of

Master of Science

Centre for Catalysis Research and Innovation
Department of Chemistry
Ottawa-Carleton Chemistry Institute
Faculty of Science
University of Ottawa

© Jennifer Bates, Ottawa, Canada, 2014

Table of Contents

List of Figures	v
List of Schemes	viii
List of Tables	ix
Abstract	x
Acknowledgements	xi
List of Abbreviations	xiii
List of Compounds	xv
 1 Introduction	 1
1.1 Background	1
1.2 Olefin metathesis	2
1.2.1 History of olefin metathesis	2
1.2.2 Olefin metathesis catalysts	4
1.2.3 Ring-closing metathesis (RCM)	6
1.2.4 Mechanism of ruthenium-catalyzed olefin metathesis	7
1.3 Decomposition of Grubbs-type catalysts	9
1.4 Scope of this thesis	9
1.5 References	10
 2. Experimental Methods	 14
2.1 General procedures	14
2.1.1 Reaction conditions	14
2.1.2 Reagents	14
2.1.3 Solvents	15
2.1.4 Deuterated solvents	15
2.1.5 NMR spectroscopy	16
2.1.6 Gas chromatography	16
2.2 Synthesis of substrates	17
2.2.1 2-Methylocta-1,7-dien-3-ol 1	17
2.2.2 Hex-5-enyl undec-10-enoate 2	17
2.3 Synthesis of ligands	18
2.3.1 <i>N</i> -Tosylhydrazone 3	18
2.3.2 Phenyl diazomethane 4	18
2.3.3 Glyoxal-bis-(2,4,6-trimethylphenyl)imine 5	19
2.3.4 <i>N,N'</i> -Bis(2,4,6-trimethylphenyl)ethylenediamine dihydrochloride 6	20
2.3.5 1,3-Bis(2,4,6-trimethylphenyl)imidazolium chloride ([H ₂ IMes(H)](Cl)) 7	20
2.3.6 1,3-Bis(2,4,6-trimethylphenyl)imidazolium tetrafluoroborate ([H ₂ IMes(H)](BF ₄)) 8	21
2.3.7 1,3-Bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene (H ₂ IMes) 9	21
2.3.8 2-Isopropoxybenzaldehyde 10	22
2.3.9 2-Isopropoxystyrene 11	23
2.4 Synthesis of ruthenium catalysts	24
2.4.1 RuCl ₂ (PPh ₃) ₃ Ru-8	24
2.4.2 RuCl ₂ (=CHPh)(PCy ₃) ₂ Ru-1a	24
2.4.3 RuCl ₂ (=CHPh)(H ₂ IMes)(PCy ₃) Ru-1b	25

2.4.4	RuCl ₂ (PCy ₃)(=CH-2-O ⁱ PrC ₆ H ₄) Ru-2a*	26
2.4.5	RuCl ₂ (H ₂ IMes)(=CH-2-O ⁱ PrC ₆ H ₄) Ru-2b* from Ru-2a*	27
2.4.6	RuCl ₂ (H ₂ IMes)(=CH-2-O ⁱ PrC ₆ H ₄) Ru-2b from Ru-1b	28
2.5	Assessing catalyst decomposition: thermolysis experiments	28
2.5.1	Representative procedure: thermolysis in the presence of Amberlyst 15 resin	29
2.5.2	Lifetime of Ru-9 and Ru-10a at various temperatures	29
2.6	Assessing rate of CM between Hoveyda catalyst Ru-2b and ¹³ C-labeled 2-isopropoxystyrene 11*	29
2.6.1	Representative procedure	29
2.7	Catalytic reactions	30
2.7.1	Representative procedure for RCM of 2-methylocta-1,7-dien-3-ol 1	30
2.7.2	Representative procedure for CM of <i>trans</i> -anethole 12 and methyl acrylate 13	31
2.7.3	Representative procedure for RCM of diethyl diallylmalonate 14	32
2.7.4	Procedure for consecutive RCM of fresh diethyl diallylmalonate 14	32
2.7.5	Representative procedure for RCM of hex-5-en-1-yl undec-10-enoate 2 [S] _i = 5 mM	32
2.7.6	Representative procedure for RCM of hex-5-en-1-yl undec-10-enoate 2 [S] _i = 440 mM	33
2.7.7	Procedure for RCM of hex-5-en-1-yl undec-10-enoate 2 , followed by addition of diethyl diallylmalonate 14	34
2.8	References	34
3	The Boomerang Mechanism in Olefin Metathesis: Fact or Fiction?	36
3.1	Introduction	36
3.2	Results and discussion	49
3.2.1	Synthesis of the ¹³ C-labeled Hoveyda catalyst Ru-2b*	49
3.2.1.1	Synthesis of Ru-2b* by cross-metathesis of Ru-1b with 11*	49
3.2.1.2	Synthesis of Ru-2b* via ligand exchange of Ru-2a* with H ₂ IMes 9	51
3.2.2	Rate of cross-metathesis between Ru-2b and 11*	52
3.2.2.1	Effect of solvent on reaction rates	52
3.2.2.2	Effect of concentration on reaction rates	54
3.2.2.3	Impact of headspace and stirring on reaction rates	55
3.2.3	Establishing the relevance of the boomerang mechanism during RCM	56
3.2.3.1	Experimental design	56
3.2.3.2	Impact of ethylene on catalyst decomposition	59
3.2.3.3	Reaction vessels and effect on reaction rates	60
3.2.3.4	Investigating the impact of stoichiometric styrenyl ether 11	62
3.2.3.5	Evaluating perturbation of the catalytic system	63
3.2.3.6	Assessing uptake of the ¹³ C-labeled styrenyl ether 11*	65
3.2.4	Exploring the boomerang mechanism for Ru-2b during CM	66
3.3	Conclusions	69
3.4	References	70
4	Ruthenium-Arylthiolate Catalysts in Z-Selective Macrocyclization	73
4.1	Introduction	73
4.2	Results and discussion	80

4.2.1	RCM macrocyclization by Ru-9	80
4.2.1.1	Effect of concentration and temperature on rate and product distribution	80
4.2.1.2	Assessing catalyst lifetime in the presence of substrate	85
4.2.2	RCM macrocyclization using <i>o</i> -dichloroarylthiolate catalyst Ru-10a	88
4.2.2.1	Effect of concentration on rate and product distribution.....	88
4.2.2.2	Effect of lower catalyst loading and temperature.....	90
4.2.3	Stability of Ru-9 in the absence of substrate	91
4.2.4	Stability of Ru-10a in the absence of substrate	93
4.3	Conclusions	94
4.4	References	96
5.	Conclusions and Future Directions	98
List of Contributions		100
Manuscripts published or submitted:.....		100
Manuscripts in preparation:		100
Poster presentations:		100

List of Figures

Chapter 1

- Figure 1.1** (a) A simplified catalytic cycle (S = substrate, P = product). (b) Energy barriers for a non-catalyzed (solid line) and catalyzed (dashed line) chemical reaction. 1
- Figure 1.2** Common types of olefin metathesis reactions. 2
- Figure 1.3** Common molybdenum and ruthenium catalysts used in olefin metathesis. 5

Chapter 3

- Figure 3.1** Products derived from reaction of **Ru-5b** with (a) PCy₃, or (b) styrenyl ether **11**. 36
- Figure 3.2** An early study of the release-return mechanism for the first-generation Hoveyda catalyst **Ru-2a**. (a) Tetranuclear species **Ru-11a** used in the crossover study. (b) Generation of **Ru-2a** from **Ru-11a** and **11**: (i) in the absence of substrate (control) or, (ii) in the presence of diallyl tosylamine **16**. 39
- Figure 3.3** Sol-gel-supported catalysts employed in the crossover study (see Scheme 3.2) by Hoveyda and co-workers. 40
- Figure 3.4** Reactions of **Ru-5b** with (a) product olefin or, (b) styrenyl ether **18**; studied computationally. Reaction with styrenyl ether **18** is favoured due to formation of the thermodynamically stable product **Ru-14**. 42
- Figure 3.5** Plenio study with evidence against the release-return mechanism. (a) RCM of DeDAM **14** with **Ru-15a**. (b) Expected effect of dissociation and re-association of fluorophore-tagged styrenyl ether ligand **19a** on fluorescence evolution. 43
- Figure 3.6** Equilibration between deuterium-labeled **Ru-16** and **Ru-2b**. (a) In the absence of substrate (control). (b) In the presence of 20 equiv *N,N*-diallylacetamide **20**. 45
- Figure 3.7** (a) Potential pathways for uptake of **11*** during metathesis. (i) “Boomerang” pathway: capture of **11*** by **Ru-5b**. (ii) Background reaction: reaction of **Ru-2b** and **11***. (b) Representative ¹H NMR spectrum (alkylidene region) depicting the distinct signals for labeled **Ru-2b*** (doublet, red) and non-labeled **Ru-2b** (singlet, black). 47
- Figure 3.8** CM of **Ru-2b** with styrenyl ether **11***, showing slower reaction in C₆D₆ than CD₂Cl₂. Reactions performed in a sealed J. Young NMR tube (RT, 21 mM Ru). Final ratio of **Ru-2b**:**Ru-2b***: 53:47 in C₆D₆; 49:51 in CD₂Cl₂. 53
- Figure 3.9** Effect of concentration on the rate of reaction (21 mM vs. 1 mM). Reactions performed in a sealed J. Young NMR tube. Final ratio of **Ru-2b**:**Ru-2b*** was 53:47. 55
- Figure 3.10** Effect of reaction vessel on CM rate: comparison of open, stirred Kontes flask with sealed J. Young NMR tube. Final ratio of **Ru-2b**:**Ru-2b*** was 53:47. 56
- Figure 3.11** Effect of ruthenium concentration on (a) RCM reaction rate or, (b) signal to noise ratio (S/N) of the alkylidene signal. Determined by ¹H NMR analysis. 58

Figure 3.12 ^1H NMR spectrum at >99% conversion for RCM reaction performed with 0.44 mM ruthenium showing low signal to noise ratio (S/N).....	58
Figure 3.13 Effect of reaction vessel on the amount of Ru-2b remaining during the RCM of 1 at two different catalyst loadings (1 mol% or 5 mol%). Determined at 93-95% conversion (10-30 min) by ^1H NMR analysis.....	60
Figure 3.14 Effect of reaction vessel on reaction rates. Determined by GC (for reactions performed in a Schlenk tube) or ^1H NMR analysis (for reactions performed in a J. Young NMR tube).....	61
Figure 3.15 Effect of 1 equiv 11 on reaction rates in (a) sealed J. Young NMR tube (^1H NMR analysis) or, (b) open Schlenk tube with stirring (GC analysis).	63
Figure 3.16 Effect of added 11 (1 or 5 equiv) on reaction rates to assess perturbation of the system (determined by GC). Reactions performed in an open Schlenk tube with stirring.	64
Figure 3.17 Rate plot illustrating first-order dependence on substrate concentration.....	64
Figure 3.18 Rate of CM between Ru-2b and 11* (background equilibration reaction) under exact conditions of RCM. Final ratio of Ru-2b:Ru-2b* was 55:45.....	65
Figure 3.19 RCM of 1 with Ru-2b and 11* vs. Ru-2b* and 11 . (a) Rate profiles. (b) Ratio of Ru-2b:Ru-2b* at 10 min (95% conversion), measured by integrating the NMR signals for $\text{Ru}=\text{CHAr}$	66
Figure 3.20 Effect of 1 equiv 11 on reaction rates when performed in an open Schlenk tube with stirring (determined by GC).	68
Figure 3.21 Rate of CM between Ru-2b and 11* (background equilibration reaction) under exact conditions of CM. Final ratio of Ru-2b:Ru-2b* was 54:46.	69
Figure 3.22 Active species present during CM of acrylates and phenylpropenoids.	69

Chapter 4

Figure 4.1 Representative molybdenum and tungsten monoaryloxide-pyrrolide (MAP) complexes. TBS = <i>t</i> -butyldimethylsilyl.	73
Figure 4.2 Metallacyclobutane symmetry and product selectivity. (a) Grubbs catalysts; (b) monoaryloxide catalysts; (c) (thio)catecholate catalysts.....	75
Figure 4.3 (a) State-of-the-art Z-selective ruthenium metathesis catalysts. (b) Ruthenium-aryloxide catalyst that effects RCM macrocyclization with minimal oligomerization.	76
Figure 4.4 Homocoupling of 1-octene 28 showing loss of stereoselectivity over time.	77
Figure 4.5 Ability of various catalysts to promote Z-selective RCM macrocyclization of 2 to form 16-membered lactone 29	78
Figure 4.6 (a) Ruthenium-arylthiolate catalysts studied in this work. (b) Z-Selectivity of Ru-9 and Ru-10b in homocoupling of 1-octene 28 . (c) Equilibrium between the five- and four-coordinate complexes, Ru-10 and Ru-21 respectively, due to the hemilabile arylthiolate ligand.....	79

Figure 4.7 Product distribution in RCM macrocyclization of 2 with Ru-9 . The initial diene concentration was 5 mM.	82
Figure 4.8 RCM macrocyclization of 2 (545 mM) using Ru-9 . (a) At 40 °C, followed by dilution to 5 mM and addition of 5 mol% Ru-9 . (b) At 40 °C, diluted to 5 mM and heated to 60 °C.	84
Figure 4.9 Ability of Ru-9 to effect RCM of 14 (5 mM) into 32 with 5 mol% virgin catalyst (control, dashed line) and once substrate was added (20 equiv to Ru) to RCM macrocyclization reaction at 2.5 d (solid line).	86
Figure 4.10 Product distribution in the RCM macrocyclization of 2 . Conditions: (a) 5 mol% Ru-9 at an initial diene concentration of 545 mM, (b) diluted to 5 mM, (c) added 20 equiv DeDAM 14 , (d) added an additional 20 equiv of 2	88
Figure 4.11 Product distribution of RCM macrocyclization of 2 with 5 mol% Ru-10a at an initial diene concentration of (a) 5 mM or, (b) 440 mM, diluted to 5 mM and additional catalyst charge of 5 mol% Ru-10a	89
Figure 4.12 Effect of temperature on RCM macrocyclization of 2 . Conditions: 1 mol% Ru-10a in DCE at (a) 40 °C or, (b) reflux (83 °C).	90
Figure 4.13 Examining the solution stability of Ru-9 in DCE at 40 °C over time.	92
Figure 4.14 ¹ H NMR spectra for decomposition of Ru-10a in DCE at 40 °C over time. (The poor peaks shapes are due to analysis in protio-DCE, which limits the efficacy of shimming)	93
Figure 4.15 Thermolysis of Ru-10a in CD ₂ Cl ₂ at 35 °C. (a) Rate curve of the decomposition of Ru-10a . (b) ¹ H NMR spectra showing decomposition products.	94

List of Schemes

Chapter 1

- Scheme 1.1** (a) Proposed intermediates described in early mechanistic reports of olefin metathesis. (b) The widely accepted Chauvin mechanism for olefin metathesis. .3
- Scheme 1.2** Simplified RCM equilibria resulting from irreversible loss of ethylene. (a) Direct RCM. (b) Oligomerization-backbiting pathway.....6
- Scheme 1.3** The dissociative mechanism for olefin metathesis with Grubbs catalysts **Ru-1**. .8

Chapter 3

- Scheme 3.1** Schematic illustrating the release-return mechanism.....37
- Scheme 3.2** Crossover study designed by Hoveyda and co-workers to investigate the release-return mechanism. Following RCM, **Ru-12a** was removed and treated with **11**.
.....40
- Scheme 3.3** Metathesis reactions studied in exploring the relevance of the release-return mechanism for **Ru-2b**. (a) RCM reaction. (b) CM reaction. Decane was used as an internal standard (I.S.) for GC analysis; dimethyl terephthalate and TMB as an internal standard (I.S.) for ¹H NMR analysis.....49
- Scheme 3.4** Potential routes to ¹³C-labeled **Ru-2b***. (a) Marciniak route, involving CM of **Ru-1b** with **11***. (b) By ligand exchange of **Ru-2a*** (prepared from CM of the **Ru-1a** with **11***) with H₂IMes **9**.....50
- Scheme 3.5** Formation of doubly-labeled stilbene **25*** from CM of **Ru-2b*** and **11***.....54
- Scheme 3.6** RCM of **1** into trisubstituted olefin **21**. Conditions: 1 mol% **Ru-2b** (1 mM), C₆D₆, 100 mM **1**, decane (I.S.), TMB (I.S.), 1 mol% **11**.....57
- Scheme 3.7** CM of anethole (**12**) with methyl acrylate (**13**) to form desired cinnamate product (**22**) as well as additional CM and self-metathesis (SM) by-products. ..67

Chapter 4

- Scheme 4.1** Rationale for Z-selectivity of molybdenum and tungsten catalysts.74
- Scheme 4.2** RCM equilibria presuming irreversible loss of ethylene. (a) Direct RCM. (b) Oligomerization-backbiting pathway.77
- Scheme 4.3** RCM macrocyclization reaction of **2** performed with **Ru-9** and **Ru-10a**.....81

List of Tables

Chapter 2

Table 2.1 All reaction conditions employed for background reactions.....	30
---	----

Chapter 3

Table 3.1 Summary of differences in reaction of Ru-15a with DeDAM 14 and EVE.....	44
Table 3.2 Summary of key literature studies examining the release-return mechanism.....	48
Table 3.3 Detrimental impact of ethylene on RCM productivity and lifetime.	62

Abstract

Ruthenium-alkylidene catalysts are widely used in organic synthesis to generate new C=C bonds in a process known as olefin metathesis. Much research has been dedicated to examining the organometallic species responsible for this transformation, and understanding the benefits and limitations of current state-of-the-art catalysts allows for the design of new and more efficient alternatives.

Over the past decade, a topic of much debate has been the so-called “boomerang” (or release-return) mechanism, and whether it operates in the Hoveyda catalysts. The ability of the styrenyl ether ligand, once released from the catalyst during initiation, to be recaptured by the vulnerable active species, has major implications in catalyst recyclability. Chapter 3 describes the use of a ^{13}C -labeled styrenyl ether ligand, in conjunction with an unlabeled second-generation Hoveyda catalyst, to confirm the operation of this mechanism during catalysis. This study demonstrated that the labeled styrenyl ether ligand competes with the substrate for the four-coordinate active species: the labeled moiety rapidly incorporates into the Hoveyda catalyst during both ring-closing- and cross-metathesis examples.

Chapter 4 focuses on addressing the selectivity challenges associated with olefin metathesis, particularly during RCM macrocyclization reactions where *E/Z* mixtures are typically obtained. Designing catalysts that can dictate and control the stereochemistry of a product mixture minimizes waste, and ultimately reduces cost by eliminating the need for separation techniques. A great deal of research has focused on constructing catalysts with ligands that can exert the appropriate steric pressure on a metallocyclobutane intermediate, in order to generate the desired *Z*-product. Chapter 4 of this thesis examined the ability of a Hoveyda- and Grubbs-type catalyst containing monothiolate ligands, to promote *Z*-selective RCM macrocyclization. Catalyst lifetimes were also examined, in addition to the impact of altering reaction conditions, specifically concentration, on product distribution. These experiments afford information that will aid in the design of improved catalysts for *Z*-selective RCM macrocyclization.

Acknowledgements

First and foremost, I would like to thank my supervisor Prof. Deryn Fogg for your guidance over the past two years. You provided me with the opportunity to pursue graduate school which has been an adventure I will never forget. The knowledge and skills that I have learned during my time here extend beyond those in the lab, and for that I am very grateful.

To my current labmates Bianca, Ben, Justin, Carolyn, Gwen, Adrian, and Devon and past members including Nick, Chan, Alex, Pedro, Jake, Lucie, Stephan, Amy, and Josh it has been a pleasure working with all of you. Thank you for all your assistance, useful discussions and feedback, as well as all the memorable times both in and out of the lab. Most importantly, I would like to thank Dr. Bianca van Lierop. I do not know how I would have finished this degree without your guidance and friendship. B, you were there for me whether I needed assistance in the lab (especially with my columns), someone to bounce ideas off of, or a drink after a long day at work, even though we are quite incapable of enjoying just one. The memories we have created such as your first Halloween, first hockey game, beating Josh at euchre, and your more recent milestone birthday celebration were amazing. I cannot wait to share many more the longer you stay in Canada (hopefully!). Justin Lummiss, your knowledge in the lab has been incredibly valuable. I appreciate you taking the time out of your busy schedule to always answer my questions and talk things through with me. When my luck was at its worst you were always able to help me find a way to fix the problem. Josh, your love and addiction for board games and ability to produce some of the most complex spreadsheets I have ever seen is incredible nerdy, you might want to get that checked out. However, I have enjoyed beating you at every board game you own and using your excel spreadsheets for the euchre tournament which, with the beginner Australian as my partner, we beat you at as well! Ben, thank you for making me an official diploma on a subway napkin, it definitely helped motivate me especially towards the end. Also your ability to speak like Josh is scary, but what I really want to say is: you're next buddy! Gwen you were a delight to train when you first arrived and I enjoyed working alongside you in our fume hoods. Hearing you hum away as you work is quite entertaining. Lucie, I was glad to have you around the week everyone went to CSC in Montreal, even though we worked so hard. However, I think our version of group meeting at The Fox & Feather was by far the best one ever. Amy, you and Phil have always been there for me after a hard day at work and

for that I am very thankful. Stephan, the way you devour ribs is like nothing I have ever seen before. I would like to thank you for teaching me how to properly run my first successful column. Carolyn thanks for introducing me to David's tea and getting me addicted, the caffeine was definitely appreciated during the writing of this thesis.

I would also like to thank those who contributed to my research. First, I must acknowledge Glenn Facey for his expertise of NMR spectroscopy. In addition, Giovanni Occhipinti, for generously synthesizing and providing catalysts **Ru-9** and **Ru-10a**, as well as Vidar Jensen (University of Bergen) for their collaboration.

To my family, without your support I never would have made the journey to Ottawa as I know that this was farther from home than you all would have liked. Mom and dad for your love, support, and encouragement to pursue a university education and graduate degree is something I will never forget. Whenever I was stressed out, you were there to listen, give me advice, and guidance. I would not have been able to complete this degree without you.

Finally, I would like to give a very special thank you to Dan. You were incredibly supportive throughout this degree. I know you are not a fan of the big city, but I am forever grateful that you made this amazing, yet stressful journey with me to Ottawa. Your love, help, and patience during this process has been unbelievable and I cannot wait to see what adventure we share together next.

List of Abbreviations

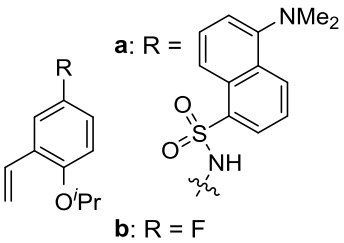
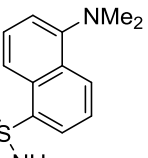
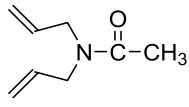
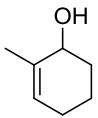
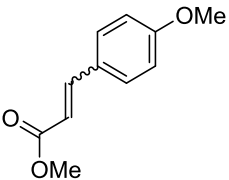
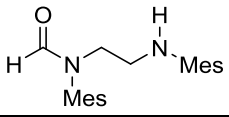
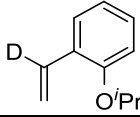
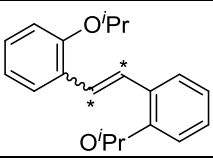
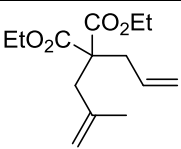
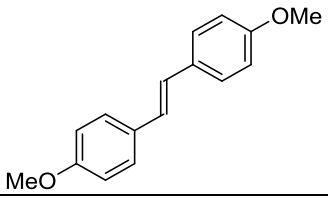
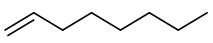
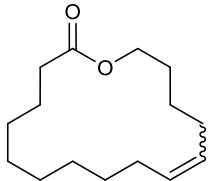
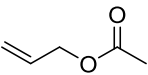
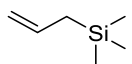
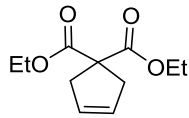
δ	Chemical shift; ppm
ADMET	Acyclic diene metathesis
Cat.	Catalyst
CM	Cross-metathesis
Cy	Cyclohexyl
DCE	1,2-Dichlorethane
DeDAM	Diethyl diallylmalonate
DMSO	Dimethyl sulfoxide
E_a	Activation energy
equiv	Equivalents
Et ₂ O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
EVE	Ethyl vinyl ether
GC	Gas chromatography
H ₂ IMes	<i>N,N'</i> -Bis-(2,4,6-trimethylphenyl)imidazolin-2-ylidene
H ₂ <i>i</i> Pr	<i>N,N'</i> -Bis-(2,6-diisopropylphenyl)imidazolin-2-ylidene
H ₂ IXy	<i>N,N'</i> -Bis-(2,6-dimethylphenyl)imidazolin-2-ylidene
Hz	Hertz (1Hz = 1 s ⁻¹)
IMes	<i>N,N'</i> -Bis-(2,4,6-trimethylphenyl)imidazol-2-ylidene
I.S.	Internal standard
KTp	Potassium hydrotris(pyrazolyl)borate
L	Neutral donor ligand
M	Metal
MAP	Monoaryloxide-pyrrolide
MCB	Metallocyclobutane

MeOH	Methanol
Mes	Mesityl, 2,4,6-trimethylphenyl
ⁿ PrOH	1-Propyl alcohol
NHC	<i>N</i> -Heterocyclic carbene
NMR	Nuclear magnetic resonance
OAr	Aryloxide
OM	Olefin metathesis
P	Product
ppm	Parts per million (μg/g)
py	Pyridine
RCM	Ring-closing metathesis
ROMP	Ring-opening metathesis polymerization
ROCM	Ring-opening cross-metathesis
RT	Room temperature
S	Substrate
[S] _i	Initial substrate concentration
SM	Self-metathesis
TBS	<i>t</i> -Butyldimethylsilyl
THF	Tetrahydrofuran
THN	1,2,3,4-Tetrahydronaphthalene
TMB	1,3,5-Trimethoxybenzene
TMS	Trimethylsilane
Trip	2,4,6- ⁱ Pr ₃ C ₆ H ₂
wt	Weight, in %
X	Anionic donor ligand

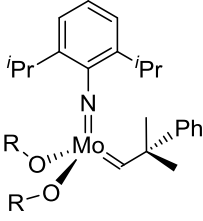
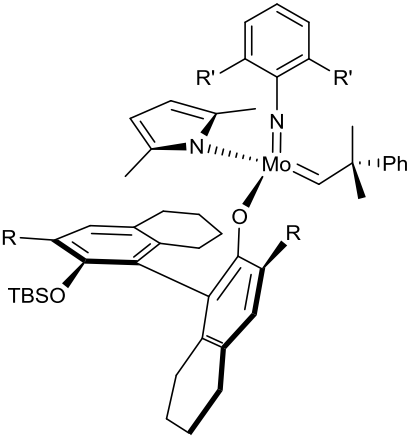
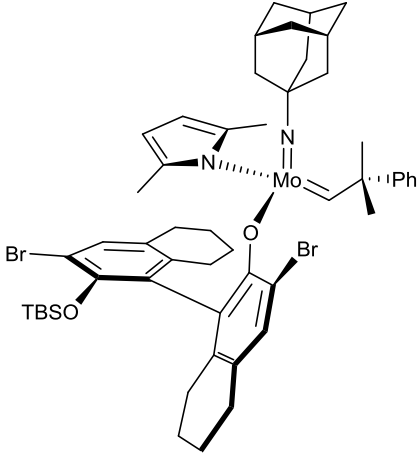
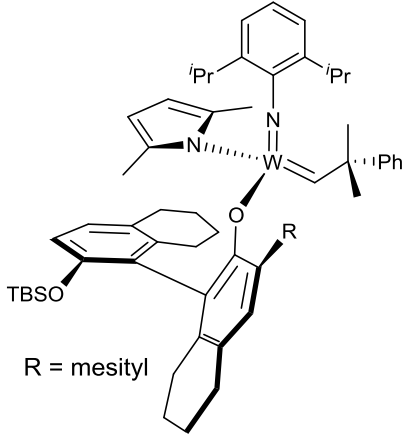
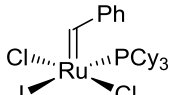
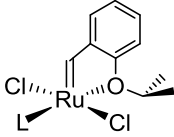
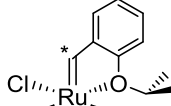
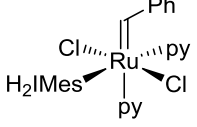
List of Compounds

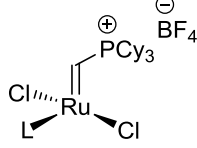
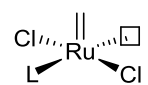
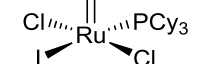
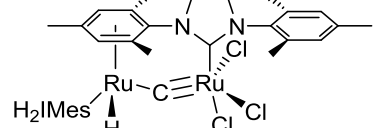
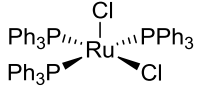
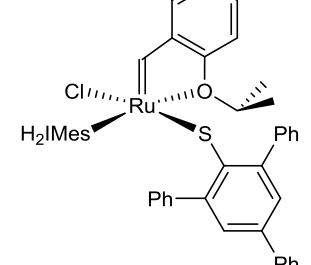
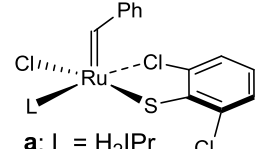
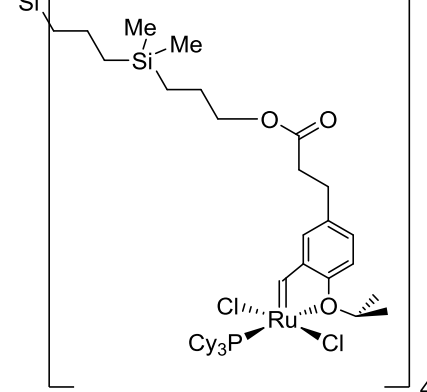
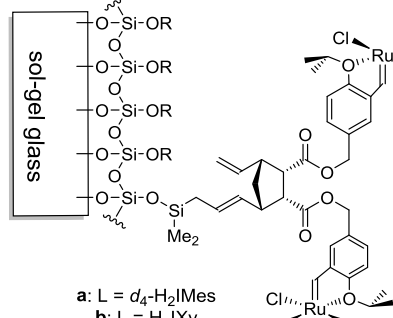
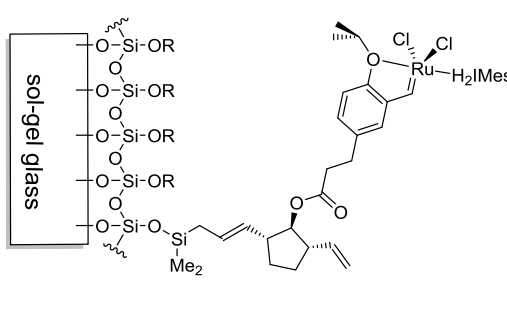
Organic Compounds

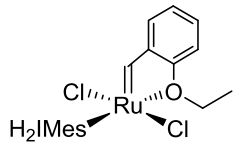
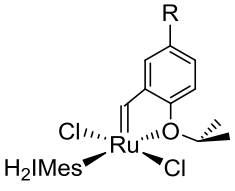
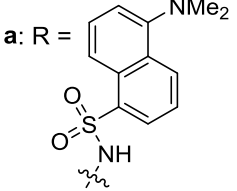
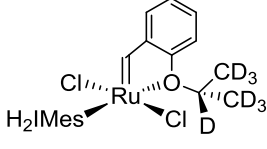
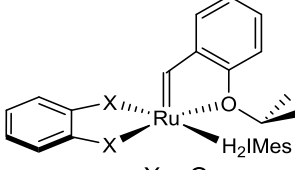
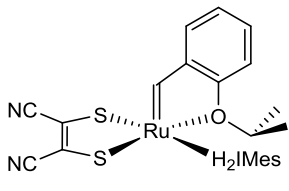
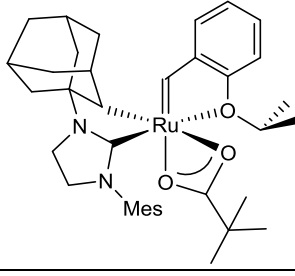
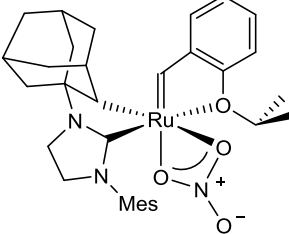
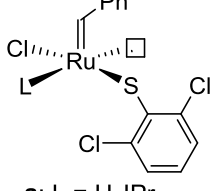
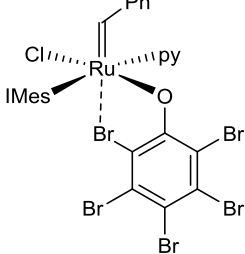
#	Compound	#	Compound
1		2	
3		4	
5		6	
7		8	
9		10	
10*		11	
11*		12	
13		14	
15		16	
17		18	

19	 a: R =  b: R = F	20	
21		22	
23		24	
25*		26	
27		28	
29		30	
31		32	

Organometallic Compounds

#	Compound	#	Compound
Mo-1	 a: R = CMe b: R = CMe₂(CF₃) c: R = CMe(CF₃)₂	Mo-2	 a: R = Br, R' = Me b: R = mesityl R' = <i>i</i>Pr
Mo-3		W-1	 R = mesityl
Ru-1	 a: L = PCy₃ b: L = H₂IMes c: L = IMes	Ru-2	 a: L = PCy₃ b: L = H₂IMes c: L = IMes d: L = <i>d</i>₄-H₂IMes e: L = H₂IXy
Ru-2*	 a: L = PCy₃ b: L = H₂IMes	Ru-3	

Ru-4	 a: L = PCy₃ b: L = H₂IMes	Ru-5	 a: L = PCy₃ b: L = H₂IMes
Ru-6	 a: L = PCy₃ b: L = H₂IMes	Ru-7	
Ru-8		Ru-9	
Ru-10	 a: L = H₂IPr b: L = H₂IMes	Ru-11	 a: L = PCy₃ b: L = H₂IMes
Ru-12	 a: L = d₄-H₂IMes b: L = H₂Ixy	Ru-13	

Ru-14		Ru-15	 a: R =  b: R = F
Ru-16		Ru-17	 a: X = O b: X = S
Ru-18		Ru-19	
Ru-20		Ru-21	 a: L = H₂IPr b: L = H₂IMes
Ru-22			

1 Introduction

1.1 Background

Catalysts are responsible for a vast range of chemical transformations, and are employed in about 90% of chemical processes.¹ In consequence, an enormous volume of research focuses on catalytic methodologies, and since 1901, at least 15 Nobel Prizes have been awarded to work relating to chemical and enzymatic catalysts.² The first was presented to F. Wilhelm Ostwald in 1909, for his investigations relating to the fundamental principles governing chemical equilibria and rates of reaction.³ Most recently, Heck, Negishi, and Suzuki were recognized for their work in palladium-catalyzed cross-coupling reactions (2010). Other notable contributions include Ziegler and Natta (1963) for their work in polymerization, and most relevant to this thesis, the work of Grubbs,⁴ Schrock,⁵ and Chauvin⁶ in olefin metathesis (2005).

The simplest definition of a catalyst is a substance that accelerates a reaction but is not consumed in the process.^{3,7} Typically, a catalyst facilitates bond-forming reactions with reactant molecules, and then reverts to its original form after each cycle (Figure 1.1a). Of prime importance is the capacity of the catalyst to lower the activation energy barrier (E_a) for a reaction, thus improving overall rates and lowering energy expenditure (Figure 1.1b).⁷ Because the catalyst is not consumed during a reaction, it can “turn-over” multiple cycles, lowering the ratio of catalyst to product, and creating a more cost-effective process.

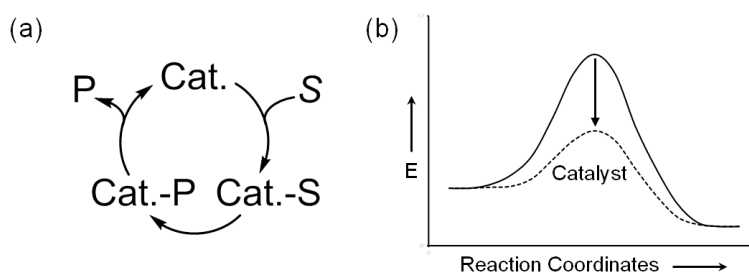


Figure 1.1 (a) A simplified catalytic cycle (S = substrate, P = product). (b) Energy barriers for a non-catalyzed (solid line) and catalyzed (dashed line) chemical reaction.

Reliance on stoichiometric reagents leads to high E-factors in industrial use, which translates into kg of waste per kg of product.⁸ The development and use of efficient catalysts thus

forms one of the 12 Principles of Green Chemistry.^{9,10} Preparation of selective, stable, and recyclable catalysts is highly desirable: greater catalyst stability enables higher turnover numbers (TON) and reduces catalyst loadings. As a result, much research has been aimed at improving the efficiency of both homogeneous and heterogeneous catalysts.⁷ This thesis examines such ideas in some specific contexts in olefin metathesis.

1.2 Olefin metathesis

1.2.1 History of olefin metathesis

Olefin metathesis is an organic reaction involving a metal catalyst, in which redistribution of olefin fragments occurs by scission and reformation of a carbon-carbon double bond. This extremely versatile process has found widespread application in academia and industry, with a recent explosion of interest in organic synthesis. Olefin metathesis encompasses a large variety of transformations, key examples being ring-closing metathesis (RCM), ring-opening metathesis polymerization (ROMP), cross-metathesis (CM), ring-opening cross-metathesis (ROCM), and acyclic diene metathesis (ADMET) (Figure 1.2).

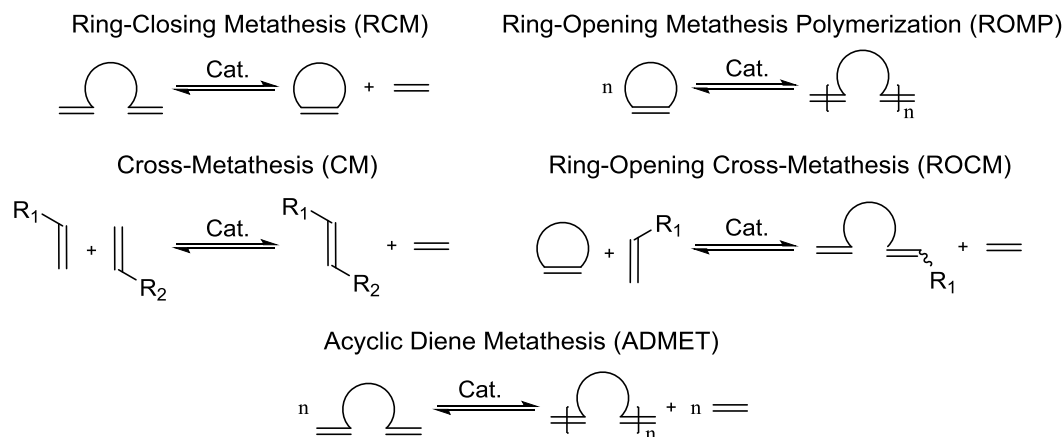
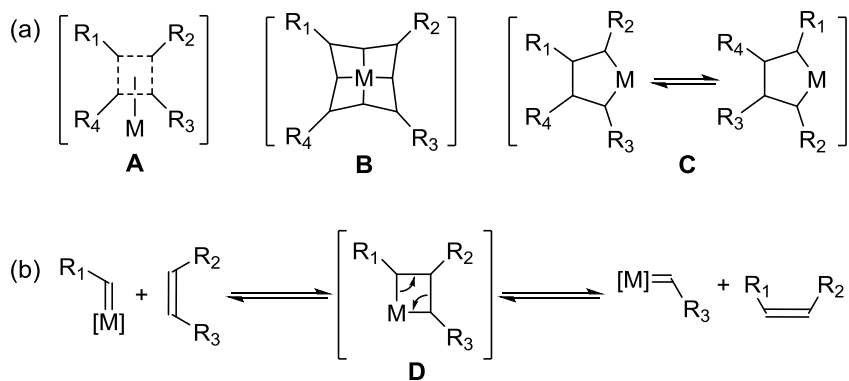


Figure 1.2 Common types of olefin metathesis reactions.

Researchers at Du Pont first discovered the process in 1956, observing the polymerization of norbornene using a TiCl_4 catalyst.¹¹ In the same year, Eleuterio¹² at Du Pont independently observed the formation of propylene, ethylene, and 1-butene after passing a feed of propylene gas over a molybdenum-on-aluminum catalyst bed. The phenomenon was unexplained at the time, but was corroborated by scientists from several petrochemical

companies.¹³ It was not until 1967 that Calderon,¹⁴ a researcher at Goodyear Tire & Rubber, proposed that these unexpected products formed via an intermolecular interchange of alkylidene groups. In his investigation, treatment of 2-pentene with a 1:1 solution of WCl_6/EtOH resulted in a 1:2:1 mixture of 2-butene, 2-pentene, and 3-hexene. Calderon coined the term “olefin metathesis” in his seminal report.

The redistribution of carbon-carbon double bonds via olefin metathesis was accounted for by several competing mechanisms.¹⁵⁻¹⁷ The earliest reports suggested formation of intermediates such as a cyclobutane ring complexed to the metal center (**A**),¹⁵ a tetramethylene complex (**B**),¹⁶ and a rearranging metallacyclopentane complex (**C**)¹⁷ (Scheme 1.1a). In 1971, Chauvin proposed a [2+2] cyclo-addition mechanism (Scheme 1.1b) that slowly won acceptance.¹⁸ Chauvin suggested that metathesis initiates via a metal-carbene complex, which forms a metallocyclobutane intermediate after reacting with an olefin (**D**). The intermediate decomposes by a [2+2] cyclo-reversion reaction, forming a new olefin, and a new metal carbene complex. Recently, Piers and co-workers¹⁹ succeeded in observing this key metallocyclobutane intermediate via low-temperature NMR spectroscopy.



Scheme 1.1 (a) Proposed intermediates described in early mechanistic reports of olefin metathesis. (b) The widely accepted Chauvin mechanism for olefin metathesis.

Experimental support for the Chauvin mechanism emerged from work by the Katz,^{20,21} Grubbs,^{22,23} and Schrock²⁴ groups. Specifically, Katz and co-workers²⁰ showed that a molybdenum-catalyzed reaction of cyclooctene with 2-butene and 4-octene, did not afford the diene expected from union of one acyclic olefin with cyclooctene (“pair-wise” exchange). Instead, they saw formation of 2,10-tetradecadiene (a 14-carbon chain), a product

consistent with Chauvin's mechanism. Product ratios also deviated from those expected from the earlier mechanisms. Katz proposed that the Chauvin mechanism accounts for the influence of the metal complex on the stereochemistry of a reaction: the preferred metallacyclobutane ring would presumably be that in which steric interactions are minimized. Designing catalysts that can favor a specific metallocyclobutane intermediate represents an on-going challenge in olefin metathesis, and is discussed in more detail in Chapter 4.

Grubbs and co-workers²² came to the same conclusion shortly after Katz, in a study utilizing deuterium-labeled (1,1,8,8-d₄) and unlabeled 1,7-octadiene. If a "pair-wise" interchange mechanism was at play, then only ethylene-d₄ and ethylene-d₀ would be generated. Significant amounts of ethylene-d₂ were however, observed with a range of homogeneous and heterogeneous tungsten catalysts. This necessitates a chain transfer of methylene groups using a metal carbene.

Schrock and co-workers²⁴ were the first to synthesize and isolate metal-alkylidene complexes, and to demonstrate that these were metathesis-active. Schrock showed that tantalum (Ta) and niobium (Nb) alkylidene complexes could initiate the metathesis of 1-butene. In some cases, productive metathesis with multiple turnovers resulted, consistent with the Chauvin mechanism. This work represented a major advance in practical as well as mechanistic terms: it laid the basis for new areas in organometallic chemistry, most immediately in the synthesis of a wide range of alkylidene catalysts, enabling the field to move beyond ill-defined, in situ-generated species for which the nature of the catalytic active species was unknown.

1.2.2 Olefin metathesis catalysts

Much subsequent research has gone into preparing, isolating, and characterizing metal carbene complexes. One of the earliest examples was reported by Casey and Burkhardt²⁵ in 1973. A tungsten carbene and 1-methoxy-1-phenylethylene reacted – albeit stoichiometrically – to give a product in which one fragment of an incoming alkene forms part of a new olefin, the other fragment is indeed incorporated into a new metal carbene complex: both the expected olefin and new stable carbene complex were observed.²⁶ Schrock's stunning advances in the synthesis of tantalum (Ta) and niobium (Nb)

alkylidenes^{24,27,28} were noted above. In subsequent work, continuing over decades (and recognized with the 2005 Nobel Prize), he spearheaded the development of highly active and selective group 6 molybdenum (Mo) and tungsten (W) alkylidene catalysts. Of particular note is a series of very effective molybdenum-imido complexes, **Mo-1a-c** (Figure 1.3).^{5,29-31} The high oxophilicity of these catalysts, however, results in high sensitivity to air, moisture, and a few functional groups including aldehydes, alcohols, and carboxylic acids.^{5,32,33} For those not skilled in anaerobic experimental techniques, these complexes are therefore challenging to handle.

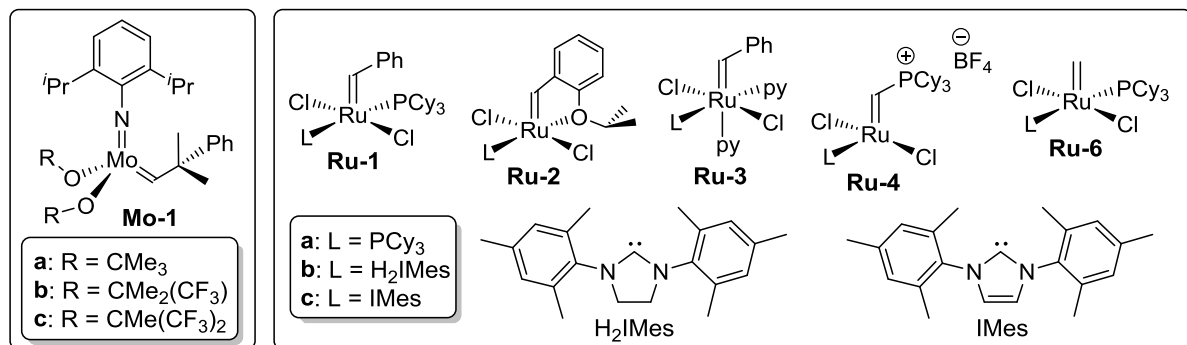


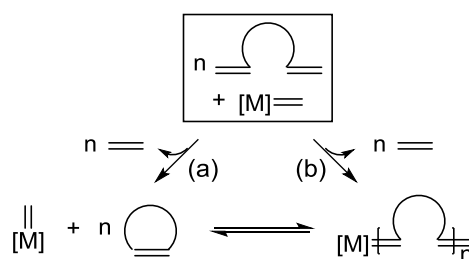
Figure 1.3 Common molybdenum and ruthenium catalysts used in olefin metathesis.

Ruthenium catalysts have emerged as a popular alternative due to their greater stability towards oxygen and water, and their functional group tolerance (Figure 1.3).³² Since Grubbs' discovery of the first-generation catalyst **Ru-1a** in 1992,³⁴ much attention has turned to the development of more reactive ruthenium metathesis catalysts. Many key advances were reported by Grubbs, later co-winner of the Nobel Prize, with Schrock and Chauvin. A particular breakthrough came in 1999, with the introduction of the so-called "second-generation" catalysts, synthesized by replacing one PCy₃ ligand with an *N*-heterocyclic carbene (NHC).³⁵⁻³⁷ In addition to increased catalytic activity, the precatalysts were found to display higher thermal stability than **Ru-1a**.³⁵ The most well studied examples contain H₂IMes (**Ru-1b**) and IMes (**Ru-1c**) ligands. The NHC ligand is more strongly bound, and metathesis therefore requires loss of the PCy₃ ligand. The Hoveyda catalysts are a phosphine-free variant bearing an *o*-ether group on the benzylidene moiety (**Ru-2**).³⁸⁻⁴⁰ Also important, especially in ROMP, are the pyridine derivatives **Ru-3** (the third-generation Grubbs catalysts; Figure 1.3).^{41,42} Higher catalyst activity results from the lability of the

pyridine ligand.^{42,43} In the extreme, the Piers phosphonium complexes **Ru-4**⁴⁴ contain no placeholder ligand. This eliminates the need for an initiation step involving loss of PCy₃, the ether donor, or pyridine: as a result, the first-generation Piers catalyst is active even at 0 °C, while its second-generation derivative turns on even at -50 °C.^{19,45} Other modifications include replacing the chloride groups with pseudohalide ligands such as aryloxides.⁴⁶⁻⁴⁹ While all of these catalysts offer advantages in specific metathesis reactions,^{50,51} **Ru-1** and **Ru-2** are most commonly used in organic synthesis, due to their commercial availability.

1.2.3 Ring-closing metathesis (RCM)

Ruthenium-catalyzed RCM is a very powerful method for the synthesis of macrocyclic products, which has recently come to high prominence in pharmaceutical research.⁵²⁻⁵⁸ RCM is an entropy-driven process in which ring strain dictates the probability of cyclization. Common ring sizes (5-6 and some 7-membered rings) have minimum strain energy, and are generally accessible by direct RCM (Scheme 1.2, path a). Ring strain increases drastically in the medium-ring regime, and then declines as ring size increases (remaining higher than in common rings).^{59,60} Oligomerization commonly competes with cyclization in this ring size. This has been widely viewed as a kinetic issue, but recent work has demonstrated that for the suitably reactive catalysts, the selectivity is thermodynamically controlled.⁶¹



Scheme 1.2 Simplified RCM equilibria resulting from irreversible loss of ethylene. (a) Direct RCM. (b) Oligomerization-backbiting pathway.

While olefin metathesis is in principle reversible, access to equilibria can be restricted by formation of unreactive or volatile products. In diene metathesis, loss of ethylene acts as a driving force, albeit one that does not select for RCM or oligomerization. This simplifies the set of accessible equilibria to that shown in Scheme 1.2.⁶¹ When oligomers are produced, the cyclic product can still be obtained if the catalyst is capable of backbiting at an internal, 1,2-

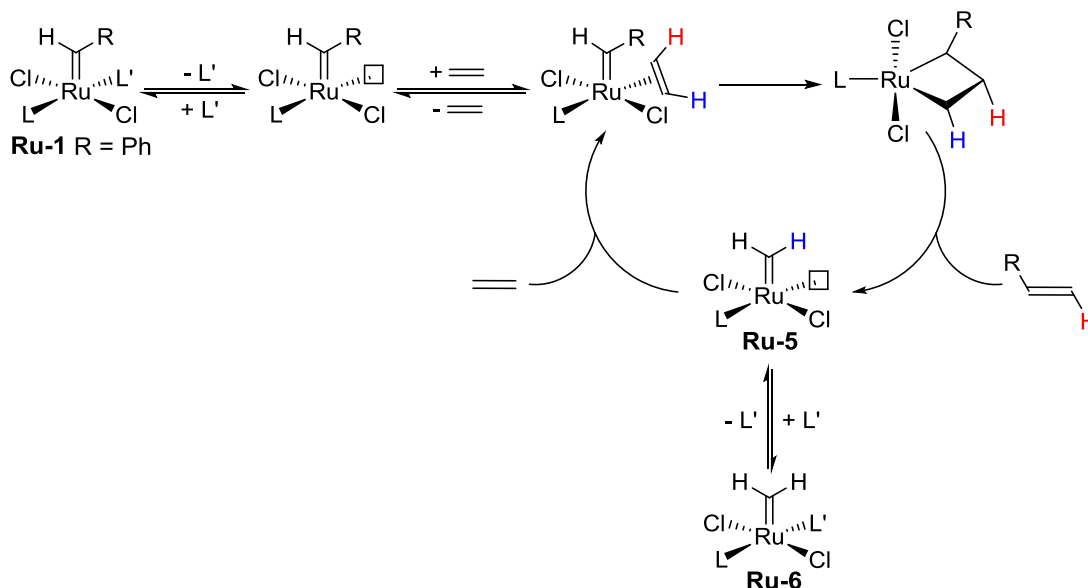
disubstituted olefin. This results in a concentration-dependent equilibrium.⁶² For a number of key catalysts, RCM was shown to proceed via an oligomerization-backbiting pathway (Scheme 1.2, path b). Importantly, the equilibrium lies in favour of oligomers if concentrations are excessive (for macrolactones, above ca. 5 mM). As ring strain increases, higher dilutions are required to shift the equilibrium towards RCM products. When performing an RCM macrocyclization, concentration is a key parameter: as well, however, the reaction must be left for a sufficient time for it to reach equilibrium.⁶¹⁻⁶³

In RCM macrocyclization reactions, the first-generation Grubbs catalyst **Ru-1a** exhibits a kinetic bias toward direct RCM (Scheme 1.2, path a).⁶¹ This is fortuitous, as it has limited ability to attack at internal olefins, as required to recycle the oligomers. In contrast, the second-generation catalysts (e.g. **Ru-1b/c**, **Ru-2b/c** and **Ru-3b/c**) exhibit a strong kinetic bias towards diene oligomerization, for reasons that are still poorly understood: these catalysts operate via equilibrium RCM.⁶⁴ However, they have a much broader substrate scope than **Ru-1a**.

1.2.4 Mechanism of ruthenium-catalyzed olefin metathesis

Mechanistic understanding is crucial to advancing the state of the art in metathesis. For the square pyramidal Grubbs catalysts, initiation involves a dissociative mechanism, outlined in Scheme 1.3.^{43,65,66} Initiation and ensuing rates of metathesis are then independent of olefin concentration. For the first- and second-generation Grubbs catalysts **Ru-1**, the rate-limiting step involves loss of PCy₃ from the basal plane, to give an empty coordination site cis to the ruthenium alkylidene. The resulting 14-electron active species can either (i) re-bind PCy₃, regenerating the precatalyst, (ii) react with olefin, entering the catalytic cycle, or (iii) decompose. Re-coordination of PCy₃ is most common with first-generation catalyst **Ru-1a** due to its low commitment nature. The NHC catalysts **Ru-1b** and **Ru-1c** have a higher commitment towards reaction with olefin.^{43,65,67} Coordination of an olefin enables productive metathesis: once bound, the olefin undergoes [2+2] cycloaddition to form the metallocyclobutane intermediate. Retro-addition forms a new olefin product and generates the 14-electron active species **Ru-5**, allowing the catalyst cycle to repeat. During the reaction, PCy₃ can re-bind to the active catalyst generating the methylidene complex **Ru-6** as a thermodynamic resting state. This species can re-enter the catalytic cycle, however, due to

its very low phosphine lability, **Ru-6** resists re-uptake.⁴³ The resting methylidene species also has a short lifetime and at 55 °C (C₆D₆), the half-life of **Ru-6a** is 40 min and **Ru-6b** is <6 h, compared to over a month for the benzylidene equivalent, **Ru-1b**.⁶⁸ In addition to the resting state methylidenes, any ruthenium species throughout the cycle can undergo decomposition; however, the most vulnerable include the 14-electron active species and the metallocyclobutane intermediate.



Scheme 1.3 The dissociative mechanism for olefin metathesis with Grubbs catalysts **Ru-1**.

In the Hoveyda catalysts **Ru-2**, as noted above, the labile ligand is the chelating ether. The active species **Ru-5** is the same as the Grubbs catalyst and metathesis of course still proceeds through a metallocyclobutane intermediate. Recent evidence, however, indicates that **Ru-2b** operates via a different mechanism of initiation than the Grubbs systems.⁶⁹⁻⁷² Interchange-associative activation is seen for electron-rich and sterically less demanding olefins.⁷⁰ Therefore, both the nature and concentration of the olefin influence the rate of initiation. Bulkier or less electron-rich olefins follow the dissociative pathway, and initiation / metathesis rates are then concentration-independent. In addition, modifications to the electronic and steric character of the styrenyl ether ligand can play a major role in the rate of initiation.⁷³⁻⁸⁴ Due to the absence of a labile PCy₃ ligand in the Hoveyda catalysts **Ru-2**, the resting state for these complexes is no longer the methylidene species **Ru-6**. It has been suggested that following metathesis, the active species **Ru-5** can recapture the styrenyl ether,

regenerating the precatalyst **Ru-2** and thus allowing these catalysts to be recyclable. This is known as the “boomerang” or release-return mechanism, and will be discussed in more detail in Chapter 3.

1.3 Decomposition of Grubbs-type catalysts

Although ruthenium is less oxophilic than earlier metals, the active species **Ru-5** is still decomposed by air.⁸⁵⁻⁸⁹ Alcohols or, particularly, alkoxides,⁹⁰ also trigger decomposition. When the benzyldiene catalysts react with methoxide, a hydride is generated and the alkylidene fragment is lost as toluene.⁹⁰ For the second-generation catalysts, the resting-state methylidene species **Ru-6** decomposes by attack of the liberated phosphine on the methylidene functionality, generating a bimolecular hydride, **Ru-7**, and $[\text{CH}_3\text{PCy}_3]\text{Cl}$.^{68,91} Our group⁹² has also shown that amines can attack the alkylidene functionality, for both the first- and second-generation catalysts **Ru-1**. Only primary amines attack the benzyldiene functionality directly.⁹² For the methylidene catalysts **Ru-6**, amine liberates free PCy_3 through ligand exchange, which is then available to attack the methylidene carbon. Other known decomposition pathways of the Grubbs-type catalysts include C-H bond activation with the alkylidene,⁹³⁻⁹⁵ and reaction with small molecules, such as CO and ethylene, during catalysis.^{96,97} The latter is a co-product in some reactions and can cause non-productive (degenerate) metathesis. This ultimately affects reaction rate and yield, as well as increasing the amount of time the catalyst spends in a vulnerable state, and hence leading to a greater chance of decomposition.^{68,98-102}

1.4 Scope of this thesis

Understanding current metathesis catalysts is essential to advancing the state of the art, as well as designing more efficient methods and active catalysts to promote a desired olefin metathesis transformation. Experimental methods used in this thesis are described in Chapter 2. Chapter 3 presents a new analysis of the much-debated “boomerang” mechanism, which could enable recycling of the Hoveyda catalyst **Ru-2b**. Chapter 4 examines a major current problem in olefin metathesis: controlling the stereoselectivity of the reaction. Many researchers have designed catalysts to promote Z-selective olefin metathesis and great strides have been made for molybdenum and tungsten catalysts in the last several years. However, improvements are still necessary for the selectivity in ruthenium-based systems. Chapter 4 of

this thesis focuses on examining two different catalysts in which a chloride ligand has been replaced by a more bulky arylthiolate. It was hoped that enough pressure would be applied on the metallocyclobutane to produce the desired Z-isomer in RCM macrocyclization. Chapter 5 provides an overview of the key findings as well as suggestions for future directions.

1.5 References

- (1) van der Hoeven, M.; Kobayashi, Y.; Diercks, R. *Technology Roadmap: Energy and GHG Reductions in the Chemical Industry via Catalytic Processes*; Technical report for International Energy Agency, International Council of Chemical Associations and DECHEMA; Corlet: France, May 2013.
- (2) Thayer, A. M. *Chem. Eng. News* **2013**, 91, 68.
- (3) All Nobel Prizes in Chemistry.
http://www.nobelprize.org/nobel_prizes/chemistry/laureates/ (accessed Sept. 8, 2013).
- (4) Grubbs, R. H. *Angew. Chem. Int. Ed.* **2006**, 45, 3760–3765.
- (5) Schrock, R. R. *Angew. Chem. Int. Ed.* **2006**, 45, 3748–3759.
- (6) Chauvin, Y. *Angew. Chem. Int. Ed.* **2006**, 45, 3741–3747.
- (7) Rothenberg, G., *Catalysis*. Wiley-VCH: Weinheim, 2008; p 279.
- (8) Sheldon, R. A. *Green Chem.* **2007**, 9, 1273–1283.
- (9) Anastas, P. T.; Kirchhoff, M. M. *Acc. Chem. Res.* **2002**, 35, 686–694.
- (10) Anastas, P. T.; Warner, J. C., *Green Chemistry: Theory and Practice*. Oxford University Press: New York, 1998.
- (11) Anderson, A. W.; Merckling, N. G. Polymeric bicyclo[2.2.1]hept-2-ene. U.S. Patent No. 2721189, 1955.
- (12) Eleuterio, H. S. *J. Mol. Catal.* **1991**, 65, 55–61.
- (13) Banks, R. L.; Bailey, G. C. *Ind. Eng. Chem. Prod. Res. Dev.* **1964**, 3, 170–173.
- (14) Calderon, N.; Chen, H. Y.; Scott, K. W. *Tetrahedron Lett.* **1967**, 3327–3329.
- (15) Calderon, N.; Ofstead, E. A.; Ward, J. P.; Judy, W. A.; Scott, K. W. *J. Am. Chem. Soc.* **1968**, 90, 4133–4140.
- (16) Lewandos, G. S.; Pettit, R. *J. Am. Chem. Soc.* **1971**, 93, 7087–7088.
- (17) Grubbs, R. H.; Brunck, T. K. *J. Am. Chem. Soc.* **1972**, 94, 2538–2540.
- (18) Hérisson, J. L.; Chauvin, Y. *Makromol. Chem.* **1971**, 141, 161–176.
- (19) Romero, P. E.; Piers, W. E. *J. Am. Chem. Soc.* **2005**, 127, 5032–5033.
- (20) Katz, T. J.; McGinnis, J. *J. Am. Chem. Soc.* **1975**, 97, 1592–1594.
- (21) Katz, T. J.; Rothchild, R. *J. Am. Chem. Soc.* **1976**, 98, 2519–2526.
- (22) Grubbs, R. H.; Burk, P. L.; Carr, D. D. *J. Am. Chem. Soc.* **1975**, 97, 3265–3267.
- (23) Grubbs, R. H.; Carr, D. D.; Hoppin, C.; Burk, P. L. *J. Am. Chem. Soc.* **1976**, 98, 3478–3483.
- (24) Schrock, R.; Rocklage, S.; Wengrovius, J.; Rupprecht, G.; Fellmann, J. *J. Mol. Catal.* **1980**, 8, 73–83.
- (25) Casey, C. P.; Burkhardt, T. J. *J. Am. Chem. Soc.* **1973**, 95, 5833–5834.
- (26) Casey, C. P.; Burkhardt, T. J. *J. Am. Chem. Soc.* **1974**, 96, 7808–7809.
- (27) Schrock, R. R. *J. Am. Chem. Soc.* **1974**, 96, 6796–6797.
- (28) Schrock, R. R. *Acc. Chem. Res.* **1979**, 12, 98–104.

- (29) Wengrovius, J. H.; Schrock, R. R.; Churchill, M. R.; Missert, J. R.; Youngs, W. J. *J. Am. Chem. Soc.* **1980**, *102*, 4515–4516.
- (30) Schrock, R. R.; DePue, R. T.; Feldman, J.; Schaverien, C. J.; Dewan, J. C.; Liu, A. H. *J. Am. Chem. Soc.* **1988**, *110*, 1423–1435.
- (31) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. J. *Am. Chem. Soc.* **1990**, *112*, 3875–3886.
- (32) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29.
- (33) Armstrong, S. K. *J. Chem. Soc., Perkin Trans.* **1998**, 371–388.
- (34) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3974–3975.
- (35) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247–2250.
- (36) Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674–2678.
- (37) Weskamp, T.; Kohl, F. J.; Hieringer, W.; Gleich, D.; Herrmann, W. A. *Angew. Chem. Int. Ed.* **1999**, *38*, 2416–2419.
- (38) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791–799.
- (39) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.
- (40) Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973–9976.
- (41) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *Organometallics* **2001**, *20*, 5314–5318.
- (42) Love, J. A.; Morgan, J. P.; Trnka, T. M.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2002**, *41*, 4035–4037.
- (43) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543–6554.
- (44) Romero, P. E.; Piers, W. E.; McDonald, R. *Angew. Chem. Int. Ed.* **2004**, *43*, 6161–6165.
- (45) Romero, P. E.; Piers, W. E. *J. Am. Chem. Soc.* **2007**, *129*, 1698–1704.
- (46) Conrad, J. C.; Amoroso, D.; Czechura, P.; Yap, G. P. A.; Fogg, D. E. *Organometallics* **2003**, *22*, 3634–3636.
- (47) Conrad, J. C.; Parnas, H. H.; Snelgrove, J. L.; Fogg, D. E. *J. Am. Chem. Soc.* **2005**, *127*, 11882–11883.
- (48) Monfette, S.; Fogg, D. E. *Organometallics* **2006**, *25*, 1940–1944.
- (49) Monfette, S.; Camm, K. D.; Gorelsky, S. I.; Fogg, D. E. *Organometallics* **2009**, *28*, 944–946.
- (50) Ritter, T.; Hejl, A.; Wenzel, A. G.; Funk, T. W.; Grubbs, R. H. *Organometallics* **2006**, *25*, 5740–5745.
- (51) Bieniek, M.; Michrowska, A.; Usanov, D. L.; Grela, K. *Chem. Eur. J.* **2008**, *14*, 806–818.
- (52) 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.
- (53) Machauer, R.; Veenstra, S.; Rondeau, J.-M.; Tintelnot-Blomley, M.; Betschart, C.; Neumann, U.; Paganetti, P. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1361–1365.
- (54) Liverton, N. J.; Holloway, M. K.; McCauley, J. A.; Rudd, M. T.; Butcher, J. W.; Carroll, S. S.; DiMuzio, J.; Fandozzi, C.; Gilbert, K. F.; Mao, S.-S.; McIntyre, C. J.; Nguyen,

- K. T.; Romano, J. J.; Stahlhut, M.; Wan, B.-L.; Olsen, D. B.; Vacca, J. P. *J. Am. Chem. Soc.* **2008**, *130*, 4607–4609.
- (55) McCauley, J. A.; Rudd, M. T.; Nguyen, K. T.; McIntyre, C. J.; Romano, J. J.; Bush, K. J.; Varga, S. L.; Ross, C. W., III; Carroll, S. S.; DiMuzio, J.; Stahlhut, M. W.; Olsen, D. B.; Lyle, T. A.; Vacca, J. P.; Liverton, N. J. *Angew. Chem. Int. Ed.* **2008**, *47*, 9104–9107.
- (56) Song, Z. J.; Tellers, D. M.; Journet, M.; Kuethe, J. T.; Lieberman, D.; Humphrey, G.; Zhang, F.; Peng, Z.; Waters, M. S.; Zewge, D.; Nolting, A.; Zhao, D.; Reamer, R. A.; Dormer, P. G.; Belyk, K. M.; Davies, I. W.; Devine, P. N.; Tschaen, D. M. *J. Org. Chem.* **2011**, *76*, 7804–7815.
- (57) Kong, J.; Chen, C.-y.; Balsells-Padros, J.; Cao, Y.; Dunn, R. F.; Dolman, S. J.; Janey, J.; Li, H.; Zacuto, M. J. *J. Org. Chem.* **2012**, *77*, 3820–3828.
- (58) Farina, V.; Shu, C.; Zeng, X.; Wei, X.; Han, Z.; Yee, N. K.; Senanayake, C. H. *Org. Process Res. Dev.* **2009**, *13*, 250–254.
- (59) Schleyer, P. V. R.; Williams, J. E.; Blanchard, K. R. *J. Am. Chem. Soc.* **1970**, *92*, 2378–2386.
- (60) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95–102.
- (61) Monfette, S.; Fogg, D. E. *Chem. Rev.* **2009**, *109*, 3783–3816.
- (62) 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.
- (63) Monfette, S.; Crane, A. K.; Duarte Silva, J. A.; Facey, G. A.; dos Santos, E. N.; Araujo, M. H.; Fogg, D. E. *Inorg. Chim. Acta* **2010**, *363*, 481–486.
- (64) Monfette, S. Exploration of Ligand Effects, Substrate Effects and Reactor Effects on Macrocyclization via Ring-Closing Metathesis: A Rational Approach to Efficient Cyclization. Ph.D. Dissertation, University of Ottawa, Ottawa, ON, 2010.
- (65) Sanford, M. S.; Ulman, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 749–750.
- (66) Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887–3897.
- (67) Adlhart, C.; Chen, P. *Helv. Chim. Acta* **2003**, *86*, 941–949.
- (68) Hong, S. H.; Wenzel, A. G.; Salguero, T. T.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2007**, *129*, 7961–7968.
- (69) Vorfalt, T.; Wannowius, K. J.; Plenio, H. *Angew. Chem. Int. Ed.* **2010**, *49*, 5533–5536.
- (70) Thiel, V.; Hendann, M.; Wannowius, K.-J. r.; Plenio, H. *J. Am. Chem. Soc.* **2012**, *134*, 1104–1114.
- (71) Ashworth, I. W.; Hillier, I. H.; Nelson, D. J.; Percy, J. M.; Vincent, M. A. *Chem. Comm.* **2011**, *47*, 5428–5430.
- (72) Ashworth, I. W.; Hillier, I. H.; Nelson, D. J.; Percy, J. M.; Vincent, M. A. *ACS Catal.* **2013**, *3*, 1929–1939.
- (73) Wakamatsu, H.; Blechert, S. *Angew. Chem. Int. Ed.* **2002**, *41*, 794–796.
- (74) Wakamatsu, H.; Blechert, S. *Angew. Chem. Int. Ed.* **2002**, *41*, 2403–2405.
- (75) Zaja, M.; Connon, S. J.; Dunne, A. M.; Rivard, M.; Buschmann, N.; Jiricek, J.; Blechert, S. *Tetrahedron* **2003**, *59*, 6545–6558.
- (76) Grela, K.; Harutyunyan, S.; Michrowska, A. *Angew. Chem. Int. Ed.* **2002**, *41*, 4038–4040.
- (77) Michrowska, A.; Bujok, R.; Harutyunyan, S.; Sashuk, V.; Dolgonos, G.; Grela, K. *J. Am. Chem. Soc.* **2004**, *126*, 9318–9325.
- (78) Dunne, A. M.; Mix, S.; Blechert, S. *Tetrahedron Lett.* **2003**, *44*, 2733–2736.
- (79) Gulajski, L.; Michrowska, A.; Bujok, R.; Grela, K. *J. Mol. Catal. A* **2006**, *254*, 118–123.

- (80) Grela, K.; Kim, M. *Eur. J. Org. Chem.* **2003**, 963–966.
- (81) Rix, D.; Caijo, F.; Laurent, I.; Boeda, F.; Clavier, H.; Nolan, S. P.; Mauduit, M. *J. Org. Chem.* **2008**, 73, 4225–4228.
- (82) Connon, S. J.; Rivard, M.; Zaja, M.; Blechert, S. *Adv. Synth. Catal.* **2003**, 345, 572–575.
- (83) Buschmann, N.; Wakamatsu, H.; Blechert, S. *Synlett* **2004**, 667–670.
- (84) Maechling, S.; Zaja, M.; Blechert, S. *Adv. Synth. Catal.* **2005**, 347, 1413–1422.
- (85) Dinger, M. B.; Mol, J. C. *Organometallics* **2003**, 22, 1089–1095.
- (86) Dinger, M. B.; Mol, J. C. *Eur. J. Inorg. Chem.* **2003**, 2827–2833.
- (87) Banti, D.; Mol, J. C. *J. Organomet. Chem.* **2004**, 689, 3113–3116.
- (88) 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.
- (89) Beach, N. J.; Camm, K. D.; Fogg, D. E. *Organometallics* **2010**, 29, 5450–5455.
- (90) Beach, N. J.; Lummiss, J. A. M.; Bates, J. M.; Fogg, D. E. *Organometallics* **2012**, 31, 2349–2356.
- (91) Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2004**, 126, 7414–7415.
- (92) Lummiss, J. A. M.; Ireland, B. J.; Sommers, J. M.; Fogg, D. E. *ChemCatChem* **2013**, Early View.
- (93) Hong, S. H.; Chlenov, A.; Day, M. W.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2007**, 46, 5148–5151.
- (94) Vehlouw, K.; Gessler, S.; Blechert, S. *Angew. Chem. Int. Ed.* **2007**, 46, 8082–8085.
- (95) Leitao, E. M.; Dubberley, S. R.; Piers, W. E.; Wu, Q.; McDonald, R. *Chem. Eur. J.* **2008**, 14, 11565–11572.
- (96) Galan, B. R.; Gembicky, M.; Dominiak, P. M.; Keister, J. B.; Diver, S. T. *J. Am. Chem. Soc.* **2005**, 127, 15702–15703.
- (97) Galan, B. R.; Pitak, M.; Gembicky, M.; Keister, J. B.; Diver, S. T. *J. Am. Chem. Soc.* **2009**, 131, 6822–6832.
- (98) van Rensburg, W. J.; Steynberg, P. J.; Meyer, W. H.; Kirk, M. M.; Forman, G. S. *J. Am. Chem. Soc.* **2004**, 126, 14332–14333.
- (99) Lysenko, Z.; Maughon, B. R.; Mokhtar-Zadeh, T.; Tulchinsky, M. L. *J. Organomet. Chem.* **2006**, 691, 5197–5203.
- (100) 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.
- (101) Monfette, S.; Eyholzer, M.; Roberge, D. M.; Fogg, D. E. *Chem. Eur. J.* **2010**, 16, 11720–11725.
- (102) Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, 64, 7202–7207.

2. Experimental Methods

2.1 General procedures

2.1.1 Reaction conditions

Reactions were carried out under N₂ (BOC Gases, industrial grade) in an MBraun glovebox or using standard Schlenk techniques unless otherwise stated. The N₂ stream was dried by passage through a column of activated (blue) Drierite. All glassware was cleaned and oven-dried prior to use (150 °C) and allowed to cool under vacuum. Flash column chromatography was carried out in air using silica gel (60 Å, Aldrich) as the stationary phase.

2.1.2 Reagents

Reagents were used as received with the exception of olefin substrates and 1,2,3,4-tetrahydronaphthalene (THN), which were degassed as described below. Hydrated ruthenium trichloride, magnesium turnings (99.9+%), *n*-butyllithium (2.5 M solution in hexanes, AcroSeal®), methyltriphenylphosphonium bromide (98%), and 2,4,6-trimethylaniline (97%) were purchased from Acros Organics. Triphenylphosphine (99%) and tricyclohexylphosphine (97%) were purchased from Strem Chemicals. Benzaldehyde (>99%), triethylene glycol (99%), sodium hydride (95%), formic acid (>95%), tetrafluoroboric acid solution (48 wt % in H₂O), triphenylphosphine oxide (98%), 1,3,5-trimethoxybenzene (≥99%), 1,2,3,4-tetrahydronaphthalene (anhydrous, 99%), *trans*-anethole **12** (99%), methyl acrylate **13** (99%, with ≤100 ppm monomethyl ether hydroquinone as inhibitor), 10-undecenoyl chloride (97%), 5-hexen-1-ol (98%), diethyl diallylmalonate **14** (98%), 5-bromo-1-pentene (95%), *N,N*-dimethylformamide (anhydrous, 99.8%), Amberlyst® 15 hydrogen form (dry), sodium borohydride (purum p.a., ≥96%), glyoxal solution (40 wt % in H₂O), phosphorus pentoxide (powder, ACS reagent, ≥98%), iodine (ACS reagent, ≥99.8%), and decane (anhydrous, ≥99%) were purchased from Aldrich. Pyridine (anhydrous, >99.5%), *p*-toluenesulfonyl hydrazine (98%), triethylorthoformate (98%), 1-bromo-2-isopropoxybenzene (97%), and methacrolein (96%, stabilized with hydroquinone) were purchased from Alfa Aesar. ¹³C-Labeled *N,N*-dimethylformamide (Me₂N¹³CHO, 99%) was purchased from Cambridge Isotope Laboratories, Inc., potassium

tris(pyrazolyl)borate from TCI Chemicals (>97%), and dimethyl terephthalate from Matheson Coleman & Bell. Compounds **Ru-9** and **Ru-10a** were kindly provided by Vidar Jensen (University of Bergen) in collaborative work.

Methyltriphenylphosphonium bromide (MePPh₃Br) was dried under vacuum for 12 h prior to use. In certain experiments performed to synthesize second-generation catalysts (vide infra), Amberlyst 15 resin was used off-the-shelf to hydrolyze and remove the excess H₂IMes **9**; in others it was dried by heating under vacuum for 12 h, prior to storage in the glovebox. All liquid substrates such as 2-methylocta-1-7-dien-3-ol **1**, hex-5-enyl undec-10-enoate **2**, 2-isopropoxystyrene **11** and **11***, *trans*-anethole **12**, methyl acrylate **13**, and dimethyl diallylmalonate **14** were subjected to five consecutive freeze-pump-thaw degassing cycles prior to storage in the glovebox freezer (−35 °C) where they were protected from light. THN, used as an internal standard in gas chromatography (GC) experiments, was pre-dried over MgSO₄ for 12 h, then refluxed over sodium benzophenone ketyl for 6 h prior to distillation.

2.1.3 Solvents

Oxygen- and water-free hexanes, toluene, C₆H₆, CH₂Cl₂, THF, and Et₂O were obtained using a Glass Contour or Anhydrous Engineering solvent purification system, and stored in the glovebox. Other solvents were purified and degassed by standard distillation methods:¹ methanol from magnesium and iodide, and acetone from Drierite. Pentane (Fisher ACS grade) and 1,2-dichloroethane (DCE, Fisher ACS grade) were pre-dried over MgSO₄ (12 h) then refluxed over phosphorus pentoxide (6 h) prior to distillation. All solvents were stored in the glovebox over activated Linde 4 Å molecular sieves, except methanol (3 Å sieves), 1,2-dichloroethane (5 Å sieves; amber bottle), and acetone, which was not stored over sieves.

2.1.4 Deuterated solvents

Deuterated solvents (Cambridge Isotope Laboratories, Ltd. or Aldrich) were used as received for NMR analysis of air-stable species. Deuterated solvents, used for analysis of oxygen- or moisture-sensitive compounds, were dried and degassed. C₆D₆ was degassed by five freeze-pump-thaw cycles and CDCl₃ was distilled from CaH₂ or degassed by five freeze-pump-thaw cycles and stored in an amber bottle in the glovebox. All other NMR solvents were stored as

described in Section 2.1.3 above. To prevent contamination of the NMR solvents, the glovebox atmosphere was purged to remove vapors prior to opening these storage vessels.

2.1.5 NMR spectroscopy

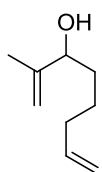
^1H (300, 400, 500 MHz), $^{13}\text{C}\{^1\text{H}\}$ (75 or 125 MHz), and $^{31}\text{P}\{^1\text{H}\}$ (121 or 202 MHz) NMR spectra were recorded on Bruker Avance-300, Avance-400 or Avance-500 spectrometers at 298 K. Spectra were referenced to the residual proton or carbon signals of the deuterated solvent (^1H , ^{13}C NMR) or externally to 85% H_3PO_4 (^{31}P) at 0 ppm. Spectra of organometallic compounds were measured under anaerobic conditions in NMR tubes equipped with J-Young valves or Rotoflo NMR tubes with PTFE/silicon septum caps.

2.1.6 Gas chromatography

Gas chromatography (GC) was performed on an Agilent 6890 or 7890A Series GC-FID, each equipped with an Agilent 7683 Series autosampler. For optimal separation, a chemically-bonded Varian CP-wax 52 CB carbowax column was used for analysis of polar compounds, e.g. hex-5-en-1-yl undec-10-enoate **2**, and an Agilent HP-5 polysiloxane column was used for compounds that require high temperatures to elute (e.g. stilbene **27**). Both columns were 30 m in length and 320 μm in diameter. Both contained an inlet split ratio of 10:1, an inlet temperature of 250 $^\circ\text{C}$ with helium (UHP grade) as the carrier gas to maintain column pressure at 11.512 psi. The FID response was maintained between 50-2000 μA , using analyte concentrations of ca. 5 mM. Retention times for dienes and products were confirmed with samples authenticated by GC-MS and NMR analysis. GC-FID quantification was established by constructing calibration curves of peak area vs. concentration in the relevant concentration regime, to account for the dependence on detector response for substrates, products, 1,2,3,4-tetrahydronaphthalene (THN), and decane. Both THN and decane were used as internal GC standards. Yields in catalytic runs were determined from the integrated peak areas, referenced against decane or THN, and compared to the initial integration ratio of substrate : internal standard. For RCM macrocyclization reactions, oligomers cannot be observed by GC as they are involatile, therefore oligomer yields were determined by difference.

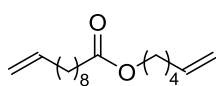
2.2 Synthesis of substrates

2.2.1 2-Methylocta-1,7-dien-3-ol **1**²



Synthesis of known compound **1** was performed under N₂ according to a literature method,² with slight modification to the work-up as noted below. A three-neck round-bottomed flask was loaded with Mg turnings (0.82 g, 0.034 mmol). Dry Et₂O (30 mL) was transferred by cannula into the flask (Flask A), and a crystal of I₂ was added. The orange solution was placed in a 45 °C oil bath. Neat 5-bromo-1-pentene (2 mL, 0.017 mmol) was added via an equalized-pressure dropping funnel over 30 min to afford a clear, colourless solution. This was heated at reflux for 1 h. A second three-neck round-bottomed flask (Flask B) was attached to the Schlenk line and methacrolein (2 mL, 0.024 mmol, 1.4 equiv) was added by syringe. Dry Et₂O (3 mL) was transferred by cannula to the flask and it was cooled to –15 °C in a NaCl/crushed ice bath. The Grignard solution in Flask A was cooled to RT and cannula filtered into the methacrolein solution (Flask B) over 20 min using a PTFE cannula with a glass microfibre filter on the end. The solution was stirred at –15 °C for 30 min, after which it was warmed to RT over 2.5 h. The reaction was quenched by pouring into a beaker containing crushed ice with saturated NH₄Cl (50 mL). To this was added 2 M HCl (50 mL) and the aqueous layer was extracted with EtOAc (4 × 40 mL). The combined organic layers were washed with brine (1 × 80 mL) and distilled water (1 × 80 mL), then dried over MgSO₄ and filtered. The solvent was then removed under vacuum and the crude product was purified by column chromatography (SiO₂; 10% EtOAc:hexanes; R_f = 0.18). Yield: 1.014 g (43%). ¹H NMR spectroscopy data were consistent with literature values.² ¹H NMR (CDCl₃, 300 MHz): δ 5.80 (m, 1H, CH=CH₂), 5.04 (m, 1H, =CH₂), 4.98 (m, 1H, =CH₂), 4.94 (m, 1H, =CH₂), 4.83 (m, 1H, =CH₂), 4.07 (t, ³J_{HH} = 6.2 Hz, 1H, CHOH), 2.08 (m, 2H, CH₂CHOH), 1.72 (s, 3H, CH₃), 1.60-1.33 (m, 4H, CH₂CH₂CH). The OH signal was not observed.

2.2.2 Hex-5-enyl undec-10-enoate **2**

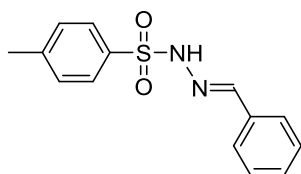


To a round-bottomed flask was added dry CH₂Cl₂ (150 mL), pyridine (20 mL), and 5-hexen-1-ol (3 mL, 0.026 mmol). By syringe, 10-undecenoyl chloride (5.4 mL, 0.025 mmol, 1 equiv) was added slowly. The solution was stirred under N₂ for 16 h at RT, after which the solvent was evaporated under vacuum. The white solid was

dissolved in hexanes (100 mL) and distilled water (50 mL) was added. The aqueous layer was extracted with hexanes (2 × 50 mL) and the combined organic layers were washed with 5% HCl (3 × 75 mL), saturated NaHCO₃ (3 × 50 mL), brine (1 × 50 mL), and distilled water (1 × 50 mL). The organic extract was then dried with MgSO₄ and filtered. The crude product was concentrated to a clear, colourless oil and purified by column chromatography (SiO₂; 5% EtOAc:hexanes; R_f = 0.38). Yield: 5.924 g (89%). Due to the complexity of the aliphatic region, only key ¹H NMR spectroscopy values are given here. ¹H NMR (CDCl₃, 300 MHz): δ 5.87-5.73 (m, 2H, =CH), 5.05-4.90 (m, 4H, =CH₂), 4.07 (t, ³J_{HH} = 6.6 Hz, 2H, OCH₂).

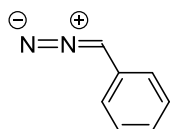
2.3 Synthesis of ligands

2.3.1 *N*-Tosylhydrazone **3**³



Reaction carried out in air. A scaled-up version of the published procedure³ is given, with slight modification as the solution was heated to dissolve all *p*-toluenesulfonylhydrazide prior to the addition of benzaldehyde. A 500 mL round-bottomed flask with a stirred suspension of *p*-toluenesulfonylhydrazide (50.3 g, 0.270 mol) in MeOH (300 mL) was placed in a 40 °C oil bath. Once the solid was dissolved, the yellow solution was cooled to RT and benzaldehyde was added (28.7 g, 0.270 mol, 1 equiv). The reaction mixture was placed in an ice bath and a white precipitate began to form. The solid was filtered, washed with cold hexanes, and dried under vacuum. The filtrate was concentrated under vacuum to afford a second crop of the desired **3**. Yield: 66.65 g (90%). ¹H NMR (CDCl₃, 300 MHz): δ 8.03 (br s, 1H, NH), 7.88 (d, ³J_{HH} = 8.3 Hz, 2H, ArH), 7.77 (s, 1H, CH), 7.59-7.56 (m, 2H, ArH), 7.38-7.30 (m, 5H, ArH), 2.40 (s, 3H, CH₃).

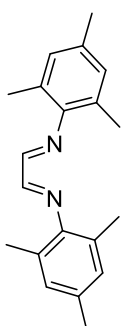
2.3.2 Phenyl diazomethane **4**³



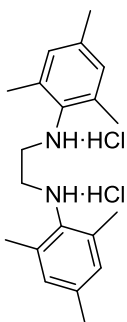
Reaction carried out in air. The product was kept for a maximum of 3 h before use. Synthesis of known compound **4** was performed with modifications to a literature method,³ with use of triethylene glycol as the reaction solvent and KOH as the base (not use of NaOMe). Residual NaOMe could comprise synthesis of **Ru-1a** by generating ruthenium hydride complexes.⁴ It is possible that use of KOH and triethylene glycol could also generate an alkoxide, which would have a similar

effect, but increased steric bulk would limit attack on the alkylidene. In addition, the compound was purified by extraction, not by vacuum pyrolysis. A 1 L round-bottomed flask was loaded with *N*-tosylhydrazone **3** (71.05 g, 0.260 mol) and triethylene glycol (550 mL). The stirred suspension was placed in a 70 °C oil bath to dissolve the solid forming a pale yellow solution (ca. 1 h). Addition of a solution of KOH (35 g, 0.624 mol, 2.4 equiv) in distilled water (112 mL) afforded an orange-red solution. The reaction was stirred for 10 min at 70 °C and then cooled to RT using an ice bath. Ice-cold distilled water (100 mL) was added and the product was extracted with ice-cold hexanes (5 × 150 mL). The combined organic fractions were washed with brine (1 × 200 mL), dried over MgSO₄, and filtered. The solvent was then removed under vacuum to afford a dark red oil. *Note: exposure to vacuum should be minimized to avoid loss of volatile 4.* Yield: 12.8 g (38%). Compound **4** was employed without analysis for purity, and stored over dry ice until ready for use.

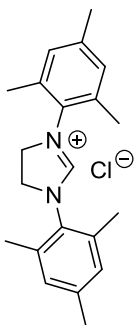
2.3.3 Glyoxal-bis-(2,4,6-trimethylphenyl)imine **5**⁵



Reaction carried out in air. Synthesis of known compound **5** was performed according to the method reported by Arduengo,⁵ with slight modification to reaction solvent (MeOH vs. ⁿPrOH in the reported method). In addition, no heat was necessary, but rather an acid catalyst at RT was employed. To a stirred solution of 2,4,6-trimethylaniline (9.69 g, 71.7 mmol) in MeOH (50 mL) was added glyoxal (40 wt % in H₂O, 4.1 mL, 35.8 mmol, 0.5 equiv). Additional MeOH (10 mL) was added along with one drop of formic acid as a catalyst. A yellow precipitate formed and additional MeOH (10 mL) was added before the solution was left to stir at RT for 24 h. The yellow product was collected by filtration, washed with MeOH until washings were colourless, and dried under vacuum. Product continued to precipitate out in the filtrate and was also collected by filtration, washed with methanol, and dried under vacuum. Yield: 8.0 g (76%). ¹H NMR spectroscopy data were consistent with literature values.⁵ ¹H NMR (CDCl₃, 300 MHz): δ 8.12 (s, 2H, NCH), 6.92 (s, 4H, Mes CH), 2.31 (s, 6H, Mes *p*-CH₃), 2.18 (s, 12H, Mes *o*-CH₃).

2.3.4 *N,N'*-Bis(2,4,6-trimethylphenyl)ethylenediamine dihydrochloride **6**⁵

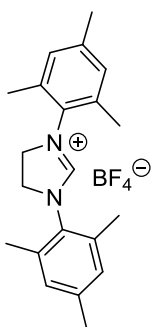
Reaction carried out in air. Synthesis of known compound **6** was performed according to the method reported by Arduengo,⁵ with slight modification during work-up with addition of 3 M HCl until the reaction mixture was acidified to pH 1. The reaction was performed in two 10 g batches as large-scale syntheses were found to compromise yields (as observed by other group members). A yellow solution of glyoxal-bis-(2,4,6-trimethylphenyl)imine **5** (10 g, 34.2 mmol) in dry THF (200 mL) was cooled to 0 °C. Over the next hour 1 g portions of NaBH₄ (5.31 g, 140 mmol, 4.1 equiv) were added every 10 min. The yellow solution was warmed to RT and stirred for 16 h. The solution was heated at reflux for 2 h, after which it was cooled and placed in an ice bath (0 °C). The reaction was diluted with distilled water (100 mL) and then acidified to pH 1 using 3 M HCl dropwise. The white precipitate from both batches was collected by filtration and washed with distilled water. The solid was dried under vacuum. Yield: 17.82 g (70%). ¹H NMR spectroscopy data were consistent with literature values.⁵ ¹H NMR (DMSO-d₆, 300 MHz): δ 6.90 (s, 4H, Mes CH), 3.38 (s, 4H, NCH₂), 2.35 (s, 12H, Mes *o*-CH₃), 2.20 (s, 6H, Mes *p*-CH₃).

2.3.5 1,3-Bis(2,4,6-trimethylphenyl)imidazolium chloride ([H₂IMes(H)](Cl)) **7**⁵

Reaction carried out in air. Synthesis of known compound **7** was performed according to the method reported by Arduengo,⁵ with slight modification. To precipitate **7**, the reaction was cooled to 0 °C not RT as in the reported method. A 250 mL round-bottomed flask was loaded with *N,N'*-bis(2,4,6-trimethylphenyl)ethylenediamine dihydrochloride **6** (17.82 g, 48.2 mmol), triethyl orthoformate (160 mL), and eight drops of formic acid. The stirred suspension was heated to 135 °C in a distillation apparatus until evolution of ethanol ceased. To ensure all EtOH had been distilled off, the apparatus was put under a slight vacuum with a water aspirator. The solution was cooled and placed in an ice bath to precipitate white **7**. The solid was collected by filtration, washed with ice-cold Et₂O (3 × 50 mL), and dried under vacuum. Yield: 15.72 g (95%). ¹H NMR spectroscopy data were consistent with literature values.⁵ ¹H NMR (DMSO-d₆, 300 MHz): δ 9.04 (s, 1H, N=CH),

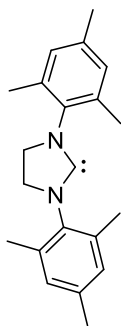
7.09 (s, 4H, Mes CH), 4.45 (s, 4H, NCH₂), 2.35 (s, 12H, Mes *o*-CH₃), 2.29 (s, 6H, Mes *p*-CH₃).

2.3.6 1,3-Bis(2,4,6-trimethylphenyl)imidazolium tetrafluoroborate ([H₂IMes(H)](BF₄)) **8**⁶



Reaction carried out in air. Synthesis of known compound **8** was performed according to a literature method,⁶ with slight modification; specifically, the work-up involved washing the white precipitate (vs. extraction in the reported method). In addition, the reported route begins with 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene chloride as the starting material where here the imidazolium chloride version **7** is used. In a large beaker, 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride **7** (15.72 g, 45.8 mmol) was stirred vigorously in distilled water (900 mL) for 20 min. The suspension was then filtered to remove residual salts. To the filtrate was added HBF₄ dropwise (8 mL of 48% wt solution in H₂O, 61.2 mmol, 1.34 equiv), to form a white precipitate. The solution was stirred for 15 min, after which the solid was filtered, washed with hexanes (4 × 80 mL) and Et₂O (1 × 80 mL), and dried under vacuum. Yield: 16.79 g (93%). ¹H NMR (CDCl₃, 300 MHz): δ 7.90 (s, 1H, N=CH), 6.99 (s, 4H, Mes CH), 4.54 (s, 4H, NCH₂), 2.36 (s, 12H, Mes *o*-CH₃), 2.31 (s, 6H, Mes *p*-CH₃).

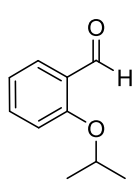
2.3.7 1,3-Bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene (H₂IMes) **9**⁵



Synthesis of known compound **9** was performed according to the method reported by Arduengo,⁵ with slight modification. The reaction was performed with [H₂IMes(H)](BF₄) **8** and NaH as the base, instead of [H₂IMes(H)](Cl) and KH as in the reported method. An additional filtration step was introduced prior to recrystallization to remove any potential contaminants. In the glovebox, a round-bottomed flask was loaded with 1,3-bis(2,4,6-trimethylphenyl)imidazolium tetrafluoroborate **8** (10.0 g, 25.4 mmol) and dry THF (300 mL). To the suspension was added slowly NaH (1.58 g, 65.8 mmol, 2.6 equiv) and the solution was left to stir for 16 h at RT. The reaction mixture was filtered through Celite, an aliquot was removed for ¹H NMR analysis to confirm complete reaction with minimal hydrolysis, and the balance of the filtrate was stripped to dryness. The residue was dissolved in a minimum amount of C₆H₆ (ca. 50 mL), filtered through Celite, and the solvent was

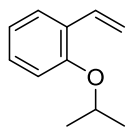
removed under vacuum. The solid was washed with hexanes (3×15 mL) to give pure H_2IMes **9** as a white powder. The yellow filtrate was filtered through Celite and recrystallized at -35 °C (in the glovebox freezer) to collect additional H_2IMes **9**. Combined yield: 4.44 g (57%). ^1H NMR spectroscopy data were consistent with literature values.⁵ ^1H NMR (C_6D_6 , 300 MHz): δ 6.84 (s, 4H, Mes CH), 3.27 (s, 4H, NCH_2), 2.31 (s, 12H, Mes *o*- CH_3), 2.17 (s, 6H, Mes *p*- CH_3).

2.3.8 2-Isopropoxybenzaldehyde **10**⁷



Synthesis of 2-isopropoxybenzaldehyde **10** was performed according to the method reported by Marciniak,⁷ with use of dry *N,N*-dimethylformamide. The product was not purified, but was used within 4 h of preparation. A three-neck round-bottomed flask, which contained a dropping funnel and a stir bar, was attached to the Schlenk line and dry Et_2O (100 mL) was transferred into it by cannula. A solution of $n\text{BuLi}$ in hexanes (11 mL, 2.5 M, 27.5 mmol) was added by syringe, and the solution was cooled to 0 °C. To the reaction flask was added 2-isopropoxybromobenzene (5.91 g, 27.5 mmol). A white solid precipitated out as the mixture was warmed to RT over 2 h. The solution was cooled to -78 °C, and a solution of dry *N,N*-dimethylformamide (2.12 mL, 27.5 mmol) in dry Et_2O (20 mL) was added via the dropping funnel. The solution was warmed to RT and treated dropwise with saturated NH_4Cl (60 mL) to quench the reaction. The organic phase was separated and the aqueous phase was extracted with Et_2O (3×60 mL). The combined ethereal layers were washed with brine (1×60 mL), dried with MgSO_4 , and filtered. The solvent was evaporated to give a light yellow liquid. Yield: 4.29 g (95%). Crude ^1H NMR (CDCl_3 , 300 MHz): δ 10.49 (s, 1H, CHO), 7.82 (dd, $^3J_{\text{HH}} = 7.9$ Hz, $^4J_{\text{HH}} = 1.8$ Hz, 1H, ArCH), 7.51 (m, 1H, ArCH), 6.98 (m, 2H, ArCH), 4.68 (sept, $^3J_{\text{HH}} = 6.1$ Hz, 1H, OCH), 1.40 (d, $^3J_{\text{HH}} = 6.1$ Hz, 6H, CH_3).

The same procedure was used to prepare the ^{13}C -labeled analogue from ^{13}C -labeled *N,N*-dimethylformamide (0.5 mL, 6.46 mmol). ^{13}C -Labeled 2-isopropoxybenzaldehyde **10*** was also used immediately, without purification. Yield: 847 mg (80%). Crude ^1H NMR (CDCl_3 , 300 MHz): δ 10.49 (d, $^1J_{\text{HC}} = 180.8$ Hz, 1H, CHO), 7.83 (ddd, $^3J_{\text{HH}} = 7.9$ Hz, $^4J_{\text{HH}} = 1.9$ Hz, $^1J_{\text{CH}} = 4.1$ Hz, 1H, ArCH), 7.52 (m, 1H, ArCH), 6.99 (m, 2H, ArCH), 4.68 (sept, $^3J_{\text{HH}} = 6.1$ Hz, 1H, OCH), 1.41 (d, $^3J_{\text{HH}} = 6.1$ Hz, 6H, CH_3).

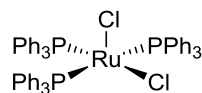
2.3.9 2-Isopropoxystyrene **11**⁷

Synthesis of 2-isopropoxystyrene **11** was performed according to the method reported by Marciniak,⁷ with slight modification (i.e. use of 1.4 equiv of the Wittig reagent, rather than 1.03 equiv). In the glovebox, a Schlenk flask was charged with MePPh₃Br (13.75 g, 38.5 mmol) and dry THF (189 mL). The stirred white suspension was attached to a Schlenk line and cooled to 0 °C. A solution of ⁿBuLi in hexanes (15.4 mL, 2.5 M, 38.5 mmol) was slowly added by syringe, causing the MePPh₃Br to dissolve. The red solution was stirred for 30 min at 0 °C, then warmed to RT over 1 h. To this mixture was added by cannula a solution of 2-isopropoxybenzaldehyde **10** (4.29 g, 26 mmol) in dry THF (5 mL). The aldehyde flask was rinsed several times with THF, transferred to the reaction flask, and the orange-red solution was stirred under N₂ for 16 h. The reaction was quenched with 80 mL distilled water and the solvent was evaporated under vacuum. The product was extracted with Et₂O (4 × 80 mL) and the combined organic layers were washed with brine (2 × 80 mL), dried with MgSO₄, and filtered. The solvent was then removed under vacuum. The yellow oil was suspended in hexanes/Et₂O (1:1, 30 mL), and filtered through a Celite plug, to remove the O=PPh₃ by-product. The Celite was washed with the 1:1 solution and the filtrate was stripped to dryness. This oil was again suspended, filtered and rinsed through a Celite plug, and stripped to dryness. The crude product was purified by column chromatography (SiO₂; 10% CH₂Cl₂:hexanes; R_f = 0.35) to yield a clear, colourless oil. Yield: 2.626 g (62%). ¹H NMR spectroscopy data were consistent with literature values.⁷ ¹H NMR (CDCl₃, 300 MHz): δ 7.50-7.47 (m, 1H, ArCH), 7.23-7.17 (m, 1H, ArCH), 7.07 (dd, ³J_{HH} = 11.2 Hz, ³J_{HH} = 17.8 Hz, 1H, CH=CH₂), 6.94-6.87 (m, 2H, ArCH), 5.73 (dd, ²J_{HH} = 1.6 Hz, ³J_{HH} = 17.8 Hz, 1H, *trans*-CH₂=CH), 5.23 (dd, ²J_{HH} = 1.6 Hz, ³J_{HH} = 11.2 Hz, 1H, *cis*-CH₂=CH), 4.54 (sept, ³J_{HH} = 6.1 Hz, 1H, OCH), 1.35 (d, ³J_{HH} = 6.1 Hz, 6H, CH₃). ¹H NMR (C₆D₆, 300 MHz): δ 7.8 (dd, ⁴J_{HH} = 1.7 Hz, ³J_{HH} = 7.7 Hz, 1H, ArCH) 7.35 (dd, ³J_{HH} = 11.2 Hz, ³J_{HH} = 17.8 Hz, 1H, CH=CH₂), 7.1-7.04 (m, 1H, ArCH), 6.86-6.81 (m, 1H, ArCH), 6.64 (d, ³J_{HH} = 8.3, 1H, ArCH), 5.75 (dd, ²J_{HH} = 1.6 Hz, ³J_{HH} = 17.8 Hz, 1H, *trans*-CH₂=CH), 5.21 (dd, ²J_{HH} = 1.6 Hz, ³J_{HH} = 11.2 Hz, 1H, *cis*-CH₂=CH), 4.16 (sept, ³J_{HH} = 6 Hz, 1H, OCH), 1.07 (d, ³J_{HH} = 6 Hz, 6H, CH₃).

The same procedure was used to prepare the ^{13}C -labeled analogue **11*** from ^{13}C -labeled 2-isopropoxybenzaldehyde **10*** (847 mg, 5.16 mmol), which was reacted with 1.12 equiv of the Wittig reagent (as this was prior to optimization with use of 1.4 equiv). The crude product was purified by column chromatography (SiO_2 ; 2% EtOAc:hexanes; $R_f = 0.57$). Yield: 248 mg (29%). ^1H NMR (CDCl_3 , 300 MHz): δ 7.50-7.46 (m, 1H, ArCH), 7.22-7.17 (m, 1H, ArCH), 7.06 (ddd, $^3J_{\text{HH}} = 11.1$ Hz, $^3J_{\text{HH}} = 17.8$ Hz, $^1J_{\text{HC}} = 156.9$ Hz, 1H, $^{13}\text{CH}=\text{CH}_2$), 6.93-6.85 (m, 2H, ArCH), 5.72 (ddd, $^2J_{\text{HH}} = 1.6$ Hz, $^3J_{\text{HH}} = 17.8$ Hz, $^2J_{\text{HC}} = 4$ Hz, 1H, *trans*- $\text{CH}_2=\text{CH}$), 5.22 (dd, $^2J_{\text{HH}} = 1.6$ Hz, $^3J_{\text{HH}} = 11.2$ Hz, 1H, *cis*- $\text{CH}_2=\text{CH}$), 4.54 (sept, $^3J_{\text{HH}} = 6.1$ Hz, 1H, OCH), 1.35 (d, $^3J_{\text{HH}} = 6.1$ Hz, 6H, CH_3).

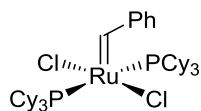
2.4 Synthesis of ruthenium catalysts

2.4.1 $\text{RuCl}_2(\text{PPh}_3)_3$ **Ru-8**⁸



In accordance with a literature procedure,⁸ a three-neck round-bottomed flask was loaded with $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (3 g, 11.5 mmol) and MeOH (120 mL). The stirred solution was refluxed under N_2 for 1 h. The solution was cooled and PPh_3 (18.2 g, 69.2 mmol, 6 equiv) was added. The solution was refluxed for an additional 3 h to afford a brown solution, and allowed to cool. The solid was filtered in air, washed with hexanes (200 mL), and dried under vacuum. In the glovebox, it was further washed with dry Et_2O (5×150 mL) to remove excess PPh_3 . The purified product was dried under vacuum to yield **Ru-8** as a brown solid. Yield: 9.39 g (85%). Spectroscopic values matched those reported;⁹ key NMR values are provided for convenience. $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 121.5 MHz): δ 41.18 (br s), -5.36 (s, 10% free PPh_3).

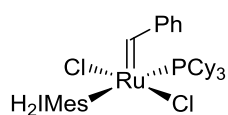
2.4.2 $\text{RuCl}_2(=\text{CHPh})(\text{PCy}_3)_2$ **Ru-1a**¹⁰



The compound **Ru-1a** was prepared by minor modification of the reported method;¹⁰ specifically, hexanes was used for dissolving both **4** and PCy_3 (vs. pentane and CH_2Cl_2 in reported route), and reaction times were extended. In the glovebox, a three-neck round-bottomed flask was loaded with $\text{RuCl}_2(\text{PPh}_3)_3$ **Ru-8** (14.56 g, 15.2 mmol) and dry CH_2Cl_2 (416 mL). The flask was transferred to the Schlenk line and the brown solution was cooled to -78 °C in a dry ice/acetone bath. To the stirred solution, PhCHN_2 **4** (3.83 g, 32.4 mmol, 2.1 equiv) in dry hexanes (41 mL) was

transferred by cannula over 10 min, causing a colour change to green-brown. The reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for an additional 20 min, and warmed to $0\text{ }^{\circ}\text{C}$ using an ice bath for 1 h. A $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum was acquired to ensure no **Ru-8** remained. Cannula addition of PCy_3 (9.37 g, 33.4 mmol, 2.2 equiv) in dry hexanes (104 mL) caused a colour change to dark red-purple. The solution was left to warm to RT over 1.5 h, after which the volatiles were removed under vacuum (Schlenk line). The red-purple solution was brought into the glovebox, and washed with dry methanol (620 mL) and dry acetone (250 mL). The purified product was dried under vacuum to give **Ru-1a** as a purple solid. Yield: 9.17 g (73%). Spectroscopic values matched those reported;¹⁰ key NMR values are provided for convenience. $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 121.5 MHz): δ 36.37 (s). ^1H NMR (CDCl_3 , 300 MHz): δ 19.98 (s, 1H, $\text{Ru}=\text{CHPh}$).

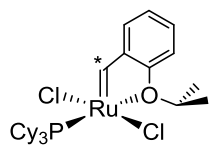
2.4.3 $\text{RuCl}_2(=\text{CHPh})(\text{H}_2\text{IMes})(\text{PCy}_3)$ **Ru-1b**¹¹



Our group recently reported a convenient, high-yielding alternative to the original synthesis¹² of **Ru-1b**; key improvements were use of free H_2IMes **9** (which improves purity) and a phosphine-scavenging resin (which improves yields).¹¹ An adaptation of this literature procedure was required; specifically, additional resin was necessary for removal of remaining free PCy_3 . In the glovebox, a round-bottomed flask was loaded with **Ru-1a** (502 mg, 0.61 mmol) in dry THF (30 mL). To the purple solution was added H_2IMes **9** (197 mg, 0.64 mmol, 1.05 equiv). The reaction mixture was stirred at RT for 3.5 h. An aliquot was removed for analysis by ^1H NMR spectroscopy which showed traces of **Ru-1a** still present. Additional H_2IMes **9** (3 mg, 0.01 mmol) was added, and the solution was stirred for 1 h, after which NMR analysis indicated that no **Ru-1a** remained. To the red-purple solution was added off-the-shelf Amberlyst 15 resin (522 mg, 2.45 mmol, 4 equiv) and the reaction mixture was stirred for 2 h. Amberlyst 15 resin was used off-the-shelf to hydrolyze and remove the excess H_2IMes **9**. Again, an aliquot was removed for $^{31}\text{P}\{^1\text{H}\}$ NMR analysis. As free PCy_3 was observed, further Amberlyst 15 resin (263 mg, 1.24 mmol, 2 equiv) was added, and the solution stirred for another 1 h. The resin was then filtered off and rinsed with THF ($6 \times 1\text{ mL}$) until the washings appeared colourless. The filtrate was stripped to dryness to give **Ru-1b** as a pink solid. Yield: 450 mg (87%). Spectroscopic values matched those reported;¹² key NMR

values are provided for convenience. $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 121.5 MHz): δ 29.69 (s). ^1H NMR (CDCl_3 , 300 MHz): δ 19.14 (s, 1H, $\text{Ru}=\text{CHPh}$).

2.4.4 $\text{RuCl}_2(\text{PCy}_3)(=\text{CH}-2-\text{O}^i\text{PrC}_6\text{H}_4)$ **Ru-2a***¹¹

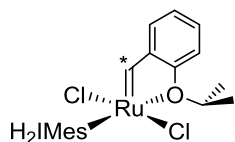


The compound **Ru-2a*** was prepared by the method reported by our group,¹¹ itself an improvement on the original route,¹³ with use of ^{13}C -labeled 2-isopropoxystyrene **11***. Key improvements were use of free H_2IMes **9** and a phosphine-scavenging resin (reasons described in Section 2.4.3). In the glovebox, a Schlenk tube was charged with **Ru-1a** (504 mg, 0.613 mmol) and dry THF (20 mL). ^{13}C -Labeled 2-isopropoxystyrene **11*** (105 mg, 0.641 mmol, 1.05 equiv) was weighed in a vial and transferred to the reaction mixture; the vial was rinsed with additional THF and the washings were transferred to the reaction flask. To the purple solution was added dry Amberlyst 15 resin (526 mg, 2.47 mmol, 4 equiv). The stirred reaction mixture was transferred to a Schlenk line and heated at 50 °C for 3 h. The solution was then cooled to RT and returned to the glovebox. An aliquot was removed and analyzed (NMR) to ensure no **Ru-1a** or free PCy_3 remained. The brown solution was filtered to remove the resin, which was rinsed with THF (6×2 mL). The combined filtrate was stripped to dryness, and the residue was extracted with cold pentane (3×5 mL, -35 °C) to remove the styrene co-product yielding **Ru-2a*** as a brown solid. Yield: 339 mg (92%). ^1H and $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy confirmed the desired **Ru-2a***, in addition to a by-product observed at δ_{P} 43.1 ppm (s, CDCl_3 ; 2% of total integration). The product was carried forward without removal of this impurity. Key spectroscopic values are provided for convenience. $^{31}\text{P}\{^1\text{H}\}$ NMR (C_6D_6 , 121.5 MHz): δ 60.59 (d, $^2J_{\text{PC}} = 14.4$ Hz). ^1H NMR (C_6D_6 , 300 MHz): δ 17.37 (dd, $^3J_{\text{HP}} = 4.6$ Hz, $^1J_{\text{HC}} = 162.9$ Hz, 1H, $\text{Ru}=\text{}^{13}\text{CHAr}$). $^{13}\text{C}\{^1\text{H}\}$ NMR (C_6D_6 , 75.5 MHz): δ 275.5 (d, $^2J_{\text{CP}} = 14.4$ Hz, $\text{Ru}=\text{}^{13}\text{CHAr}$).

A minor modification of this procedure was used to prepare **Ru-2a** from unlabeled 2-isopropoxystyrene **11**. Specifically, the impurity noted above was removed by dissolving the solid in 2:1 CH_2Cl_2 /hexanes and loading onto a short silica plug inside the glovebox. Elution of a brown band and removal of solvent afforded pure **Ru-2a** as a brown solid. Yield: 1.61 g (72%). Spectroscopic values matched those reported;¹³ key spectroscopic values are provided

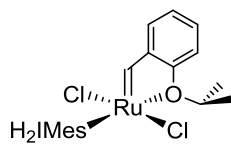
for convenience. $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 121.5 MHz): δ 59.36 (s). ^1H NMR (CDCl_3 , 300 MHz): δ 17.42 (d, $^3J_{\text{HP}} = 4.5$ Hz, 1H, $\text{Ru}=\text{CHAr}$).

2.4.5 $\text{RuCl}_2(\text{H}_2\text{IMes})(=\text{CH}-2\text{-O}^i\text{PrC}_6\text{H}_4)$ **Ru-2b*** from **Ru-2a***¹¹



The compound **Ru-2b*** was prepared by minor modification of our reported method,¹¹ itself an improvement on the original route.¹⁴ Key improvements were use of free H_2IMes **9** and a phosphine-scavenging resin (reasons described in Section 2.4.3). Additionally, the reaction time was extended compared to the reported route. In the glovebox, to a Schlenk round-bottomed flask was added **Ru-2a*** (339 mg, 0.56 mmol) and dry THF (7 mL). To the brown solution, white crystalline H_2IMes **9** (190 mg, 0.62 mmol, 1.1 equiv) was added which was stirred vigorously for 2 h in the glovebox. Off-the-shelf Amberlyst 15 (481 mg, 2.26 mmol, 4 equiv) was then added and the solution was transferred to a Schlenk line and stirred at 40 °C. The orange-brown solution turned green, over a period of 2 h. It was allowed to cool to RT, and returned to the glovebox. Analysis by $^{31}\text{P}\{^1\text{H}\}$ NMR revealed free PCy_3 , and a further charge of Amberlyst 15 resin (240 mg, 1.13 mmol, 2 equiv) was added. The reaction was stirred at 40 °C (Schlenk line) for an additional hour, returned to the glovebox, and filtered to remove the resin. The resin was rinsed with THF (6×2 mL) and the combined filtrate was stripped of solvent. The residue was dissolved in 3:1 CH_2Cl_2 /hexanes and loaded onto a short silica plug inside the glovebox. Elution of a bright green band and removal of solvent afforded green **Ru-2b***. Yield: 274 mg (77%). Spectroscopic values matched those reported;⁷ key spectroscopic values are provided for convenience. ^1H NMR (C_6D_6 , 300 MHz): δ 16.72 (d, $^1J_{\text{HC}} = 167.1$ Hz, 1H, $\text{Ru}=\text{}^{13}\text{CHAr}$). $^{13}\text{C}\{^1\text{H}\}$ NMR (C_6D_6 , 75.5 MHz): δ 292.5 (s, $\text{Ru}=\text{}^{13}\text{CHAr}$).

This procedure was also used to prepare **Ru-2b** from pure unlabeled **Ru-2a**; in this case there was no need for purification using a short silica plug. Yield: 1.01 g (97%). Spectroscopic values matched those reported;¹⁴ key spectroscopic values are provided for convenience. ^1H NMR (CDCl_3 , 300 MHz): δ 16.56 (s, 1H, $\text{Ru}=\text{CHAr}$).

2.4.6 $\text{RuCl}_2(\text{H}_2\text{IMes})(=\text{CH}-2\text{-O}^i\text{PrC}_6\text{H}_4)$ **Ru-2b** from **Ru-1b**¹⁵

The compound **Ru-2b** was prepared by minor modification of the reported method;¹⁵ specifically, the reaction was heated to 50 °C for 3 h (rather than at 40 °C for 1.5 h). In the glovebox, a Schlenk tube was charged with **Ru-1b** (300 mg, 0.35 mmol) and dry THF (6 mL). 2-Isopropoxystyrene **11** (59.8 mg, 0.37 mmol, 1.05 equiv) was weighed in a vial and transferred to the reaction mixture; the vial was rinsed with additional THF (3 mL) and transferred to the flask. To the pink solution was added dry Amberlyst 15 resin (300 mg, 1.41 mmol, 4 equiv). The stirred reaction mixture was transferred to a Schlenk line and heated at 50 °C for 3 h. The solution was cooled to RT and returned to the glovebox. The solution was filtered to remove the resin, which was rinsed with THF (6 × 2 mL). The combined filtrate was stripped to dryness, and the residue was extracted with cold pentane (4 × 2 mL, -35 °C) to remove the styrene co-product, yielding **Ru-2b** as a green solid. Yield: 207 mg (93%). ¹H NMR analysis (CDCl_3) revealed the expected singlet for **Ru-2b** at 16.56 ppm, but an unknown alkylidene by-product was also present (17.78 ppm, 2-5%). Attempts to remove this impurity by washing with hexanes and reprecipitation from THF/hexanes were unsuccessful.

In an alternative approach a solution of **Ru-1b** (49.7 mg, 0.059 mmol) and 2-isopropoxystyrene **11** (10.9 mg, 0.067 mmol) in THF (2 mL) was heated to 40 °C on a Schlenk manifold for 2 h. The orange-red solution was cooled, and dry Amberlyst 15 resin (50.4 mg, 0.24 mmol, 4 equiv) was added in the glovebox. The reaction mixture was returned to the Schlenk line and heated to 40 °C for an additional 3 h. After removal of the resin by filtration and washing with THF (4 × 1 mL), NMR analysis revealed incomplete reaction (92% conversion) and multiple by-products (δ_{H} 17.77, 19.13 ppm; δ_{P} 50.68, 43.1, 39.1, 36.1, 32.2, 29.55, 28.47, 21.67 ppm). No attempts at purification were made.

2.5 Assessing catalyst decomposition: thermolysis experiments

We suspected that the impurities formed during the synthesis of Hoveyda catalyst **Ru-2b** (from **Ru-1b**) could result from heating Grubbs catalyst **Ru-1b** in the presence of Amberlyst 15 resin. Therefore, the following experiment was carried out with **Ru-1b**, as well as **Ru-1a** and **Ru-2a/b**, to assess decomposition of these species in the presence of Amberlyst 15 resin and heat.

2.5.1 Representative procedure: thermolysis in the presence of Amberlyst 15 resin

A solution of the Grubbs catalysts **Ru-1b** (10 mg, 0.012 mmol) and TMB (0.7 mg, 4 μ mol; I.S.) in dry THF (1 mL) was transferred to a J. Young NMR tube containing a capillary with PPh₃ in C₆D₆ (I.S.). ³¹P{¹H} and ¹H NMR spectra were acquired to establish the initial integration of catalyst relative to the internal standards. In the glovebox, the solution was transferred into a 4 mL screw-cap vial, and dry Amberlyst 15 (10.1 mg, 0.048 mmol) was added, along with a stir bar. The vial was capped, taped, placed in an aluminum block heated to 50 °C, and stirred vigorously for 2 h. The vial was returned to the glovebox and the solution transferred to a J. Young NMR tube. ³¹P{¹H} and ¹H NMR spectra were acquired to assess the amount of precatalyst remaining.

2.5.2 Lifetime of **Ru-9** and **Ru-10a** at various temperatures

A solution of monothiolate ruthenium catalyst **Ru-10a** (10 mg, 0.016 mmol) and dimethyl terephthalate (0.9 mg, 5 μ mol, 0.25 equiv) in CD₂Cl₂ (900 μ L) was transferred to a NMR tube equipped with a J. Young valve. A ¹H NMR spectrum was acquired to establish the initial integration of catalyst relative to internal standard. The J. Young NMR tube was placed in a 35 °C oil bath and periodically removed to acquire a ¹H NMR spectrum until no **Ru-10a** remained. The same procedure was followed to assess the lifetime of **Ru-10a** and **Ru-9** at 40 °C in DCE. When performed with **Ru-9**, the experiment was stopped after one month even though 72% catalyst still remained.

2.6 Assessing rate of CM between Hoveyda catalyst **Ru-2b** and ¹³C-labeled 2-isopropoxystyrene **11***

2.6.1 Representative procedure

A 50 mL Kontes flask was loaded with TMB (24 μ L of a 32 mM solution, 0.76 μ mol, 0.33 equiv relative to Ru; I.S.), Hoveyda catalyst **Ru-2b** (75 μ L of a 30 mM solution, 2.3 μ mol), and C₆D₆ (2.1 mL). An aliquot from the stirred solution was placed in a J. Young NMR tube and a ¹H NMR spectrum was acquired to establish the initial integration of catalyst relative to TMB. The solution in the NMR tube was returned to the Kontes flask in the glovebox and to it was added ¹³C-labeled 2-isopropoxystyrene **11*** (30 μ L of a 75 mM solution, 2.24 μ mol) giving a ruthenium concentration of 1 mM. The flask was sealed, and stirring was continued

at RT. Aliquots were periodically removed, and transferred to a J. Young NMR tube for ^1H NMR analysis. Following analysis, the solution was returned to the Kontes flask in the glovebox. The same procedure was followed when reactions were carried out in a sealed J. Young NMR tube to assess the effect of headspace (sealed vs. open) on the rate of reaction. ^1H NMR spectra were acquired every 20 min until the reaction reached equilibrium (ca. 3 d). For reactions in DCE, dimethyl terephthalate (δ_{H} 8.08 ppm) was used as an internal NMR standard, to shift the signal downfield removing it away from the signals for methyl acrylate (δ_{H} 6.15-6.05 ppm, multiplet), which during catalysis overlaps with the aromatic signals for TMB (δ_{H} 6.07 ppm).

Table 2.1 All reaction conditions employed for background reactions.^a

Reaction	Solvent	[Ru] (mM)	Temperature (°C)
Ru-2b + 11 *	DCE	2	50 ^b
Ru-2b + 11 *	CD ₂ Cl ₂	21	RT
Ru-2b + 11 *	C ₆ D ₆	21	RT
Ru-2b + 11 *	C ₆ D ₆	1	RT
Ru-2b * + 11	C ₆ D ₆	1	RT

^a All reactions were performed both in a J. Young NMR tube and in a Schlenk tube. ^b Performed in a sand bath in the glovebox.

2.7 Catalytic reactions

2.7.1 Representative procedure for RCM of 2-methylocta-1,7-dien-3-ol **1**

In the glovebox, a J. Young NMR tube (Flask A) was loaded with TMB (16 μL of a 32 mM solution, 0.5 μmol , 0.34 equiv to Ru; I.S.), Hoveyda catalyst **Ru-2b** (50 μL of a 30 mM solution, 1.5 μmol , 1 mol%), and C₆D₆ (450 μL). A ^1H NMR spectrum was acquired to establish the initial ratio of catalyst relative to TMB. To a 10 mL Schlenk tube (Flask B) with a stir bar was added substrate **1** (200 μL of a 750 mM solution, 0.15 mmol), decane (100 μL of a 1.5 M solution, 0.15 mmol; I.S.), ^{13}C -labeled 2-isopropoxystyrene **11*** (20 μL of a 75 mM solution, 1.5 μmol , 1 equiv relative to Ru), and C₆D₆ (450 μL). An aliquot was removed for GC analysis to establish the initial integration ratio of substrate **1** relative to decane. The green catalyst solution in Flask A was added to Flask B. The J. Young NMR tube was rinsed with C₆D₆ (2 $\times$ 100 μL) and the solution was transferred to Flask B to give a final substrate concentration of 100 mM. The reaction flask was left open to a N₂-filled glovebox for the duration of the reaction, and the solution remained green over this period of time. Samples

were removed periodically (about 30 μL), quenched with KTp (8 μL of a 39 mM solution in THF, 0.3 μmol , 10 equiv relative to Ru), and diluted to 1 mL with C_6H_6 in the glovebox to be analyzed by GC. After 10 min (95% conversion by GC) an aliquot was removed (about 500-700 μL) and placed in a J. Young NMR tube, which was removed from the box immediately, cooled in an ice bath (2 min), and subjected to ^1H NMR analysis. Starting material **1** (5%) was observed, indicating the reaction was indeed at 95% conversion (consistent with GC).

A similar procedure was employed in the RCM of **1** with either: **Ru-2b** + **11**, **Ru-2b*** + **11**, **Ru-2b** + 5 equiv **11**, and **Ru-2b** + 0 equiv **11**. In each case the appropriate amount of C_6D_6 was added to give a final substrate concentration of 100 mM.

The same procedure was followed when RCM of **1** was carried out in a sealed J. Young NMR tube without use of decane as a GC internal standard. The reaction was instead monitored by ^1H NMR spectroscopy, acquiring a spectrum every 10 min for 3 h. Additional experiments were performed with unlabeled **Ru-2b** and **11** in a sealed J. Young NMR tube: here the substrate concentration was held constant at 78 mM, while varying the concentration of ruthenium (0.44 to 4.3 mM). The concentration of unlabeled 2-isopropoxystyrene **11** was maintained at 1 equiv vs. Ru.

2.7.2 Representative procedure for CM of *trans*-anethole **12** and methyl acrylate **13**

The procedure of Section 2.7.1 was followed, with use of dimethyl terephthalate as an internal standard (NMR), DCE as the reaction solvent, a temperature of 50 $^\circ\text{C}$ (with use of a sand bath in the glovebox), and a final substrate concentration of 200 mM. An aliquot was removed from the substrate stock solution (*trans*-anethole **12** and decane, 330 mM) for GC analysis to establish the initial ratio of *trans*-anethole **12** relative to decane. Once the reaction had begun, samples were removed periodically (two drops of a pipette) and diluted to 1 mL with CH_2Cl_2 in the glovebox. The vials were removed from the glovebox, and immediately exposed to air to quench the active species. No quenching agent was required as removal from heat, dilution, and exposure to air was found to prevent “run-on” metathesis. GC analysis was then carried out. An ^1H NMR spectrum was acquired after 1 h 50 min (92% conversion) and showed the presence of starting material **12** (9%), indicating 91% conversion (92% by GC). No further reaction was observed during acquisition of the spectrum.

A similar procedure was followed when reactions were performed with no additional 2-isopropoxystyrene **11** or with use of unlabeled 2-isopropoxystyrene **11**.

2.7.3 Representative procedure for RCM of diethyl diallylmalonate **14**

In the glovebox, to a 4 mL screw cap vial was added diethyl diallylmalonate **14** (47.5 mg, 0.2 mmol) and THN (27 μ L, 0.2 mmol). The solution was added to a Schlenk tube and the vial was rinsed well with a known amount of DCE which was also added to the reaction flask. The stirred solution was diluted with additional DCE (38 mL was used in total) to give a final substrate concentration of 5 mM. An aliquot (0.5 mL) was removed and diluted with CH_2Cl_2 (0.5 mL) for GC analysis to establish initial integration ratios. The Schlenk tube was placed in a 40 °C sand bath in the glovebox and allowed to equilibrate to temperature. Monothiolate ruthenium catalyst **Ru-9** (9.3 mg, 0.01 mmol, 5 mol%) was then added to the reaction and the weigh boat was rinsed into the reaction flask with 1 mL DCE. The stirred green solution was capped, and the Schlenk key was left open to the glovebox atmosphere. Periodically aliquots (ca. 0.5 mL) were removed, quenched with KTp (5 μ L of a 250 mM solution in THF, 1.3 μ mol, 10 equiv to Ru), and analyzed by GC.

2.7.4 Procedure for consecutive RCM of fresh diethyl diallylmalonate **14**

The procedure of Section 2.7.3 was followed, except that additional **14** (20 equiv to remaining Ru) was added to the reaction mixture every 24 h for 4 d. Aliquots (0.5 mL) were removed with a microlitre syringe to track the remaining volume of solution to calculate the remaining concentration of catalyst (assuming no deactivation). The solution was removed from the heat 15 min prior to adding substrate **14**. Following addition of **14**, the solution was stirred for 1 min, an aliquot (0.5 mL) was removed, and the reaction flask was returned to the sand bath. The aliquot was diluted with CH_2Cl_2 (0.5 mL) and quenched with KTp (10 equiv) for GC analysis to establish new integration ratios.

2.7.5 Representative procedure for RCM of hex-5-en-1-yl undec-10-enoate **2** $[\text{S}]_i = 5 \text{ mM}$

The procedure of Section 2.7.3 was followed, with use of hex-5-en-1-yl undec-10-enoate **2** as the substrate and **Ru-10a** as the catalyst. Once the product distribution had stalled (41 h), an aliquot (4 mL) was removed from the solution and added to a second stirred Schlenk tube containing DCE (36 mL, $[\text{S}] = 0.5 \text{ mM}$). Sampling and quenching was as in Section 2.7.3

with KTp (10 equiv). Once the product distribution had stalled again (62 h 5 min), a fresh stock solution of **Ru-10a** was prepared (9.8 mg in 7 mL, 1.76 mM) and an aliquot (480 μ L, 5 mol% assuming only diene **2** was present) was added to the solution. Sampling and quenching was as in Section 2.7.3 with KTp (10 equiv).

The same procedure was followed when reactions were performed with 5 mol% **Ru-9**, and at 1 mol% **Ru-10a**. When performed at reflux with 1 mol% **Ru-10a**, the Schlenk tube was transferred to a Schlenk line along with a condenser and placed in an oil bath. Aliquots were removed by syringe through the side arm and were not quenched with KTp but rather exposed to air prior to analysis by GC.

2.7.6 Representative procedure for RCM of hex-5-en-1-yl undec-10-enoate **2** [S]_i = 440 mM

In the glovebox, a 2.3 M substrate stock solution was prepared in a 1 mL vial with **2** (100.1 mg, 0.376 mmol) and THN (50 μ L, 0.368 mmol). An aliquot (one drop) was removed from the stirred solution and diluted to 1 mL with CH₂Cl₂ for GC analysis to establish initial integration ratios. In a second 1 mL vial was dissolved green solid **Ru-10a** (11.8 mg, 0.015 mmol) in DCE (553 μ L). To the stirred catalyst solution was added the substrate stock solution (130 μ L, 0.298 mmol) giving a substrate concentration of 440 mM. The vial was capped with a septum which contained a needle to allow the reaction to vent to the N₂ atmosphere. The solution was placed in a 40 °C sand bath. Periodically aliquots (ca. 5 μ L) were removed, quenched (10 equiv KTp), and analyzed by GC. Once the substrate had been fully consumed and the product distribution had stalled (5 h 20 min), an aliquot (500 μ L) was removed from the solution and added to another Schlenk tube containing DCE (43 mL, [S] = 5 mM). Sampling and quenching was as in Section 2.7.3 with KTp (10 equiv). Once the product distribution had stalled again (51 h 5 min), a fresh stock solution of **Ru-10a** was prepared (9.8 mg in 7 mL, 1.76 mM) and an aliquot (4.42 mL, 5 mol% assuming only diene **2** was present) was added to the solution. Sampling and quenching was as in Section 2.7.3 with KTp (10 equiv).

The same procedure was employed when reactions were performed with **Ru-9**. When performed at 60 °C (after dilution), the reaction flask was transferred to a Schlenk line along

with a condenser and placed in an oil bath. Aliquots were removed by syringe through the side arm and were not quenched with KTp but rather exposed to air prior to analysis by GC.

2.7.7 Procedure for RCM of hex-5-en-1-yl undec-10-enoate **2**, followed by addition of diethyl diallylmalonate **14**

A solution of diethyl diallylmalonate **14** (24.4 mg, 0.102 mmol) and decane (20 μ L, 0.103 mmol) in DCE (250 μ L) was prepared and an aliquot (1 drop) was withdrawn and diluted to 1 mL with CH_2Cl_2 for GC analysis to establish initial integration ratios. In a separate Schlenk tube, RCM of **2** was carried out according to a modified procedure described in Section 2.7.6. After 60 h, the solution of **14** prepared above was added. RCM of **2** and **14** were monitored simultaneously until diethyl diallylmalonate **14** was fully consumed. A portion of the solution (10 mL) was placed in a second Schlenk tube and cooled to RT. An additional 20 equiv of hex-5-en-1-yl undec-10-enoate **2** (13.3 mg, 0.05 mmol) was added to the reaction mixture (at 78 h). The solution was stirred for 1 min, an aliquot (1 mL) was removed, and quenched (10 equiv KTp) for GC analysis to establish new integration ratios. The solution was placed back in the 40 °C sand bath and the reaction was monitored by GC until the substrate was consumed and the product distribution ceased to evolve.

2.8 References

- (1) Armarego, W. L. F.; Perrin, D. D., *Purification of Common Laboratory Chemicals*. 4th Ed. ed.; Butterworth-Heinemann: Oxford, 1997; p 529.
- (2) McGrath, N. A.; Lee, C. A.; Araki, H.; Brichacek, M.; Njardarson, J. T. *Angew. Chem. Int. Ed.* **2008**, *47*, 9450-9453.
- (3) Creary, X. *Org. Synth.* **1986**, *64*, 207–216.
- (4) Beach, N. J.; Lummiss, J. A. M.; Bates, J. M.; Fogg, D. E. *Organometallics* **2012**, *31*, 2349–2356.
- (5) Arduengo, A. J.; Krafczyk, R.; Schmutzler, R.; Craig, H. A.; Goerlich, J. R.; Marshall, W. J.; Unverzagt, M. *Tetrahedron* **1999**, *55*, 14523–14534.
- (6) Bantreil, X.; Nolan, S. P. *Nature Protoc.* **2011**, *6*, 69–77.
- (7) Marciniak, B.; Rogalski, S.; Potrzebowski, M. J.; Pietraszuk, C. *ChemCatChem* **2011**, *3*, 904–910.
- (8) Stephenson, T. A.; Wilkinson, G. J. *Inorg. Nucl. Chem.* **1966**, *28*, 945–956.
- (9) Hoffman, P. R.; Caulton, K. G. *J. Am. Chem. Soc.* **1975**, *97*, 4221–4228.
- (10) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100–110.
- (11) van Lierop, B. J.; Reckling, A. M.; Lummiss, J. A. M.; Fogg, D. E. *ChemCatChem* **2012**, *4*, 2020–2025.
- (12) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.

- (13) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791–799.
- (14) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.
- (15) Monsaert, S. F.; Verpoort, F. W. C. Process for preparation of ruthenium-based carbene catalysts with chelating alkylidene ligands. WO Patent App. WO 2011/091980 A1; CA+ 383210.

3 The Boomerang Mechanism in Olefin Metathesis: Fact or Fiction?

3.1 Introduction

Phosphine-free catalysts of the Hoveyda class, and particularly the second-generation catalyst **Ru-2b**,^{1,2} occupy a position of increasing prominence in olefin metathesis. In the context of cross-metathesis of seed oils with acrylates, reports from the Rennes and Meier groups³⁻⁸ described higher productivity – that is, higher total turnover numbers – for **Ru-2b** relative to the Grubbs catalyst **Ru-1b**, despite the fact that the two catalysts form a common active species, four-coordinate methyldiene species **Ru-5b** (Figure 3.1). Likewise, reports from pharma have demonstrated that **Ru-2b** out-performs **Ru-1b** in some demanding RCM applications.⁹⁻¹¹ As molecular metathesis catalysts enter a new phase of deployment in process chemistry,^{12,13} understanding the mechanistic basis of their performance takes on added importance.

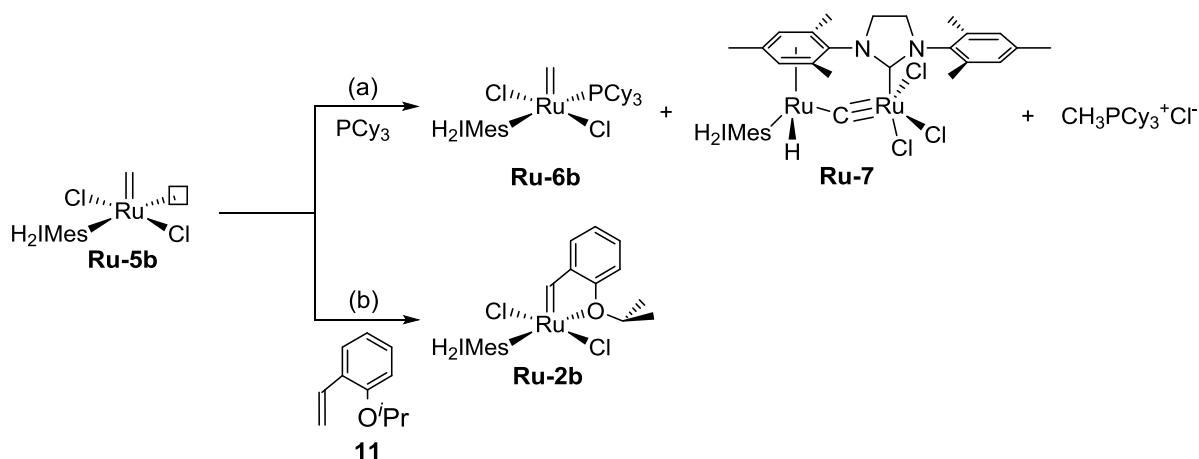
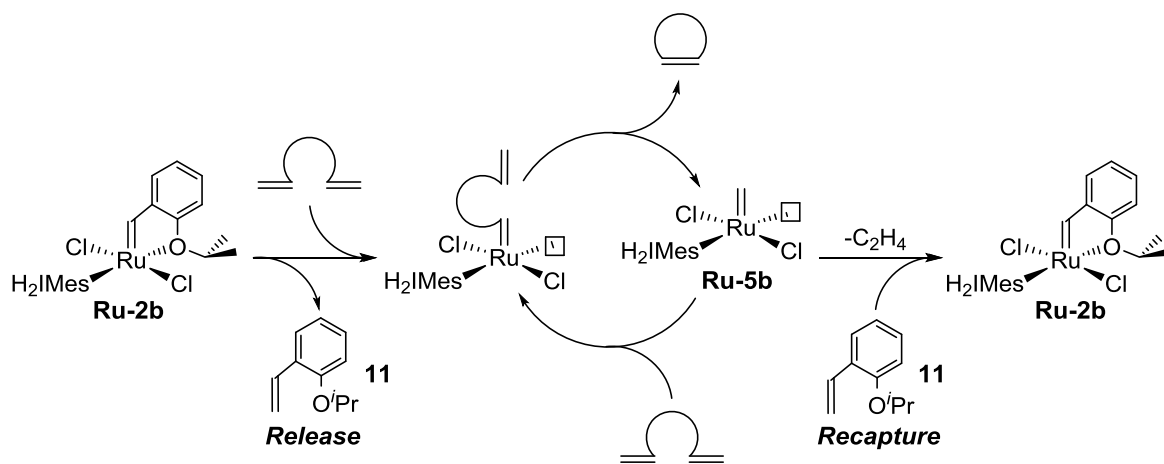


Figure 3.1 Products derived from reaction of **Ru-5b** with (a) PCy_3 , or (b) styrenyl ether **11**.

The basis for the improved productivity of **Ru-2b**, vs. **Ru-1b**, has been the subject of much debate. One obvious candidate is the absence of free PCy_3 . Release of phosphine from the Grubbs catalyst **Ru-1b**, as required to generate the active methyldiene species **Ru-5b**, is reversible. While four-coordinate **Ru-5b** has a higher commitment toward reaction with olefin than with PCy_3 ,¹⁴⁻¹⁶ re-coordination of PCy_3 does occur, with two negative consequences (Figure 3.1a). First, this sequesters the methyldiene species in the form of five-coordinate **Ru-6b**, an off-cycle resting state. Owing to its very low phosphine lability,¹⁶ **Ru-6b** resists re-uptake into the catalytic cycle. Exacerbating the problem, **Ru-6b** is also

susceptible to attack by free PCy_3 at the methylidene site, and this deactivates the catalyst by abstracting the methylidene ligand as $[\text{CH}_3\text{PCy}_3]\text{Cl}$.^{17,18} Finally, emerging evidence indicates that **Ru-2b** benefits from operation via interchange-associative pathways, at least for sterically undemanding olefins,¹⁹⁻²² whereas **Ru-1b** is constrained to reaction via the vulnerable four-coordinate intermediate **Ru-5b**.¹⁶

More controversial is the potential role of the styrenyl ether ligand **11** in extending the lifetime of **Ru-2b**. In their original report, Hoveyda and co-workers^{1,23} suggested that the active species **Ru-5b** effectively recaptures **11**, regenerating the initial catalyst (Scheme 3.1). This occurs once substrate is depleted, at a stage when catalyst deactivation would otherwise increase. This “boomerang” or “release-return” mechanism was proposed to prolong catalyst lifetime, without impeding reaction with substrate. Operation of such a mechanism could permit use of **Ru-2b** in a wider range of applications. For example, **Ru-2b** is surprisingly little used in RCM despite its impressive performance.²⁴ In addition, prolonged catalyst lifetimes means lower catalyst loadings are possible for systems that use the Hoveyda catalyst **Ru-2b** over the Grubbs catalyst **Ru-1b**. The inability of **11** to effectively compete with substrate olefin for binding to ruthenium²⁵ was predicated on the higher proportion of olefin present (valid up to the 99% conversion level), and the deactivated nature of the styrenyl olefin. If such a mechanism is operative for catalysts that contain a styrenyl ether ligand **11**, incorporation of this ligand may be crucial to designing and developing more active and recyclable metathesis catalysts in the future.



Scheme 3.1 Schematic illustrating the release-return mechanism.

Early studies by Hoveyda and co-workers^{1,23} showed that both the first- and second-generation Hoveyda catalysts **Ru-2a** and **Ru-2b** could be recovered, typically in a >80% yield, after RCM reactions carried out using 5 mol% catalyst. In some cases a catalyst recovery up to 98% was achieved after silica gel chromatography. The release-return mechanism was proposed to be responsible for this recyclability. However, Grubbs²⁶ has suggested that at such high catalyst loadings, very small amounts of released, highly active **Ru-5b** could be responsible for the observed activity, and the recovered material is virgin catalyst that was never initiated. For a few of the reactions with **Ru-2b**, it was shown that catalyst loadings lower than 5 mol% are indeed sufficient.¹ At 1 mol% **Ru-2b** the RCM of 3-(allyloxy)-2,4-dimethylpenta-1,4-diene **15** still proceeded rapidly, with >98% conversion in 10 min. Work by Blechert and co-workers²⁷ has shown that low catalyst loadings (e.g. 0.02 mol% **Ru-2b**) effect quantitative RCM of DeDAM **14** (18 h, CH₂Cl₂, 45 °C). Attempts to probe the release-return mechanism using such reactive substrates may therefore be skewed by the low demands of the reaction, which will leave higher proportions of virgin catalyst.

In another experiment cited as supporting the plausibility of the release-return mechanism, Hoveyda and co-workers^{1,23} showed that **Ru-2a/b** could be isolated from RCM reactions using the Grubbs catalysts **Ru-1a/b** in the presence of styrenyl ether **11** (2 equiv). Of more direct relevance, Hoveyda¹ has shown that the active species **Ru-5a** is competent to recapture free styrenyl ether **11**, regenerating the first-generation Hoveyda catalyst **Ru-2a**. This was shown with the tetraruthenium species **Ru-11a** (Figure 3.2). In the RCM of **16** with **Ru-11a** and 0.8 equiv **11**, ca. 70% of the styrenyl ether was recovered as **Ru-2a** after 15 min. While in either of these cases, **Ru-2a** could also be formed by CM of uninitiated ruthenium centers with free styrenyl ether, a control reaction between **Ru-11a** and free **11** under identical conditions revealed <2% **Ru-2a** after 3 h. The authors concluded that **Ru-5a** was first released from tetranuclear **Ru-11a**, and then captured the free styrenyl ether **11** to generate the first-generation Hoveyda catalyst **Ru-2a**. Unfortunately, however, these experiments were not performed with the second-generation **Ru-11b**, as control experiments indicated a rapid redistribution of ruthenium species even in the absence of substrate (specifically, ¹H NMR analysis indicated a 52:48 ratio of dendritic to monomeric **Ru-2b** after 3 h at RT).²⁸ Rapid redistribution of the ruthenium species during catalysis is a problem because this

formation of **Ru-2b** could then be due either to recapture of styrenyl ether **11** via the boomerang mechanism, or to CM of **Ru-11b** with **11**.

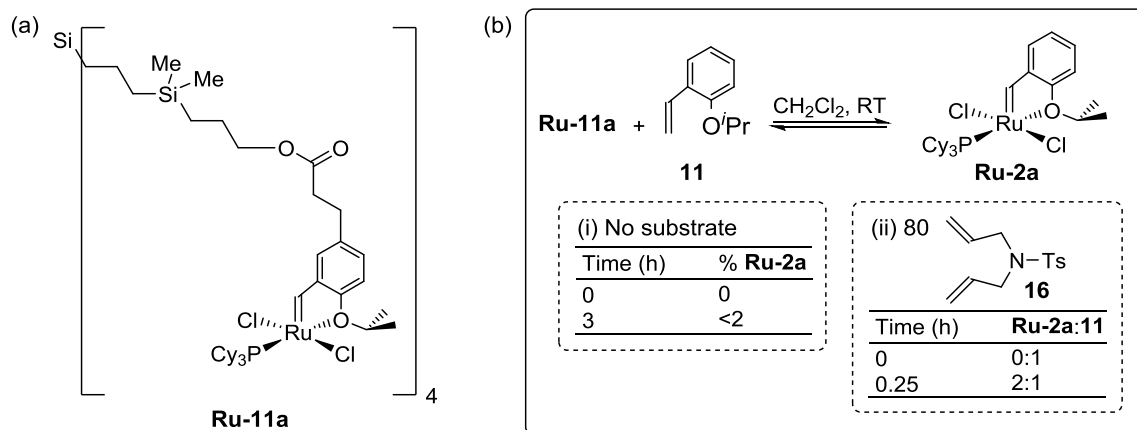


Figure 3.2 An early study of the release-return mechanism for the first-generation Hoveyda catalyst **Ru-2a**.¹ (a) Tetranuclear species **Ru-11a** used in the crossover study. (b) Generation of **Ru-2a** from **Ru-11a** and **11**: (i) in the absence of substrate (control) or, (ii) in the presence of diallyl tosylamine **16**.

The second-generation catalyst **Ru-2b** is now heavily used in metathesis reactions, owing to its high activity and efficiency in comparison to **Ru-2a**.¹ The relevance of the release-return mechanism is therefore of great interest for this catalyst, rather than its little-used first-generation analogue. No consensus has emerged from studies designed to probe the validity of the release-return mechanism for **Ru-2b**.^{1,28-34} The conclusions of these studies (key examples of which are discussed below) are contradictory, and each study contains some limitations.

For the second-generation system, the first direct experimental examination of the boomerang mechanism was a 2005 study by Hoveyda and co-workers.²⁸ Three sol-gel supported derivatives of **Ru-2b**, each bearing a different NHC ligand (**Ru-12a/b** and **Ru-13**, Figure 3.3) were used in a crossover study. Five cycles of the RCM of **17** (Scheme 3.2) were performed with four sol-gel pellets all in one pot (2 equiv **Ru-12a**, 1 equiv **Ru-12b**, 1 equiv **Ru-13**; 10 mol% Ru total; each pellet bore an identifying mark). Following RCM, the deuterium-labeled pellets **Ru-12a** were removed, rinsed with CH₂Cl₂ and treated with styrenyl ether **11** to cleave the catalyst. Following chromatographic purification of the

released complexes, ^1H NMR analysis of diagnostic alkylidene and alkyl signals indicated only 2% crossover (**Ru-2b/d**: 16.56 ppm ($\text{Ru}=\text{CHR}$), **Ru-2e**: 16.45 ppm ($\text{Ru}=\text{CHR}$), **Ru-2b**: 4.18 ppm (NCH_2)). A control experiment without substrate, under otherwise identical conditions, indicated no crossover or leaching. The small but measurable amount of return (2%) in the presence of substrate was proposed as evidence that the release-return mechanism is feasible.

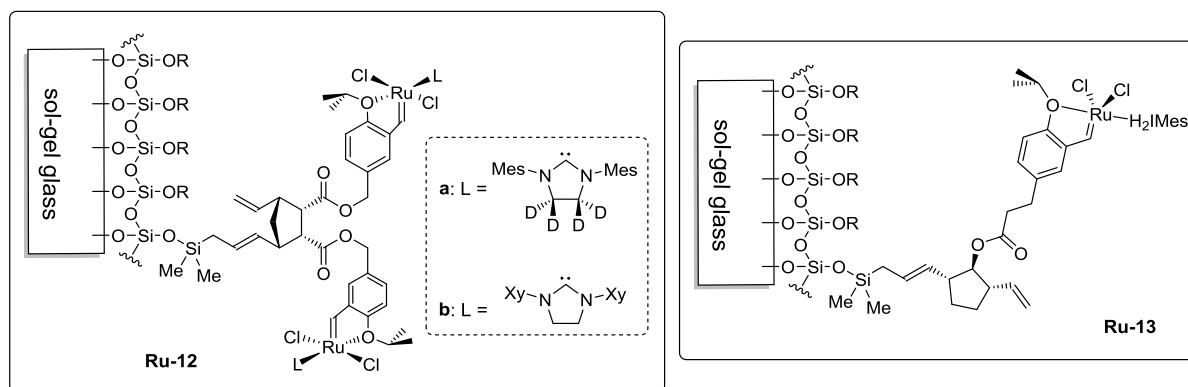
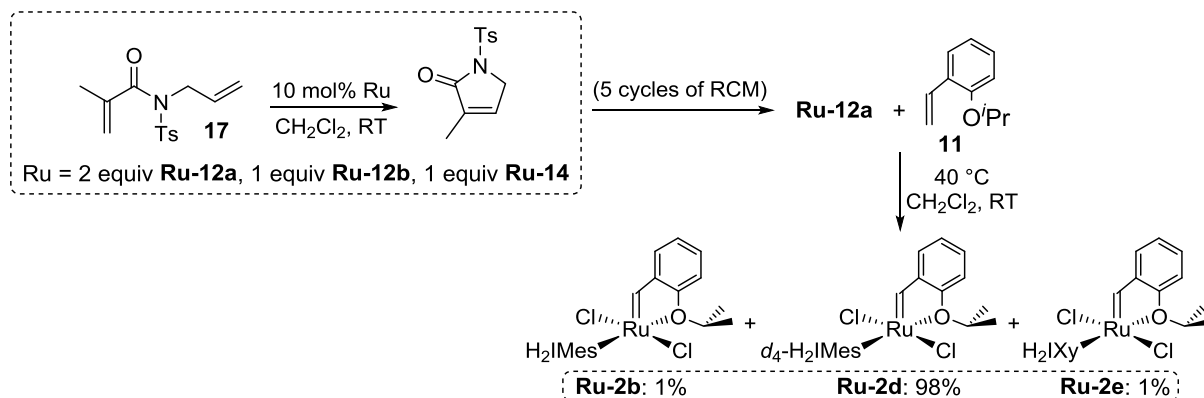


Figure 3.3 Sol-gel-supported catalysts employed in the crossover study (see Scheme 3.2) by Hoveyda and co-workers.²⁸



Scheme 3.2 Crossover study designed by Hoveyda and co-workers²⁸ to investigate the release-return mechanism. Following RCM, **Ru-12a** was removed and treated with **11**.

A more skeptical view might take this as good evidence against operation of the boomerang mechanism to any significant extent. However, several factors may limit the relevance of this experiment to target-directed catalytic reactions. First, the high catalyst loadings (10 mol%) would inhibit complete initiation, and hence minimize re-uptake of the styrenyl ether. Second, modifications to the styrenyl ether ligand **11** have been shown to have a major impact on rates of reaction, particularly on initiation.^{32,34-44} Tethering the styrenyl ether ligand **11** to a sol-gel support could retard or accelerate initiation. Retardation would cause under-reporting of re-uptake. Conversely, if all the catalyst was initiated, the ca. 2% crossover observed could indicate that the release-return mechanism is essentially irrelevant, as suggested above. However, perturbations that facilitate release of the styrenyl ether ligand **11** could also inhibit recapture by **Ru-5b**, minimizing the extent of crossover.

A 2013 computational study by Solans-Monfort and co-workers³³ argues against the relevance of re-uptake. Analogues of **Ru-2b** were examined, most relevant of which was **Ru-14**, where the isopropyl group was (perplexingly) truncated to ethyl (Figure 3.4). **Ru-2b** itself was not studied. The calculated energy barrier for catalyst regeneration – that is, reaction of **Ru-5b** with the styrenyl ether **18** – was found to be lower than the barrier to catalyst initiation. While this suggests that re-uptake could be feasible, the calculated energy barrier to reaction of the four-coordinate methyldiene **Ru-5b** with product olefin was even lower. Given the greater abundance of product olefin vs. styrenyl ether **18**, strong competition with regeneration was proposed. This neglects the thermodynamic stability of the styrenyl ether complex, however, which would effectively “funnel out” **Ru-14** from the cycle, hence favouring regeneration (Figure 3.4). This study also indicated that initiation is energetically disfavoured, and that incomplete catalyst initiation should be expected.

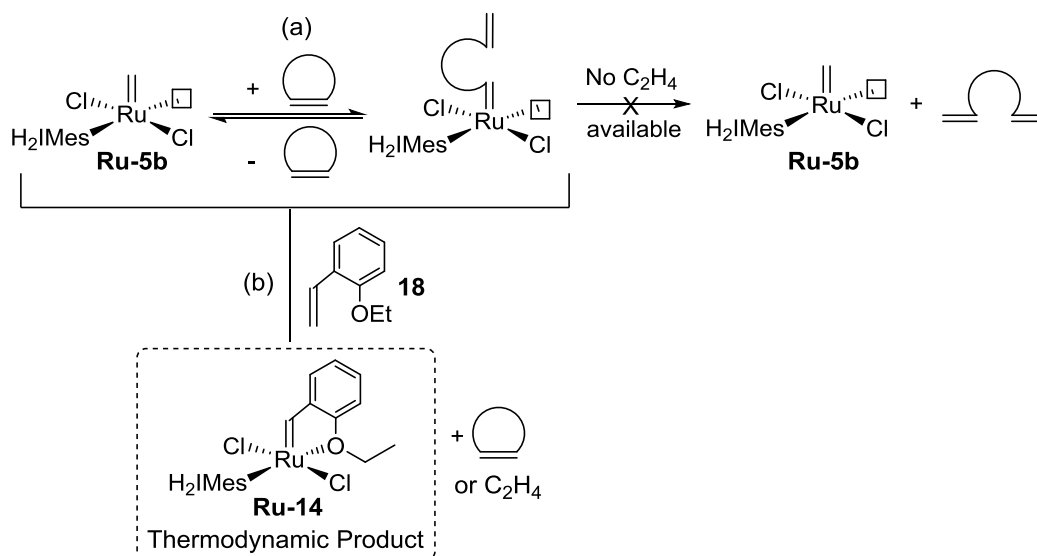


Figure 3.4 Reactions of **Ru-5b** with (a) product olefin or, (b) styrenyl ether **18**; studied computationally.³³ Reaction with styrenyl ether **18** is favoured due to formation of the thermodynamically stable product **Ru-14**.

The most persuasive experimental evidence against the release-return mechanism comes from a study by the Plenio group,³¹ using derivatives of **Ru-2b** bearing a fluorophore or a fluorine group para to the ether oxygen (**Ru-15**). For fluorophore-tagged **Ru-15a**, fluorescence is quenched when the styrenyl ether **19a** is bound to the metal centre, and restored when this ligand is released (Figure 3.5). Use of **Ru-15a** in the RCM of DeDAM **14** led to a strong increase in fluorescence relative to a solution of **Ru-15a** in the absence of substrate, reaching a plateau within 2 h. These experiments were carried out in a quartz cuvette with an attached argon balloon; stirring was not apparently possible. No quenching of fluorescence was observed over 18 h, implying that the liberated styrenyl ether tag **19a** does not re-coordinate to the metal centre. A similar conclusion was reached when performing RCM with fluorine-tagged **Ru-15b**. The chemical shift difference between the ^{19}F NMR signals for free (**19b**: -125.4 ppm) and bound (**Ru-15b**: -126.2 ppm) fluorine-tagged styrenyl ether enabled observation of the ruthenium species present after metathesis. RCM of DeDAM **14** using 0.1 mol% of fluorine-tagged **Ru-15b** revealed only **19b** after 4 h, again suggesting complete initiation with no recapture by **Ru-5b**.

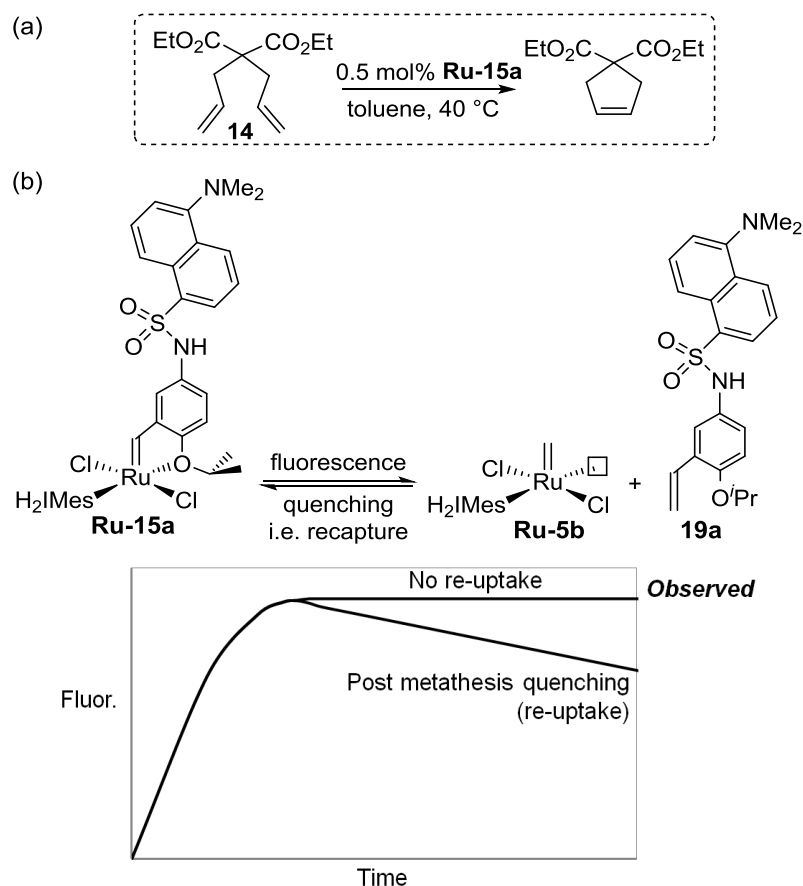


Figure 3.5 Plenio study³¹ with evidence against the release-return mechanism. (a) RCM of DeDAM **14** with **Ru-15a**. (b) Expected effect of dissociation and re-association of fluorophore-tagged styrenyl ether ligand **19a** on fluorescence evolution.

A question mark in the Plenio study is the absence of quantitative data for the initiation of **Ru-15**. As noted above, incomplete initiation will result in underreporting of re-uptake (that is, re-uptake of the styrenyl ether tag **19a** can only occur if it has been released). Plenio inferred complete initiation from separate experiments with **Ru-15a** and ethyl vinyl ether (EVE), in which the ultimate fluorescence yield was found to be independent of catalyst loading. However, there are a number of problems with this comparison. First, comparison is complicated by the use of very different reaction conditions for the two experiments (see Table 3.1). Several of these differences will favour more rapid initiation of EVE over DeDAM **14**. First, the use of different olefin concentrations is problematic. In the reaction with EVE use of ca. 5-25 times more equivalents of olefin (relative to Ru) allows fluorescence to be reached in a couple minutes vs. hours for DeDAM **14**. Reactions with

EVE will initiate faster at higher concentrations as the sterically accessible EVE reacts via an interchange-associative mechanism.¹⁹⁻²¹ Bulkier substrates such as DeDAM **14**, are constrained to initiate by a dissociative mechanism. Second, the two substrates differ substantially in their reactivity: EVE is an electron-rich olefin allowing it to react rapidly and quantitatively. Evidence for incomplete initiation for the RCM of DeDAM **14** is the fact that with **Ru-15a** the reaction took 40 min to reach full conversion, but maximum fluorescence intensity was observed only after 2 h. This suggests that release of the fluorophore-tagged styrenyl ether **19a** continues after RCM is complete.

Table 3.1 Summary of differences in reaction of **Ru-15a** with DeDAM **14** and EVE.

	DeDAM 14	EVE
Reaction	RCM	CM
Olefin	Conventional	Electron-rich
Initiation mechanism	Dissociative	Interchange-associative
Equivalents of olefin per Ru*	200	5000, 2500, 1000
Temperature	40 °C	20 °C
Reaction time	Maximum fluorescence after 2 h (40 min for quantitative conversion)	1.5-3 min to reach maximum fluorescence**

*Concentration not specified. ** Conversions not specified.

In this system, as in the Hoveyda study described above, perturbation of the styrenyl ether **11** could potentially retard initiation or inhibit re-uptake. However, similar rate plots were observed for the tagged catalysts **Ru-15**, vs. **Ru-2b** except for the fluorine-tagged **Ru-15b** where higher conversions (ca. 15%) are observed at early stages of the reaction (ca. 5 min). More problematic may be the use of reaction conditions that limit loss of ethylene. This could affect the outcome in two ways. First, retention of ethylene has been shown to accelerate decomposition of the ruthenium metathesis catalysts,^{17,45} which would impede re-uptake of the tagged styrenyl ether **19a**. Second, ethylene is expected to significantly out-compete the bulkier, less electron-rich styrenyl ether as a substrate, particularly when the stoichiometric ratios of the two dramatically favour ethylene. Unproductive metathesis between the catalyst and retained ethylene almost certainly accounts for the sustained release of the tagged styrenyl ether **19a** even after the RCM reaction was complete. Competition by ethylene for the ruthenium center, and decomposition of the active species, would (respectively) mask any decrease in fluorescence associated with recapture, and reduce the extent of re-uptake.

More convincing was a subsequent study by Grela and co-workers³⁰ using **Ru-16**, an analogue of **Ru-2b** bearing a perdeuterated isopropyl group (Figure 3.6). From the data summarized below, Grela concluded that the second-generation Hoveyda catalyst **Ru-2b** undergoes both complete initiation, and rapid regeneration via the release-return mechanism. A preliminary background reaction confirmed that CM of deuterated **Ru-16** with unlabeled styrenyl ether **11** is slow, as expected for the exceedingly low proportion (1 equiv) of **11** relative to typical substrate concentrations. Emergence of the methine signal for the isopropoxy group (measured by ¹H NMR analysis) reached a 1:1 ratio of **Ru-2b** to **Ru-16** only after 48 h at 25 °C in CD₂Cl₂ (21 mM Ru). It was not explicitly stated how this ratio was determined, and an error in compound numbering in the supporting information for the paper complicates matters further, but the methine septet for the emerging **Ru-2b** was probably integrated vs. that for **11** (reported chemical shifts: **Ru-2b**: δ_H 4.90-5.08; **11**: δ_H 4.55-4.75 ppm; both in CD₂Cl₂).

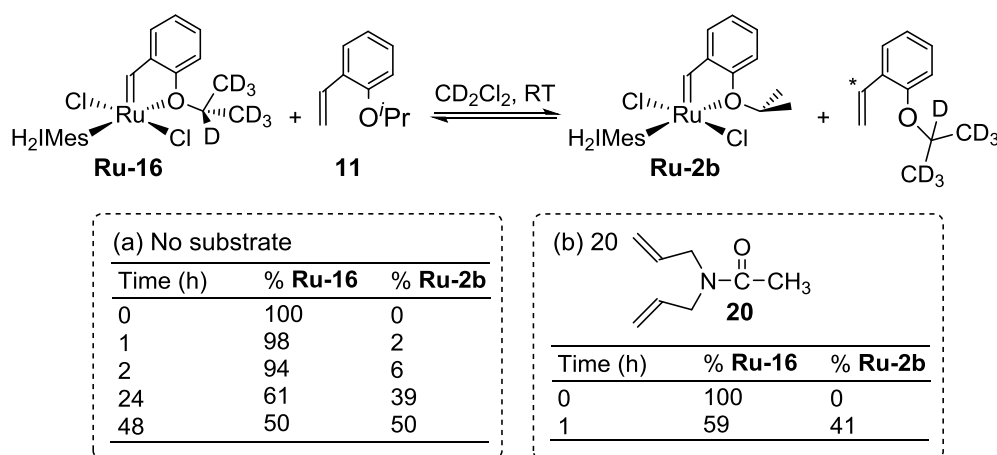


Figure 3.6 Equilibration between deuterium-labeled **Ru-16** and **Ru-2b**.³⁰ (a) In the absence of substrate (control). (b) In the presence of 20 equiv *N,N*-diallylacetamide **20**.

It should be noted that this background reaction was carried out without stirring (which would retard exchange), in a sealed NMR tube from which the ethylene co-product cannot escape (which will accelerate catalyst deactivation; loss of **Ru-5b** is expected, which will reduce emergence of the methine), and without an internal standard (which would permit assessment of the extent of decomposition). The importance of each of these limitations will be examined in Section 3.2.2 below. Nevertheless, it was inferred that the presence of **11**

should not significantly perturb metathesis of a more reactive substrate. Accordingly, RCM of *N,N*-diallylacetamide **20** was carried out using 5 mol% of deuterated **Ru-16**, in the presence of 5 mol% unlabeled **11**. (Note that while the reaction was carried out at 25 °C in CH₂Cl₂, as in the control experiment, differences in the conditions include stirring under argon, which will enable loss of ethylene, at a catalyst concentration 21 times lower). Once RCM was complete (1 h), the level of uptake was assessed. Unfortunately, however, the uptake of **11** was not assessed in the same way as in the control experiment. Instead, the catalyst species were isolated by stripping off the solvent and chromatographing the residue. The ruthenium products were isolated in 85% yield. ¹H NMR analysis of this material reportedly indicated 59% D: that is, 41% loss of the deuterium label. This is a key piece of information, but it is unclear how the loss was quantified. It cannot be by integration of the methine signals for free vs. bound **11**, as the free ligand will be lost during chromatography. Presumably the methine septet was integrated relative to some other well-defined signal that comprises both **Ru-16** and **Ru-2b**. In any case, Grela concluded that the loss in deuterium atom content could not be due to the background exchange reaction (which resulted in only ca. 2% exchange at 1 h), but must rather be due to the release-return mechanism.

This study, though strongly suggestive, is limited by the potential for loss of the ²H-label via non-metathetical pathways. It is unclear whether the deuterium atom on the isopropyl methine group can exchange with other ligand protons, as no control experiment was carried out to assess this. In a study of methyldiene catalyst **Ru-6b-d₂**, however, van Rensburg and co-workers⁴⁵ reported rapid scrambling between the Ru=CD₂ group and H₂IMes and/or PCy₃ ligands. Specifically, NMR analysis indicated incorporation of ¹H into ethylene-d₄ on exposure to the catalyst for 16 h at 40 °C in C₇D₈. In the Grela study, scrambling of the isopropoxy Me₂CD deuterium in **Ru-16** could increase the apparent extent of uptake. That is, emergence of the diagnostic methine CH signal could arise from washing out of the deuterium label, not just uptake of protio-**11** (release-return mechanism). In addition, the absence of an internal standard means that the amount of catalyst decomposition cannot be determined, although the chromatographic yield suggests that this may be up to 15%. Decomposition would presumably affect the four-coordinate species **Ru-5b** most and would therefore reduce the extent of uptake. Finally, there is the potential for added exchange between free styrenyl ether **11** and **Ru-16** when the reaction was concentrated for isolation of

the ruthenium species. While this exchange was slow at RT in the background reaction (see above), it is unclear what the rate is at the much higher concentrations of **11** (which is comparatively involatile) achieved during evaporation of the solvent.

A common limitation in the studies above is the use of highly reactive model substrates, which limits the relevance of the findings (Table 3.2). In this thesis work, the potential operation of the boomerang mechanism was probed in RCM and CM reactions involving more demanding metathesis substrates containing 1,1- or 1,2-disubstituted olefins. To establish the extent to which the styrenyl ether **11** is recaptured by four-coordinate **Ru-5b**, while minimizing perturbation of the system, metathesis was carried out using second-generation Hoveyda catalyst **Ru-2b** in the presence of equimolar ^{13}C -labeled styrenyl ether (**11***), synthesis of which was recently described by Marciniak and co-workers.⁴⁶ The rate of uptake of **11*** during catalysis was gauged from the **Ru-2b**:**Ru-2b*** ratio, assessed by integrating the alkylidene signals (Figure 3.7b). A separate experiment was designed to distinguish between capture of **11*** by **Ru-5b** (Figure 3.7a, path i), and the reaction of **11*** with virgin **Ru-2b** (Figure 3.7a, path ii).

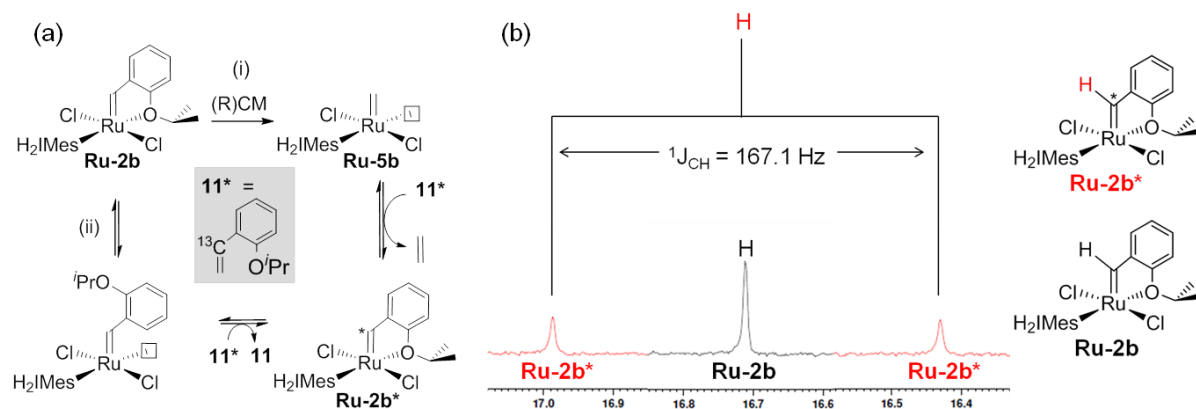
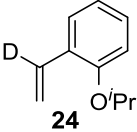
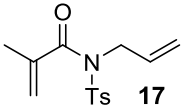
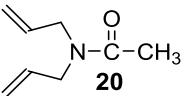
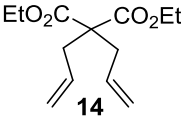
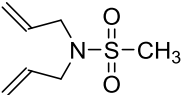


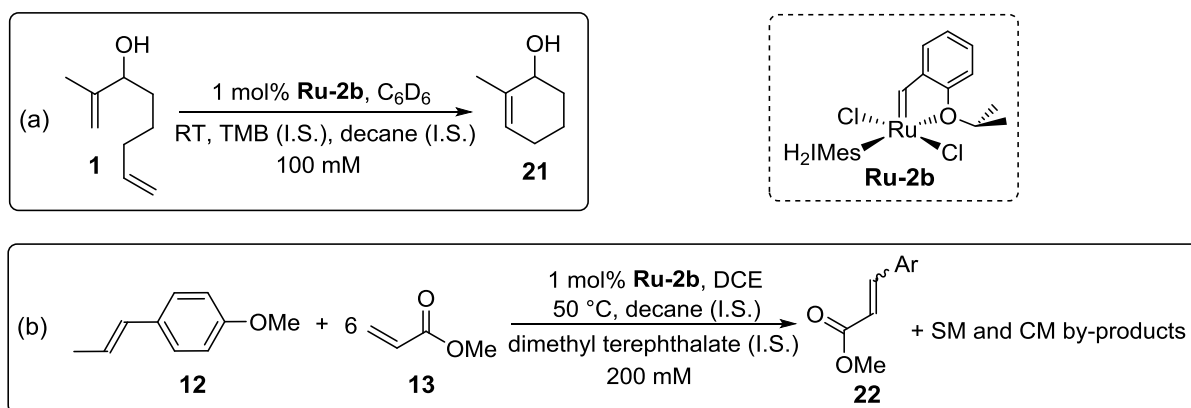
Figure 3.7 (a) Potential pathways for uptake of **11*** during metathesis. (i) "Boomerang" pathway: capture of **11*** by **Ru-5b**. (ii) Background reaction: reaction of **Ru-2b** and **11***.⁴⁷ (b) Representative ^1H NMR spectrum (alkylidene region) depicting the distinct signals for labeled **Ru-2b*** (doublet, red) and non-labeled **Ru-2b** (singlet, black).

Table 3.2 Summary of key literature studies examining the release-return mechanism.

System studied	Conclusion and limitations	Ref.
 24 Equimolar reaction with Ru-2b (C ₆ D ₆ , RT, 5 mM)	• Equilibrium reached after 52 h (45% conversion) • Not examining the ability of Ru-5b to capture styrenyl ether	34
 17 10 mol% sol-gel supported Ru-12 and Ru-13 See Figure 3.3 and Scheme 3.2	• Minimal re-uptake (2%) • Steric perturbation • Open system (plastic cap vented with a small hole) • Catalyst decomposition not quantified	28
 20 5 mol% D-labeled Ru-16 See Figure 3.6	• Supports uptake (41% in 1 h) • Non-metathetical H-D scrambling may over-report uptake • Difference from background CM reaction exaggerated by different conditions ([Ru] = 21 mM vs. 1 mM for catalysis see Figure 3.9) • Open system • Catalyst decomposition not quantified	30
 14 0.5 mol% dansyl- or fluorine-tagged Ru-15 See Figure 3.5	• Minimal re-uptake (observed no quenching of fluorophore-tagged styrenyl ether 19a) • Steric or electronic perturbations • Open system (argon balloon) • Catalyst decomposition not quantified	31
 Ru-14 Computational study with Ru-14 See Figure 3.4	• Calculated energy barriers for catalyst regeneration lower than for catalyst initiation but higher than reaction of Ru-5b with product olefin • Due to thermodynamic stability of Hoveyda complex Ru-14, regeneration would be favoured over reaction with product olefin • Incomplete initiation is expected	33

To ensure that catalyst initiation, and hence uptake of **11***, was not artificially enhanced, ambient or moderate temperatures were used. Thus, cyclization of **1** to yield trisubstituted cycloolefin **21** (earlier shown to proceed efficiently at 5 mol% catalyst)¹ was carried out at

RT in C₆D₆, and CM of anethole **12** and methyl acrylate **13** to yield cinnamate **22**⁴⁸ was carried out at 50 °C in dichloroethane (DCE) (Scheme 3.3). Reactions were performed in the glovebox, irrespective of temperature, so that samples could be withdrawn without any risk of air-induced catalyst decomposition that would limit formation of **Ru-2b***. The results outlined below provide strong evidence that the boomerang pathway is operative in metathesis reactions promoted by **Ru-2b**, and is an important contributor to improved catalyst lifetime and productivity.



Scheme 3.3 Metathesis reactions studied in exploring the relevance of the release-return mechanism for **Ru-2b**. (a) RCM reaction. (b) CM reaction. Decane was used as an internal standard (I.S.) for GC analysis; dimethyl terephthalate and TMB as an internal standard (I.S.) for ¹H NMR analysis.

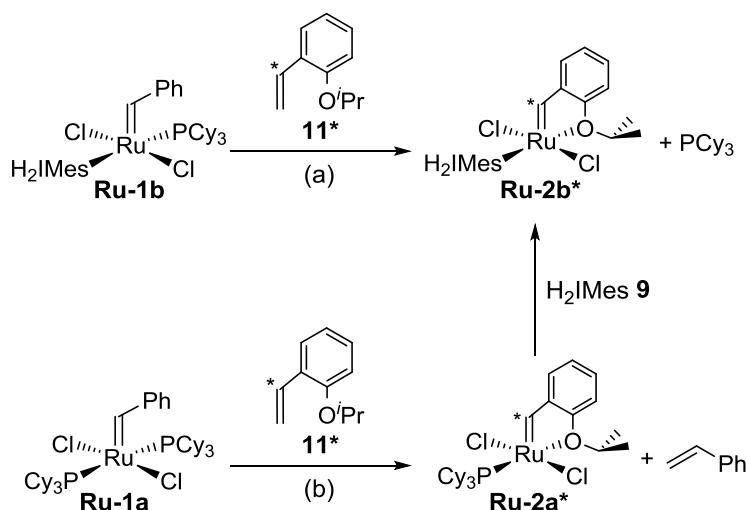
3.2 Results and discussion

3.2.1 Synthesis of the ¹³C-labeled Hoveyda catalyst **Ru-2b***

3.2.1.1 Synthesis of **Ru-2b*** by cross-metathesis of **Ru-1b** with **11***

Synthesis of **Ru-2b** has been achieved by cross-metathesis of the second-generation Grubbs catalyst **Ru-1b** with **11** (Scheme 3.4a),^{1,49-51} as well as by ligand exchange of the first-generation Hoveyda catalyst **Ru-2a** (prepared from CM of **Ru-1a** with **11**) with H₂IMes **9** (Scheme 3.4b).^{1,2,49,52,53} The former route was used by Marciniec and co-workers⁴⁶ in their recently-reported route to **Ru-2b***. These workers used CuCl (added at the outset of reaction) to scavenge the PCy₃ liberated. The product was obtained in 82% yield after purification by column chromatography. However, with use of CuCl, removal of the resulting copper-

phosphine complexes could complicate work-up and trace amounts can be detrimental to a metathesis catalyst.⁵¹



Scheme 3.4 Potential routes to ^{13}C -labeled **Ru-2b***. (a) Marciniec route,⁴⁶ involving CM of **Ru-1b** with **11***. (b) By ligand exchange of **Ru-2a*** (prepared from CM of the **Ru-1a** with **11***) with H_2IMes **9**.

In this thesis work, the released phosphine was scavenged using the ion-exchange resin Amberlyst 15, which has been successfully used to sequester free PCy_3 in the synthesis of **Ru-2b**,^{49,51} **Ru-1b**,⁴⁹ and related metathesis catalysts. In large-scale syntheses of the Grubbs and Hoveyda catalysts, Dr. Bianca van Lierop of this research group⁴⁹ found that adding Amberlyst 15 resin to the reaction mixtures allowed removal of free phosphine, eliminating the need for CuCl and chromatography. Work-up involved simply filtration and evaporation of the solvent. Prior to attempting installation of labeled **11***, however, optimization experiments were carried out with unlabeled **11** on the planned scale of the labeling reaction. Thus, metathesis exchange of the Grubbs catalyst **Ru-1b** with the styrenyl ether **11** was undertaken at $50\text{ }^\circ\text{C}$ using 4 equiv Amberlyst 15 resin. Amberlyst 15 resin was used off-the-shelf: the presence of small amounts of water in the resin was advantageous in effecting hydrolysis of residual H_2IMes **9** to *N*-mesityl-*N*-(2-(mesitylamino)ethyl)formamide **23**, the polarity of which promotes binding to the resin and hence aids purification. After 2 h the resin was filtered off and washed with THF. The solvent was removed and the solid was washed with cold pentane ($-35\text{ }^\circ\text{C}$) to yield the second-generation Hoveyda catalyst **Ru-2b**.

(207 mg, 93%). ^1H NMR analysis in CDCl_3 revealed an unassigned alkylidene singlet at 17.78 ppm (consistently 2–5%), in addition to the expected singlet for **Ru-2b** at 16.56 ppm. Attempts to remove this contaminant by washing with hexanes and reprecipitating from THF and hexanes were unsuccessful.

To examine whether the impurity could result from decomposition of the Grubbs catalyst in the presence of Amberlyst 15 resin, clean **Ru-1b** was heated at 50 °C in THF with 4 equiv of resin. Just 44% **Ru-1b** remained after 2 h, as judged by integration against an internal standard (a capillary tube containing PPh_3 in C_6D_6), but no new alkylidene signal emerged. Similar experiments with **Ru-1a** showed extensive decomposition (79%), while neither Hoveyda catalyst **Ru-2a** nor **Ru-2b** showed any decrease over 2 h. While both generations of the Hoveyda catalysts are clearly more stable than the Grubbs catalysts,¹ the identity of the contaminant remains unresolved. It is unclear why this by-product was consistently observed in this thesis work, but not the experiments carried out by Dr. van Lierop.

3.2.1.2 Synthesis of **Ru-2b*** via ligand exchange of **Ru-2a*** with **H₂IMes 9**

The direct synthesis of **Ru-2b*** from **Ru-1b** was therefore abandoned, and the approach of Scheme 3.4b was pursued. Again, optimization reactions were carried out with unlabeled **11**. In the first step of the synthesis, Grubbs catalyst **Ru-1a** and 1.05 equiv **11** were dissolved in THF and stirred with 4 equiv dry Amberlyst 15 resin at 50 °C for 2 h. After removal of the resin and solvent, NMR analysis revealed 4% remaining **Ru-1a**. The solid was therefore redissolved in THF and stirred with 0.1 equiv **11** and an additional 0.4 equiv dry Amberlyst 15 resin at 50 °C for another 2 h. The resin was then filtered off and washed with THF, after which the solvent was evaporated and the resulting solid was washed with cold pentane (–35 °C) to remove the styrene by-product and any excess **11**. NMR analysis revealed a small (ca. 2%) contaminant characterized by a $^{31}\text{P}\{^1\text{H}\}$ NMR singlet at 43.1 ppm, as well as the expected singlet for **Ru-2a** at 59.36 ppm. This impurity was removed by dissolving the crude product in 2:1 CH_2Cl_2 /hexanes and passing it through a plug of silica in the glovebox. This afforded the clean first-generation Hoveyda catalyst **Ru-2a** in 72% yield. To effect ligand exchange, a solution of **Ru-2a** in THF was stirred with a slight excess **H₂IMes 9** (1.05 equiv) at RT for 2 h. Amberlyst 15 resin (4 equiv, off-the-shelf) was then added to scavenge the released PCy_3 , and the reaction was stirred vigorously at 40 °C for 2 h. As ^1H NMR analysis

showed residual, unreacted **Ru-2a**, this material was resubjected to the Amberlyst 15-THF treatment for an additional hour at 40 °C. Work-up afforded the second-generation Hoveyda catalyst **Ru-2b** in 97% yield (overall yield from **Ru-1a** is 70%).

¹³C-Labeled **Ru-2b*** was prepared in a similar manner. Thus, the first-generation Grubbs catalyst **Ru-1a** was stirred with 1.05 equiv of **11*** in the presence of dry Amberlyst 15 resin (4 equiv) for 3 h at 50 °C. Work-up afforded brown **Ru-2a*** in 92% yield; again, the ruthenium side-product was present (2%), but the longer reaction time relative to that above resulted in complete consumption of starting **Ru-1a**. NMR analysis revealed a doublet of doublets for the alkylidene proton at 17.37 ppm (³J_{PH} = 4.6 Hz, J_{CH} = 162.9 Hz; C₆D₆); likewise, a ¹³C{¹H} NMR doublet at 275.5 ppm (²J_{PC} = 14.4 Hz). The ligand exchange was carried out on crude **Ru-2a*** by stirring with 1.1 equiv H₂IMes **9** for 2 h at RT, following which off-the-shelf Amberlyst-15 resin (4 equiv) was added and the reaction was stirred at 40 °C for 3 h. Following work-up, purification by passage through a silica plug afforded 274 mg of the green ¹³C-labeled second-generation Hoveyda catalyst **Ru-2b*** (77% yield). Without use of crude **Ru-2a***, a greater yield is expected (97% based on experiments performed above with pure **Ru-2a**) as purification is no longer required (i.e. no silica plug). ¹H NMR analysis in C₆D₆ showed the expected alkylidene doublet at 16.72 ppm (¹J_{HC} = 167.1 Hz); the corresponding ¹³C{¹H} NMR alkylidene singlet appeared at 292.5 ppm. No ³¹P{¹H} NMR signal was evident.

3.2.2 Rate of cross-metathesis between **Ru-2b** and **11***

Preliminary experiments were carried out to assess the rate of uptake of **11*** via CM between **11*** and **Ru-2b** (see Figure 3.7a, path ii), in the absence of substrate. This also provided an opportunity to explore various factors that could affect the rate of reaction, including solvent, concentration, and open or sealed vessels. The results are presented in the sections below. Conversion of **Ru-2b** to **Ru-2b*** was measured by ¹H NMR analysis by integrating the alkylidene signal against TMB until the ratio of **Ru-2b**:**Ru-2b*** reached equilibrium.

3.2.2.1 Effect of solvent on reaction rates

Complete CM of **Ru-2b** with **11*** was about two times faster in C₆D₆ than in CD₂Cl₂. For reactions at RT, equilibrium was reached in 9 h in C₆D₆, vs. 20 h in CD₂Cl₂ (Figure 3.8; both reactions 21 mM in Ru). Percy and co-workers⁵⁴ recently reported that initiation of **Ru-2b** is

ca. two times faster for the reaction of **Ru-2b** and EVE (25 °C) in aromatic solvents (benzene, toluene) than chlorinated (CH_2Cl_2 , CHCl_3). Initiation rates were measured by UV/Vis analysis at EVE concentrations ranging from 25 to 200 mM ([Ru] held at 0.1 mM throughout).

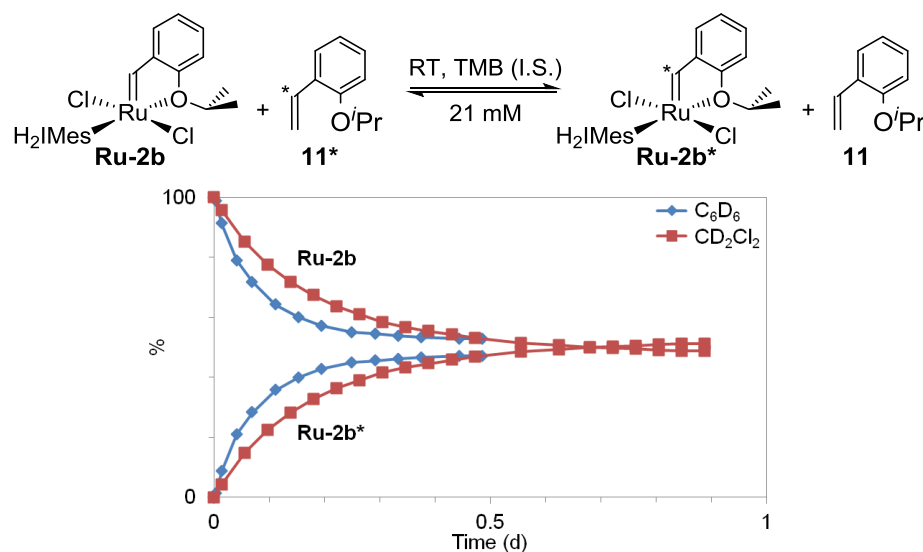
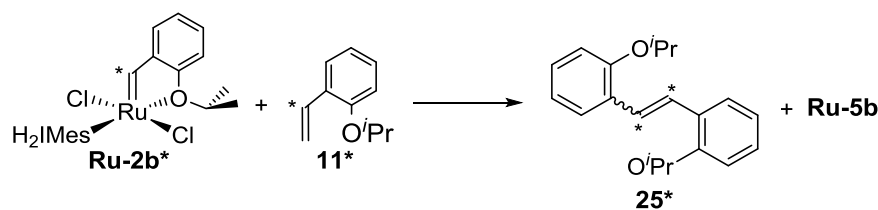


Figure 3.8 CM of **Ru-2b** with styrenyl ether **11***, showing slower reaction in C_6D_6 than CD_2Cl_2 . Reactions performed in a sealed J. Young NMR tube (RT, 21 mM Ru). Final ratio of **Ru-2b**:**Ru-2b***: 53:47 in C_6D_6 ; 49:51 in CD_2Cl_2 .

Slight differences from the originally-expected 50:50 ratio were observed (typically 53:47). A similar discrepancy was observed by Blechert and co-workers³⁴ in crossover experiments between **Ru-2b** and deuterium-labeled styrenyl ether **24** in C_6D_6 (one deuterium at the β carbon). Deviation is attributed to loss of the ^{13}C -label via self-metathesis of **11*** to yield doubly-labeled stilbene **25*** (Scheme 3.5). The disubstituted stilbene is sterically and electronically deactivated and thus resists recycling. Wherever the emerging **Ru-2b*** reacts with **11*** – which, until equilibrium is reached, remains the dominant form of the styrenyl ether – net loss of the label will result, resulting in a slightly higher proportion of **Ru-2b** (Scheme 3.5). This is observed consistently for CM in C_6D_6 (as evidenced by both the Blechert³⁴ data and the present work). Reactions in 1,2-dichloroethane (DCE) likewise equilibrated at a **Ru-2b**:**Ru-2b*** ratio of 54:46 (Section 3.2.4). In contrast, the **Ru-2b**:**Ru-2b*** ratio in CD_2Cl_2 (49:51) does not show loss of the ^{13}C -label. The difference is puzzling and at this stage remains unexplained.



Scheme 3.5 Formation of doubly-labeled stilbene **25*** from CM of **Ru-2b*** and **11***.

The timescale of equilibration is faster than the 48 h reported in the Grela study³⁰ described above using deuterated **Ru-16** and styrenyl ether **11** (CD₂Cl₂, RT, 21 mM Ru). In comparison, the first-generation Hoveyda catalyst **Ru-2a*** exchanges much more slowly with **11**: as shown by Amy Reckling of this research group,⁵⁵ CM of **Ru-2a*** and **11** took 19 d to reach a **Ru-2a**:**Ru-2a*** ratio of 53:47 (C₆D₆, 29 mM Ru). During RCM of diethylallylmethallyl malonate **26**, Grela³⁰ observed slower reaction for the first-generation catalyst **Ru-2a** vs. **Ru-2b**; specifically, 56% RCM at 3 h, vs. 96% for **Ru-2b**. Interestingly, this trend is counter to that seen for the Grubbs catalysts, where initiation (i.e. phosphine dissociation) is faster for the first-generation complex **Ru-1a** than the second-generation catalyst **Ru-1b**.^{16,56}

3.2.2.2 Effect of concentration on reaction rates

The background reactions above were carried out at a **Ru-2b** concentration of 21 mM, with equimolar **11***. This is much higher than the catalyst concentrations typically used in metathesis. Therefore, the CM of **Ru-2b** and **11*** was repeated using 1 mM **Ru-2b** (again with 1 equiv **11***; C₆D₆, RT) in a sealed J. Young NMR tube. The reaction then required 141 h (almost 6 d) to reach equilibrium (Figure 3.9). Similar behaviour was observed when both reactions (1 mM and 21 mM) were performed in an open, stirred vessel. As noted above, Blechert and co-workers³⁴ have also performed reactions between **Ru-2b** and deuterium-labeled styrenyl ether **24**. At 5 mM Ru, 45% conversion was reached after 52 h at RT (C₆D₆). In the Grela study,³⁰ the ruthenium concentration in the crossover experiment was 1 mM, but the rate of background exchange was measured at 21 mM. This means that the background reaction would over-report the amount of exchange relative to that obtained during catalysis.

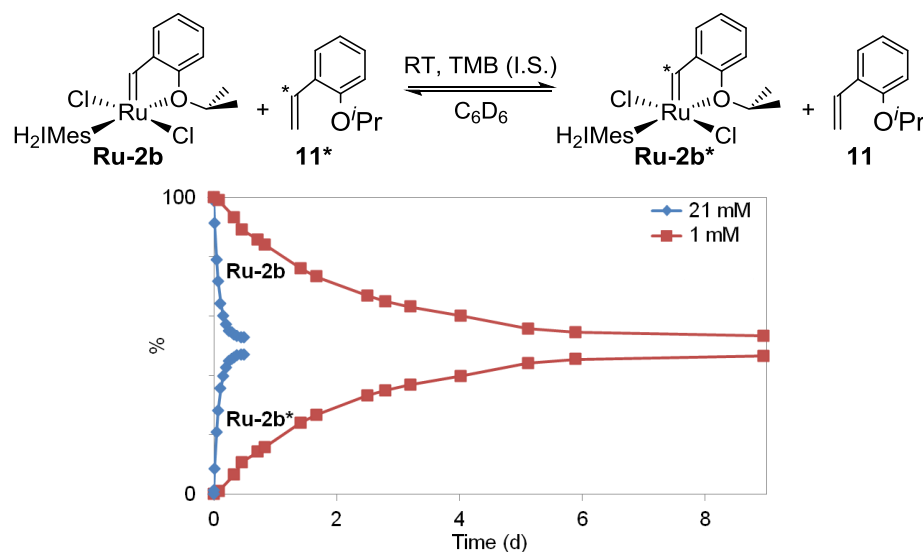


Figure 3.9 Effect of concentration on the rate of reaction (21 mM vs. 1 mM). Reactions performed in a sealed J. Young NMR tube. Final ratio of **Ru-2b**:**Ru-2b*** was 53:47.

3.2.2.3 Impact of headspace and stirring on reaction rates

Metathesis reactions are normally carried out in vessels open to an inert atmosphere (N₂ or Ar), to promote loss of the ethylene by-product (Section 3.2.3.2).⁵⁷ To examine the impact of a sealed system, identical CM reactions were carried out in a sealed J. Young NMR tube (C₆D₆, 1 mM), and in an open, stirred Kontes flask. As shown in Figure 3.10, the time to reach equilibrium was halved in the open, stirred system, decreasing from 141 h (ca. 6 d) to 70.5 h (ca. 3 d). Stirring promotes efficient mass transfer.²⁴ Grubbs⁵⁸ and Grela³⁰ have both acknowledged that results can differ when reactions are performed in closed vs. open systems; however they claim that using a closed system is valid for evaluating general differences between catalysts. Although, this may be true, Grela³⁰ cannot compare his background reaction and catalyst recovery experiments as they are performed in different reaction vessels. To gauge whether this background reaction is relevant during our catalysis, the reaction between **Ru-2b** and **11*** must be performed under identical conditions including the same solvent, ruthenium concentration, and reaction vessel.

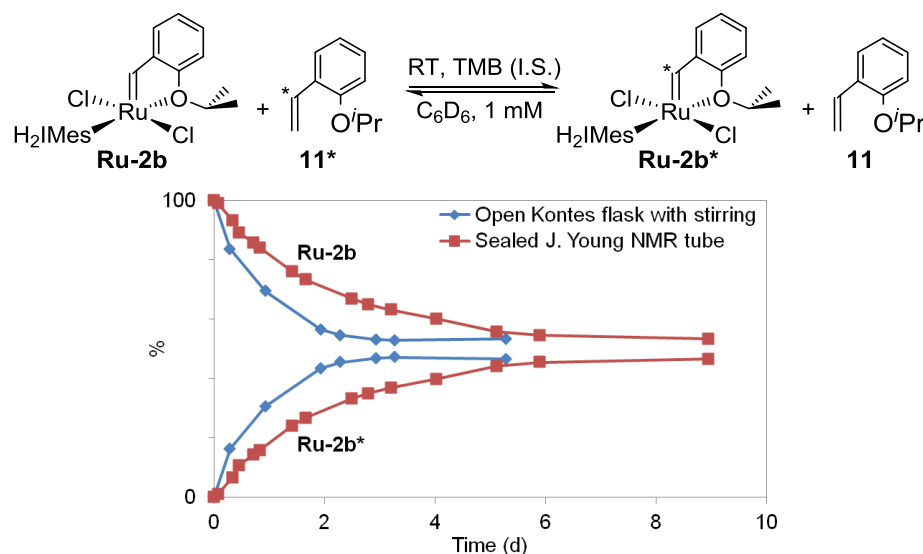
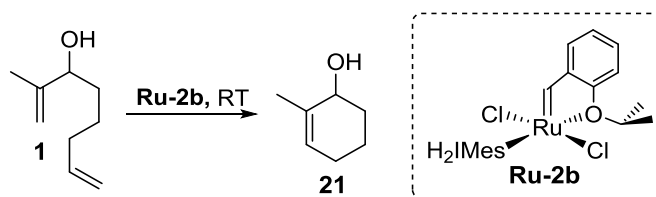


Figure 3.10 Effect of reaction vessel on CM rate: comparison of open, stirred Kontes flask with sealed J. Young NMR tube. Final ratio of **Ru-2b**:**Ru-2b*** was 53:47.

3.2.3 Establishing the relevance of the boomerang mechanism during RCM

3.2.3.1 Experimental design

To establish whether uptake of **11*** by the active species **Ru-5b** occurs under catalytically-relevant operating conditions, the RCM of **1** by **Ru-2b** was carried out in the presence of **11*** (Scheme 3.6). A further question was whether, as Hoveyda has suggested,¹ the styrenyl ether **11** is unable to compete with other olefins for binding to ruthenium, except 1,1-disubstituted substrates,²⁵ meaning that recapture occurs only after diene is completely consumed. To examine these theories with a more realistic substrate than those used in prior studies described above, we selected **1** as a relatively challenging RCM substrate. Hoveyda has reported¹ that **1** cannot be cyclized by **Ru-2a** but is 98% cyclized with **Ru-2b** in 2 h (5 mol% **Ru-2b**; 5.2 mM Ru, CH_2Cl_2 , 100 mM **1**). No rate curve was obtained. In the present work, a lower catalyst loading (1 mol %) was used, to determine whether the boomerang mechanism is operative under realistic operating conditions. Furthermore, reactions were undertaken in C_6D_6 rather than CH_2Cl_2 . Additionally, the perturbing influence of **11*** (1 equiv vs. Ru) is examined in Section 3.2.3.4 and 3.2.3.5.



Scheme 3.6 RCM of **1** into trisubstituted olefin **21**. Conditions: 1 mol% **Ru-2b** (1 mM), C₆D₆, 100 mM **1**, decane (I.S.), TMB (I.S.), 1 mol% **11**.

To better understand the effects (if any) of these procedural changes, the reactions were performed with unlabeled **11**. Prior to use of **11***, two key questions need to be answered. First, we needed to determine the minimum ruthenium concentration at which the Ru=CHAr signal can be integrated. The lowest ruthenium concentration possible was required to ensure maximum catalyst turn-on. However, the concentration cannot be so low such that the percent uptake of label cannot be properly accessed by ¹H NMR analysis. In addition, we needed to establish the ideal substrate:catalyst ratio for that concentration to get convenient reaction time. To determine if recapture occurs prior to diene consumption, a slow reaction time was desired. Therefore, RCM reactions were carried out with 1 equiv of **11** (to Ru) at various ruthenium concentrations (0.44 to 4.3 mM, [S] = 78 mM). As expected, the lower the ruthenium concentration the slower the reaction as can be seen by Figure 3.11a. Therefore, a ruthenium concentration of 0.44 mM (catalyst loading of 0.56 mol%) was found to give the slowest reaction time of 140 min. However, at such a low concentration of ruthenium, integration of the alkylidene proton was problematic. With a scan time of 5 min, the signal to noise ratio was too low (Figure 3.11b and Figure 3.12). Longer scan time translates into extended time in a sealed system, leading to problems arising from trapped ethylene (see Section 3.2.3.2). As a result, a ruthenium concentration of 0.88 mM (reaction time = 120 min) resulted in proper integration of the Ru=CHAr. Optimal conditions were therefore determined to be a substrate concentration of 100 mM and a catalyst loading of 1 mol% ([Ru] = 1mM). This resulted in satisfactory spectra being obtained within 5 min, enabling accurate snapshots of the evolving **Ru-2b**:**Ru-2b*** ratio.

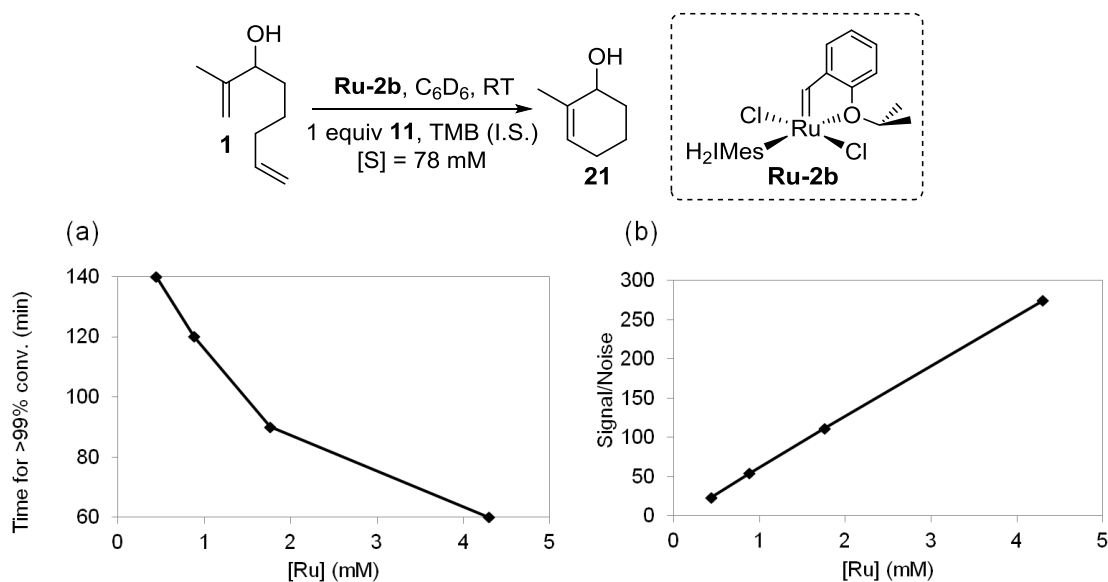


Figure 3.11 Effect of ruthenium concentration on (a) RCM reaction rate or, (b) signal to noise ratio (S/N) of the alkylidene signal. Determined by 1H NMR analysis.

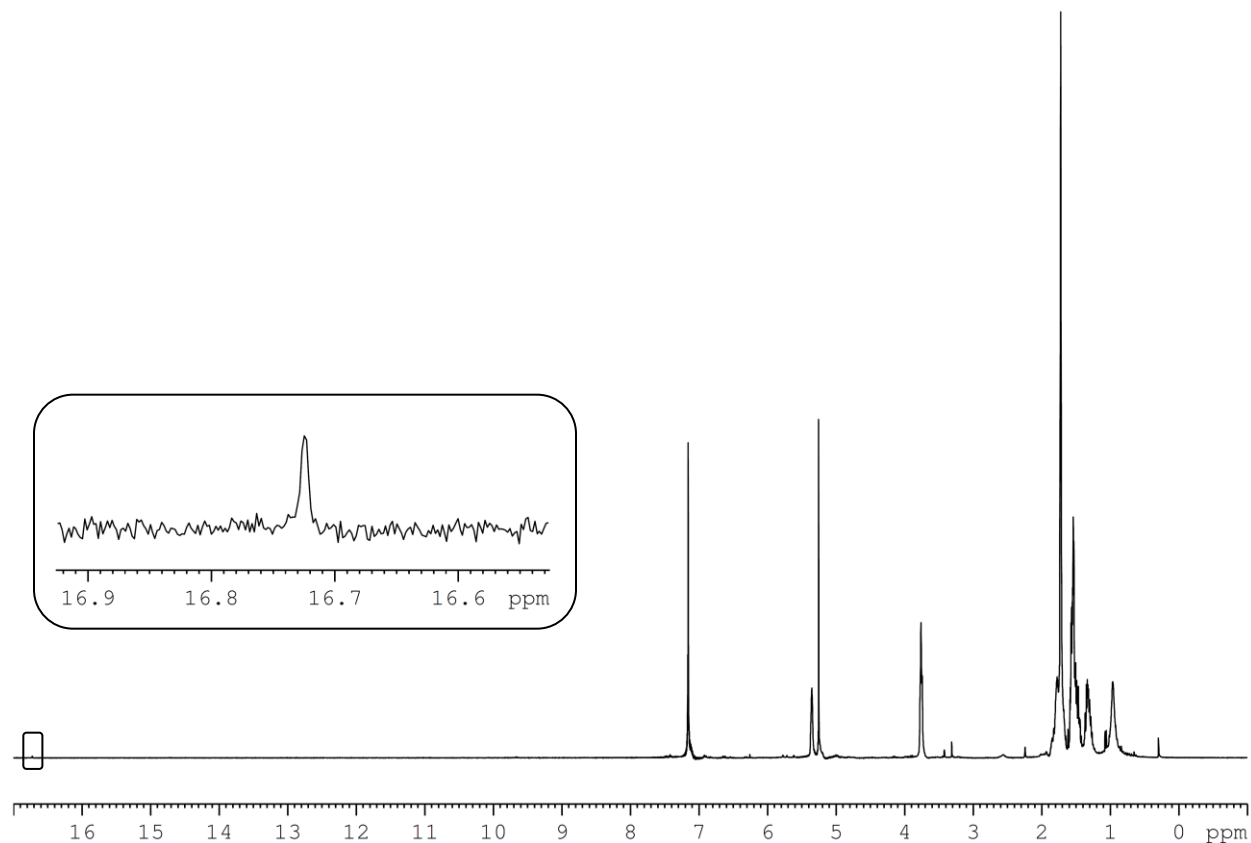


Figure 3.12 1H NMR spectrum at >99% conversion for RCM reaction performed with 0.44 mM ruthenium showing low signal to noise ratio (S/N).

3.2.3.2 Impact of ethylene on catalyst decomposition

Ethylene, a by-product of the RCM reaction, has been shown to negatively affect total turnover numbers in RCM. This is due to unproductive exchange, ultimately leading to catalyst decomposition.^{17,45,59-62} Tulchinsky and co-workers⁶⁰ treated Grubbs catalyst **Ru-1a** with ethylene prior to exposure to an olefin, and found that with longer exposure times turnover numbers declined. They determined that this effect directly correlates to the amount of active catalyst remaining. Therefore, ethylene has a major impact on catalyst deactivation. In particular, these results showed that the ruthenium methylidene **Ru-6a**, formed upon exposure of **Ru-1a** with ethylene, is unstable. Grubbs has also shown that the methylidene **Ru-6** is susceptible to decomposition,⁶² and that the Hoveyda catalyst **Ru-2b** decomposes in the presence of ethylene (C_6D_6 , 55 ° C).¹⁷ Upon exposure to C_2H_4 , unidentified ruthenium hydride species were observed after 1 d by 1H NMR analysis. However, the half-life of **Ru-2b** is over a month under the same conditions.

Degenerate metathesis of **Ru-5b** with ethylene could prevent re-uptake of styrenyl ether **11**. Furthermore, increasing the amount of time the catalyst stays in this vulnerable state due to degenerate metathesis leads to increased decomposition. We therefore wanted to determine the effect of ethylene on the amount of decomposition of Hoveyda catalyst **Ru-2b**. The RCM of **1** was performed in both a sealed J. Young NMR tube and open Schlenk tube with stirring. The amount of **Ru-2b** remaining at 93-95% conversion (10-30 min) was examined by 1H NMR analysis via integration of the alkydine proton vs. TMB. Using 1 mol% **Ru-2b**, ca. 25% more catalyst remained in the open system vs. the sealed systems (83% vs. 58%, Figure 3.13). This difference was smaller (ca. 15%) when the reaction was performed at 5 mol% (Figure 3.13). The unaccounted for ruthenium is likely a combination of decomposed catalyst and **Ru-5b** which cannot be observed by NMR analysis due to its instability in solution.⁶³ However, performing the reaction in a stirred vessel open to an inert atmosphere permits the C_2H_4 to dissipate limiting decomposition. This sensitivity, which is consistent with prior findings with isolated **Ru-2b**,¹⁷ could inhibit the operation of the release-return mechanism. In addition, it was observed that with the open system, less precatalyst remained at the lower catalyst loading (83% vs. 93%, Figure 3.13). At higher catalyst loadings, not all **Ru-2b** is needed to take part in the reaction. Therefore, more virgin catalyst is expected.

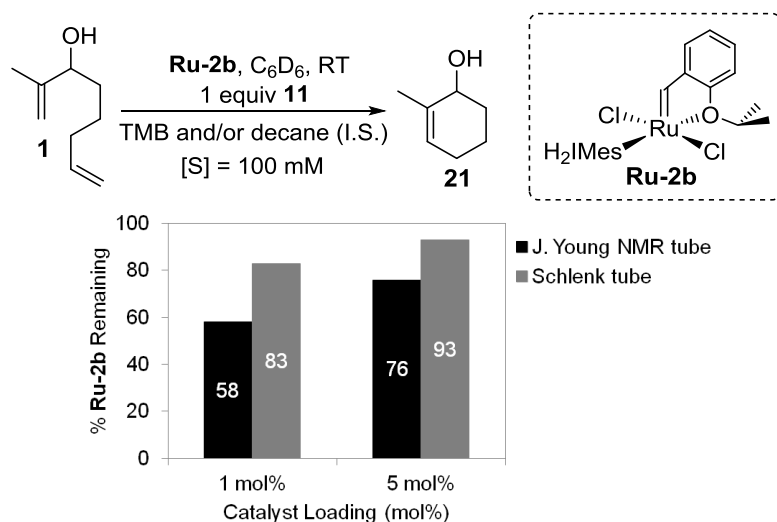


Figure 3.13 Effect of reaction vessel on the amount of **Ru-2b** remaining during the RCM of **1** at two different catalyst loadings (1 mol% or 5 mol%). Determined at 93-95% conversion (10-30 min) by 1H NMR analysis.

3.2.3.3 Reaction vessels and effect on reaction rates

Throughout the literature, variations are seen in the approach taken to monitor reactions to gain information on product yields and reaction kinetics.^{19-22,31,54} As noted above, Grubbs⁵⁸ and Grela³⁰ have acknowledged that reaction rates differ in open vs. sealed systems (likely due to formation of ethylene), but has nonetheless used closed systems to assess general differences between catalysts. A concern in using these conditions to compare catalyst performance is the probability of differential decomposition, which affects both yields and reaction rates.^{17,24,45,57,59-62} As shown in Figure 3.14, RCM of **1** is faster in an open system with stirring vs. a sealed J. Young NMR tube (45 min vs. 100 min). A 1H NMR spectrum taken after 10 min revealed 75% conversion vs. 94% in the open system (confirmed by GC). This emphasizes the importance of using appropriate reaction conditions to assay kinetics. Reaction kinetics in a sealed system are not representative of reactions in an open system.

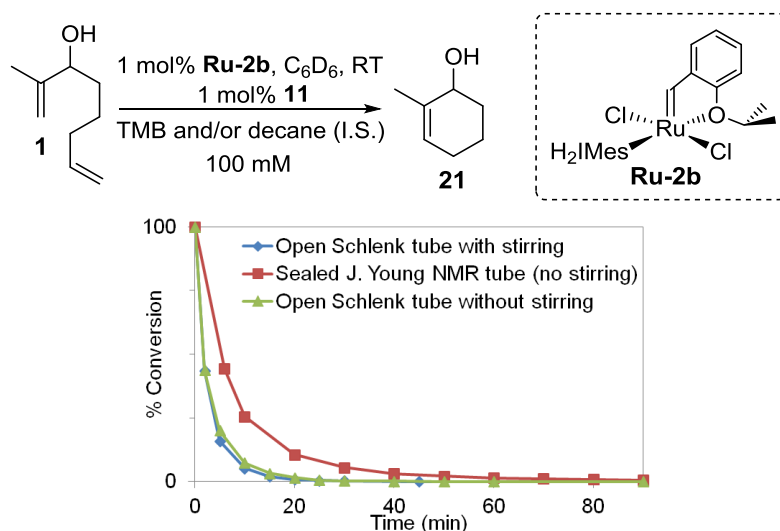


Figure 3.14 Effect of reaction vessel on reaction rates. Determined by GC (for reactions performed in a Schlenk tube) or 1H NMR analysis (for reactions performed in a J. Young NMR tube).

The slower reaction in the sealed vessel presumably reflects degenerate metathesis with ethylene, and associated catalyst decomposition (see Section 3.2.3.2).^{17,45,59-62} The small headspace in the NMR tube (which contains 0.75 mL solvent), and poor mass transfer arising from the limited gas-liquid interface, results in very different conditions than those in a Schlenk tube open to the atmosphere. In the latter, loss of ethylene is very efficient even without stirring. Thus, RCM of **1** in an open Schlenk tube without a stir bar proceeded at a rate comparable to the stirred reaction (Figure 3.14), and afforded only 0.06 equiv C_2H_4 ; 71% **Ru-2b** remained at 98% conversion (Table 3.3). Efficient liberation of the gas even without stirring is consistent with the low reported solubility of ethylene in organic solvents. Data from Lee and co-workers permits calculation of a figure of 36.7 mM ethylene in toluene at 25 °C under 1.01 bar of the gas,⁶⁴ while Justin Lummiss of this research group measured an ethylene concentration of 89 ± 1 mM in C_6D_6 at 25 °C, again under 1 atm ethylene. In the present experiments, ca. 0.35 equiv C_2H_4 (vs. the starting concentration of **1**) remained in the sealed NMR tube reactions even when metathesis was 95% complete. At this point, the amount of **Ru-2b** remaining was 58%, vs. 83% for the Schlenk tube reaction (Table 3.3).

Table 3.3 Detrimental impact of ethylene on RCM productivity and lifetime.

	Conversion ^b	% Ru-2b remaining	equiv C ₂ H ₄ ^c
open, stirred	95% (10 min)	83	0.033
open, not stirred	98% (20 min)	71	0.06
sealed, not stirred	93% (30 min)	58	0.35

^a Conditions: 1 mol% **Ru-2b**, 1 mol% **11**, C₆D₆ (100 mM **1**), RT ^b Determined by ¹H NMR analysis. Reactions reached >99% conversion within 20 min for open vessels; within 80 min for sealed. ^c Determined from integrated intensity of the C₂H₄ singlet at δ_{H} 5.25 ppm, vs. sum of olefin signals for starting diene **1** (δ_{H} 4.75 ppm) and product **21** (δ_{H} 5.36 ppm).

3.2.3.4 Investigating the impact of stoichiometric styrenyl ether **11**

To determine the perturbing effect of added **11** on the RCM kinetics, all reactions were carried out with and without added **11**. Prior to demonstrating the detrimental presence of ethylene, experiments were conducted in a sealed J. Young NMR tube. In the presence of 1 equiv **11**, reaction was ca. two times slower, taking 100 min to reach completion vs. only 60 min without additional **11** (Figure 3.15a). The same trend was observed when the reactions were performed with stirring in an open Schlenk tube (Figure 3.15b). Under these conditions, the reaction took 45 min in the presence of 1 equiv **11** vs. only 20 min without additional **11**. Blechert and co-workers⁴¹ have also observed that during the RCM of protected *N,N*-diallylamine **16**, addition of 1.2 equiv of **11** (to Ru) inhibits catalyst initiation, hindering the rate of the reaction.

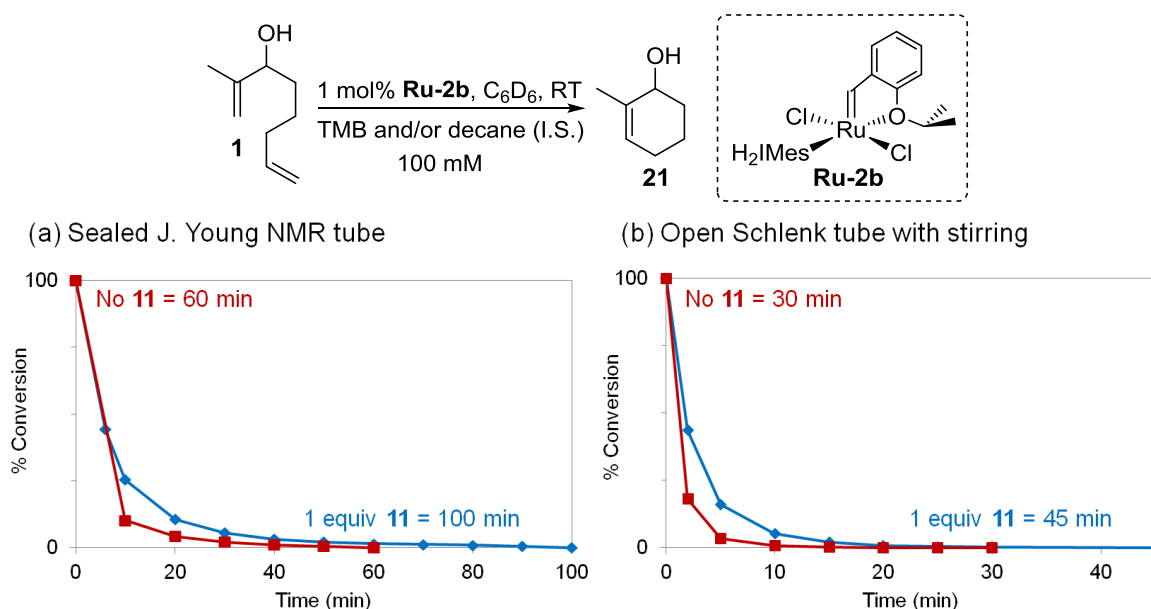


Figure 3.15 Effect of 1 equiv **11** on reaction rates in (a) sealed J. Young NMR tube (^1H NMR analysis) or, (b) open Schlenk tube with stirring (GC analysis).

As a corollary, the presence of additional **11** (1 equiv to Ru) could perturb the system (see Section 3.2.3.5) resulting in competition between the substrate and **11** for the vacant site on **Ru-5b**. We find that even at 1 mol% **11**, vs. diene, the styrenyl ether retards the RCM reaction, presumably by regenerating **Ru-2b**, which then has to re-initiate. The PCy_3 in the Grubbs catalysts **Ru-1b** likewise inhibits metathesis by temporarily sequestering four-coordinate **Ru-5b**.¹⁸ However, as noted above, the PCy_3 ligand can also abstract the methyldiene as the phosphonium chloride $[\text{CH}_3\text{PCy}_3]\text{Cl}$ causing irreversible decomposition.

Styrenyl ether **11** can therefore compete with substrate. However, it also extends catalyst lifetime. During the RCM of **1**, a larger amount of **Ru-2b** remained at 95-99% conversion with 1 equiv **11** present (83%) vs. no additional **11** (68%). Higher concentrations of the vulnerable species **Ru-5b** in the absence of **11**, means more opportunity for decomposition. Interestingly, the reaction solution retained the green colour of **Ru-2b** during the course of the RCM reaction in the presence of added **11**. In its absence, the reaction mixture turned brown immediately after **Ru-2b** was added. Therefore, **11** is capable of competing with catalyst decomposition of **Ru-5b** and extending catalyst lifetime by regenerating the stable alkylidene **Ru-2b**.

3.2.3.5 Evaluating perturbation of the catalytic system

RCM of **1** was performed using **Ru-2b*** with 5 equiv **11** (to Ru) to assess the impact of excess **11** on the catalytic system. After 1.75 h, the reaction reached 99% conversion (Figure 3.16). In the presence of 5 equiv **11**, the reaction was about five times slower, reaching ca. 55% conversion in 10 min (vs. 2 min with 1 equiv **11**). The first-order rate plot (Figure 3.17) is consistent with this: non-linearity at later stages presumably reflects catalyst decomposition. RCM in the presence of 1 equiv **11** was ca. 2.3 times slower than that in the absence of **11**. Perturbation by styrenyl ether is most pronounced at high concentrations when the substrate concentration approached that of **11**.

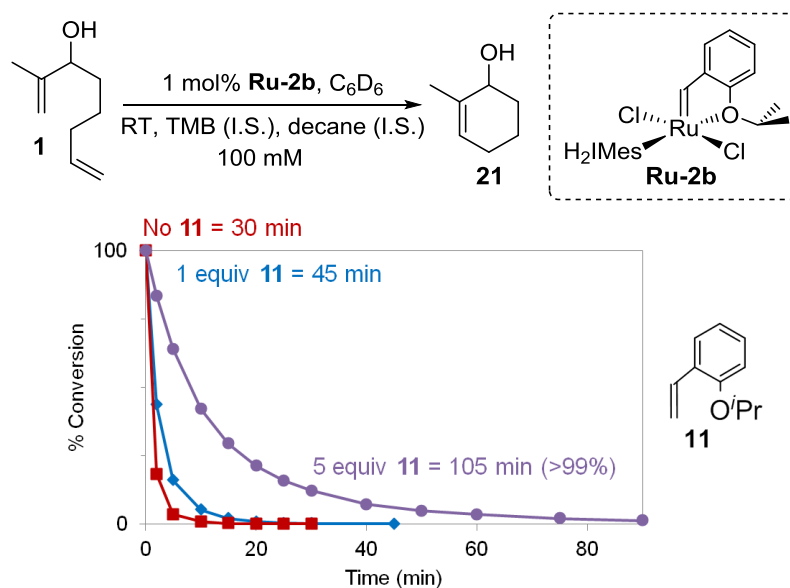


Figure 3.16 Effect of added **11** (1 or 5 equiv) on reaction rates to assess perturbation of the system (determined by GC). Reactions performed in an open Schlenk tube with stirring.

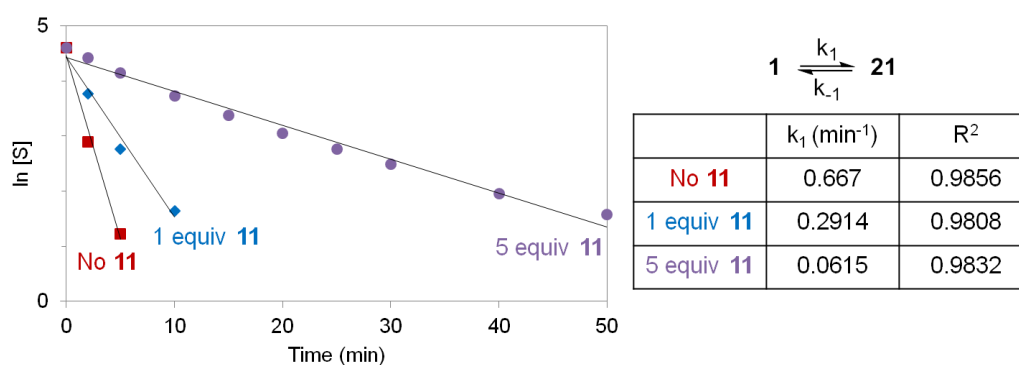


Figure 3.17 Rate plot illustrating first-order dependence on substrate concentration.

With 5 equiv **11***, the ratio of **Ru-2b**:**Ru-2b*** reached 81:19 at 98% conversion (50 min). As the expected **Ru-2b**:**Ru-2b*** ratio was obtained with either 1 or 5 equiv **11** (see Section 3.2.3.6), the entire catalyst charge was involved in the reaction. Therefore, perturbation by excess **11** will not affect the ability of **Ru-5b** to uptake the styrenyl ether but rather only the rate of metathesis.

3.2.3.6 Assessing uptake of the ^{13}C -labeled styrenyl ether **11***

After optimization of the RCM of **1** (Figure 3.18a), the reaction was carried out in the presence of 1 equiv **11*** to assess uptake of the labeled compound. The **Ru-2b**:**Ru-2b*** ratio was measured at 95% conversion – that is, prior to complete consumption of **1** – to clarify whether CM of the styrenyl ether **11*** can compete with substrate, or whether it occurs only once substrate is depleted, as suggested by earlier work.^{1,23} Remarkably, ^1H NMR analysis indicated essentially complete equilibration even at this very short reaction time (**Ru-2b**:**Ru-2b*** = 55:45). Under the same conditions, but in the absence of substrate, equilibration of **11*** requires days (Figure 3.18) generating <1% **Ru-2b*** after 10 min. Uptake of the styrenyl ether **11*** was clearly dramatically faster during catalysis, to the extent that the background reaction of **Ru-2b** with **11*** makes a negligible contribution to the proportion of **Ru-2b*** at 10 min. When the reaction was performed in a sealed J. Young NMR tube, after 30 min (95% conversion), the **Ru-2b**:**Ru-2b*** ratio was found to be 55:45 vs. 65:35 after 6 min (56% conversion). Therefore, uptake occurs prior to complete consumption and styrenyl ether **11*** can readily compete with substrate. This is strong experimental evidence for the operation of the release-return mechanism.

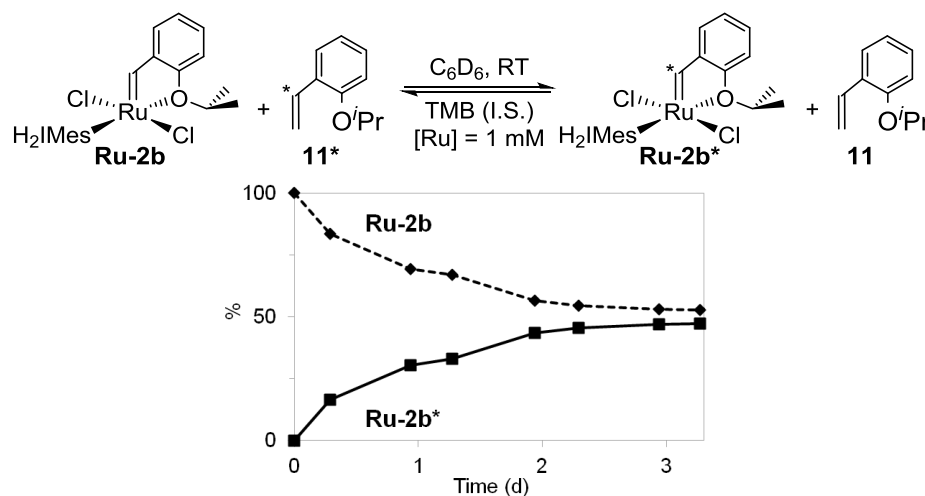


Figure 3.18 Rate of CM between **Ru-2b** and **11*** (background equilibration reaction) under exact conditions of RCM. Final ratio of **Ru-2b**:**Ru-2b*** was 55:45.

The rate profiles for the RCM of **1**, was the same regardless of whether **Ru-2b*** + **11** or **Ru-2b** + **11*** was used (Figure 3.19a). When using **Ru-2b*** as the source of the ^{13}C -label, a ^1H NMR spectrum collected at 95% conversion (10 min) showed a 45:55 ratio of **Ru-2b**:**Ru-**

2b*. The background reaction between **Ru-2b*** and **11** took just over 3 d to reach a **Ru-2b:Ru-2b*** ratio of 43:57. This reaction time was similar to the reaction performed with **Ru-2b** and **11*** (Figure 3.18). The contribution of the background CM reaction is clearly negligible on the 10 min timescale, indicating that the proportion of exchange observed during catalysis must originate in capture of **11** by **Ru-5b**. As a side note, the 45:55 ratio of **Ru-2b:Ru-2b*** observed was opposite to that found during reaction using **Ru-2b** and **11*** (55:45; Figure 3.19b). That is, in the present reaction, a higher proportion of the unlabeled styrenyl ether **11** is lost to unrecyclable stilbenoids. This is due to the higher concentration of **11** (not **11*** as in previous reactions).

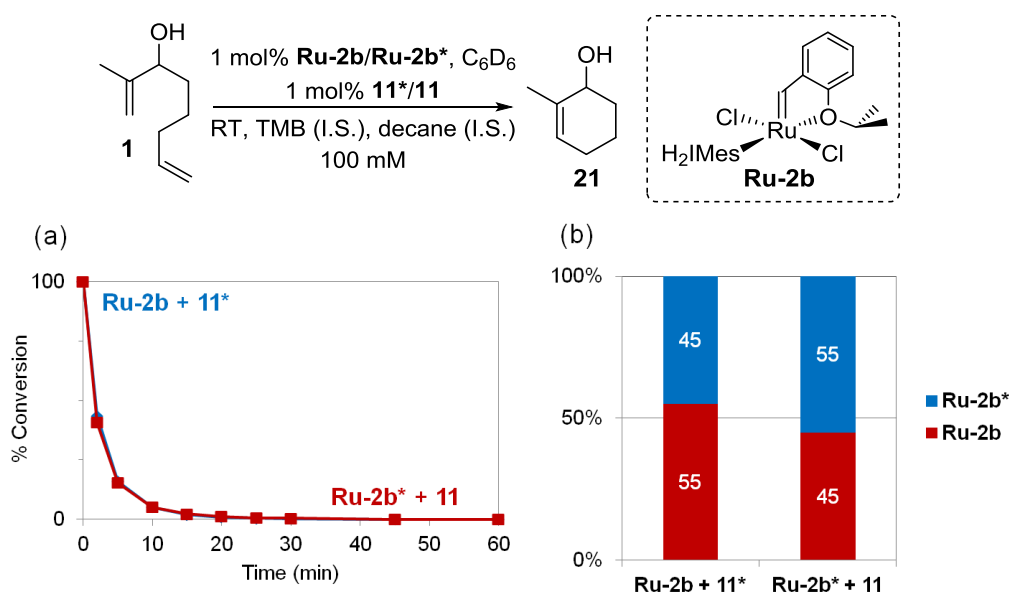
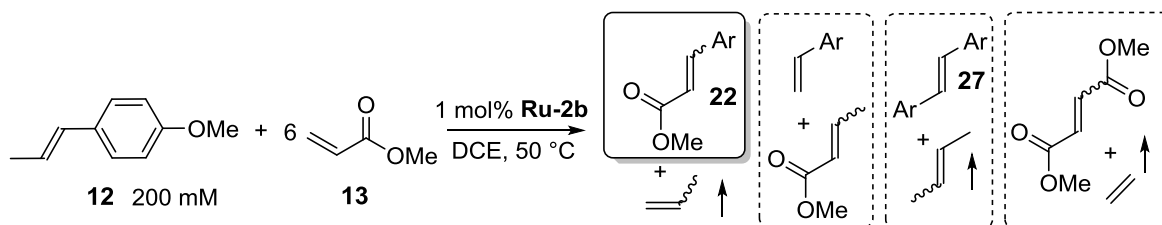


Figure 3.19 RCM of **1** with **Ru-2b** and **11*** vs. **Ru-2b*** and **11**. (a) Rate profiles. (b) Ratio of **Ru-2b:Ru-2b*** at 10 min (95% conversion), measured by integrating the NMR signals for $\text{Ru}=\text{CHAr}$.

3.2.4 Exploring the boomerang mechanism for **Ru-2b** during CM

Recent work from the Fogg group⁴⁸ described the one-step transformation of essential-oil phenylpropenoids into high-value antioxidants. The synthetic methodology involved CM of acrylates with phenylpropenoids using **Ru-2b**. This reaction was re-examined in the present study to determine if the release-return mechanism is operative in this much more demanding reaction (Scheme 3.7). The challenge in this reaction lies in the sterically encumbered trans-

disubstituted olefin in **12**, and the electron-deficient acrylate **13**. For our purposes, optimization of this reaction was required to assess uptake of the ^{13}C -label (via integration of the alkydene proton vs. dimethyl terephthalate). The reaction was therefore performed at 50 °C with 1 mol% **Ru-2b**. High temperatures are typically required to recycle the stilbenoid (**27**) to reach maximum yield of the cinnamate (**22**). However, high yields are not crucial for these experiments but rather reaching full conversion was of key interest.



Scheme 3.7 CM of anethole (**12**) with methyl acrylate (**13**) to form desired cinnamate product (**22**) as well as additional CM and self-metathesis (SM) by-products.

As with the RCM of **1**, addition of 1 equiv **11** slows the reaction rate. This effect was more significant for the CM reaction. Without additional **11**, 99% conversion was reached after 1 h, as compared to 3 h with 1 equiv **11** (Figure 3.20). While the inhibiting effect of added **11** was greater than it would be under standard conditions (i.e. when initiation of **Ru-2b** furnishes the sole source of **11**), these results indicate that the styrenyl ether **11** can be expected to inhibit metathesis for relatively demanding substrates, particularly in the late stages of reaction. That is, the styrenyl ether ligand **11** present in the Hoveyda catalysts is a latent coordinating poison, like the PCy_3 ligand present in the Grubbs catalysts.

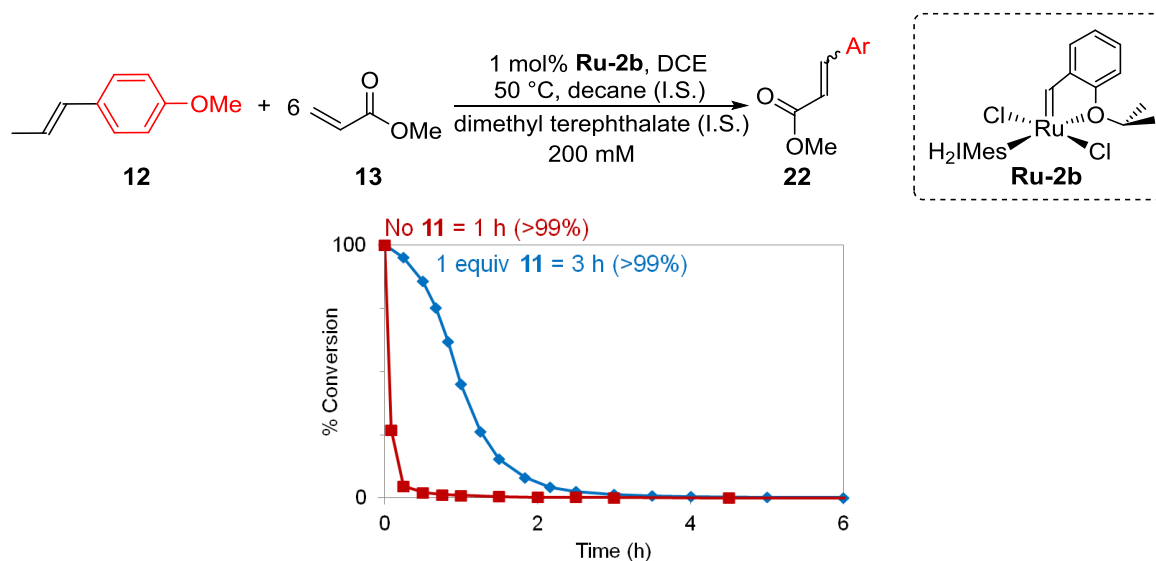


Figure 3.20 Effect of 1 equiv **11** on reaction rates when performed in an open Schlenk tube with stirring (determined by GC).

Consumption of **12** reached 92% after 110 min in the presence of 1 equiv **11***, at which point the **Ru-2b**:**Ru-2b*** ratio was 57:43. This ratio closely matches to that determined for the RCM of **1** (**Ru-2b**:**Ru-2b*** = 55:45). The change in **Ru-2b**:**Ru-2b*** ratio are attributed to differences in the progression of the reaction (92% conversion for CM reaction vs. 95% conversion for RCM reaction). In the absence of substrate, only 6% **Ru-2b*** was present at the same stage (Figure 3.21). As with the RCM reaction above, uptake of the styrenyl ether **11*** was dramatically faster under conditions of catalysis, providing strong evidence for the release-return mechanism. However, CM between acrylates and phenylpropenoids are complex reactions that can produce a variety of undesired CM and self-metathesis (SM) products as shown in Scheme 3.7. Other active species, in addition to the four-coordinate methylidene **Ru-5b**, can be produced during metathesis (Figure 3.22). This includes the ruthenium enoic carbene (**E**), formed from reaction with the excess methyl acrylate **13**. This type of alkylidene, known as an ester-alkylidene, is more reactive and less stable than “conventional” alkylidenes.^{65,66} These active species can all be generated in various amounts during catalysis. This makes it impossible to determine whether all species can recapture **11** to regenerate **Ru-2b** or if only the methylidene is saved.

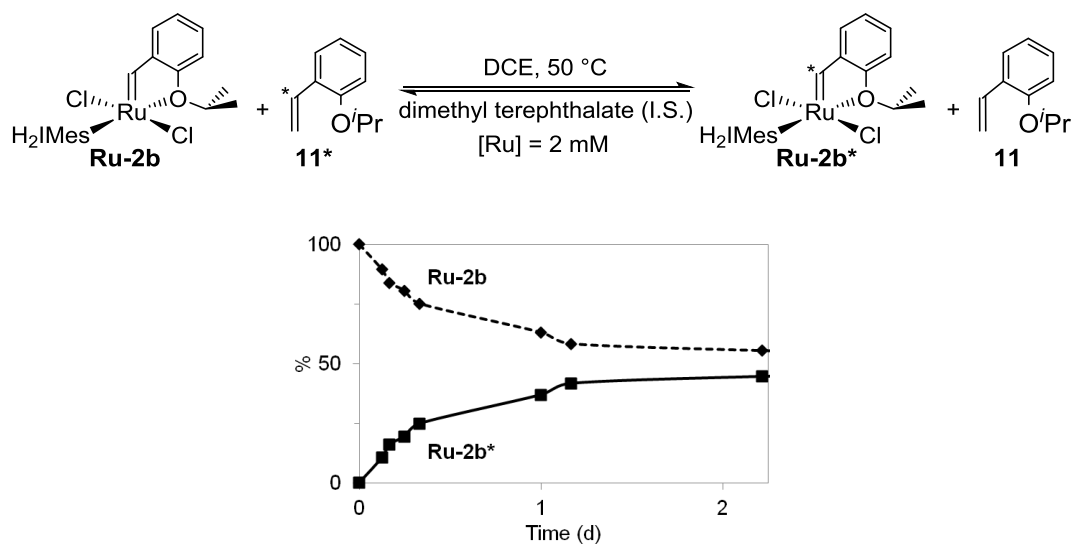


Figure 3.21 Rate of CM between **Ru-2b** and **11*** (background equilibration reaction) under exact conditions of CM. Final ratio of **Ru-2b**:**Ru-2b*** was 54:46.

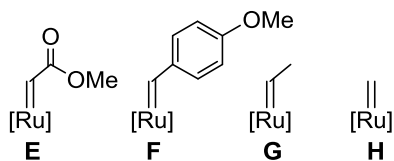


Figure 3.22 Active species present during CM of acrylates and phenylpropenoids.

3.3 Conclusions

The chapter provides strong evidence for the relevance of the boomerang mechanism in RCM and CM reactions promoted by **Ru-2b**. In contrast to prior studies, this question was probed without perturbing the reactivity of **11**, and hence its ability to be recaptured by the four-coordinate **Ru-5b**. Initiation was fast and highly efficient, and at 92-95% conversion the majority of the **11*** had been captured by **Ru-5b**. The reaction between **Ru-2b** and **11*** accounts for 1-6% of the **Ru-2b*** generated. Furthermore, the rate of initiation of this CM reaction (**Ru-2b** and **11***) depends on the solvent, concentration, and reaction conditions, particularly as the latter relates to loss of ethylene.

Recapture of **11** occurs during metathesis, rather than following complete diene consumption, as previously believed.^{1,23} This means that styrenyl ether **11** will compete with substrate for reaction with **Ru-5b**. While this saves the vulnerable active species from

decomposition, prolonging catalyst lifetime, it will also retard productive metathesis. Reaction rates were shown to be retarded by removal of **Ru-5b** from the catalytic cycle due to recapture. This was observed when excess **11** (5 equiv to Ru) was added to the reaction. Recapture will compete with product formation particularly for more challenging, sterically or electronically deactivated substrates.

Under all circumstances, equilibration of the label was achieved, indicating that **Ru-2b** is the resting-state species. Operation of the release-return mechanism provides the opportunity for off-cycle rescue of the vulnerable **Ru-5b** intermediate by styrenyl ether **11** to regenerate the stable Hoveyda catalyst **Ru-2b**. Unlike **Ru-6b**, the resting-state species for the second-generation Grubbs catalyst **Ru-1b**, **Ru-2b** is protected in the form of the benzyldiene complex, rather than a vulnerable methylidene, and – as shown above – it can readily re-enter the catalytic cycle. These results suggest that where **Ru-2b** is employed, reactions should be optimized for the lowest possible catalyst loading due to the operation of the release-return mechanism. Lower catalyst loadings will facilitate uptake in industry by lowering costs.

3.4 References

- (1) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.
- (2) Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973–9976.
- (3) Miao, X.; Fischmeister, C.; Dixneuf, P. H.; Bruneau, C.; Dubois, J. L.; Couturier, J. L. *Green Chem.* **2012**, *14*, 2179–2183.
- (4) Djigoué, G. B.; Meier, M. A. R. *Applied Catal. A* **2009**, *368*, 158–162.
- (5) Rybak, A.; Meier, M. A. R. *Green Chem.* **2008**, *10*, 1099–1104.
- (6) Rybak, A.; Meier, M. A. R. *Green Chem.* **2007**, *9*, 1356–1361.
- (7) Bilel, H.; Hamdi, N.; Zagrouba, F.; Fischmeister, C.; Bruneau, C. *RSC Adv.* **2012**, *2*, 9584–9589.
- (8) Bilel, H.; Hamdi, N.; Zagrouba, F.; Fischmeister, C.; Bruneau, C. *Green Chem.* **2011**, *13*, 1448–1452.
- (9) Kong, J.; Chen, C.-y.; Balsells-Padros, J.; Cao, Y.; Dunn, R. F.; Dolman, S. J.; Janey, J.; Li, H.; Zacuto, M. J. *J. Org. Chem.* **2012**, *77*, 3820–3828.
- (10) Wang, H.; Matsushashi, H.; Doan, B. D.; Goodman, S. N.; Ouyang, X.; Clark, W. M. *Tetrahedron* **2009**, *65*, 6291–6303.
- (11) Wang, H.; Goodman, S. N.; Dai, Q.; Stockdale, G. W.; Clark, W. M. *Org. Process Res. Dev.* **2008**, *12*, 226–234.
- (12) Bomgardner, M. M. *Chem. Eng. News* **2013**, *91*, 19–21.
- (13) Bomgardner, M. M. *Chem. Eng. News* **2013**, *91*, 17.

- (14) Adlhart, C.; Chen, P. *Helv. Chim. Acta* **2003**, *86*, 941–949.
- (15) Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887–3897.
- (16) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543–6554.
- (17) Hong, S. H.; Wenzel, A. G.; Salguero, T. T.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2007**, *129*, 7961–7968.
- (18) Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2004**, *126*, 7414–7415.
- (19) Thiel, V.; Hendann, M.; Wannowius, K.-J. r.; Plenio, H. *J. Am. Chem. Soc.* **2012**, *134*, 1104–1114.
- (20) Vorfalt, T.; Wannowius, K. J.; Plenio, H. *Angew. Chem. Int. Ed.* **2010**, *49*, 5533–5536.
- (21) Ashworth, I. W.; Hillier, I. H.; Nelson, D. J.; Percy, J. M.; Vincent, M. A. *Chem. Comm.* **2011**, *47*, 5428–5430.
- (22) Ashworth, I. W.; Hillier, I. H.; Nelson, D. J.; Percy, J. M.; Vincent, M. A. *ACS Catal.* **2013**, *3*, 1929–1939.
- (23) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791–799.
- (24) van Lierop, B. J.; Lummiss, J. A. M.; Fogg, D. E., Ring-Closing Metathesis: A How-To Guide. In *Olefin Metathesis-Theory and Practice*, Grela, K., Ed. Wiley: Weinheim, 2014.
- (25) 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.
- (26) Grubbs, R. H., *Handbook of Metathesis*. Wiley-VCH: Weinheim, 2003.
- (27) Halbach, T. S.; Mix, S.; Fischer, D.; Maechling, S.; Krause, J. O.; Sievers, C.; Blechert, S.; Nuyken, O.; Buchmeiser, M. R. *J. Org. Chem.* **2005**, *70*, 4687–4694.
- (28) Kingsbury, J. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 4510–4517.
- (29) Van Veldhuizen, J. J.; Gillingham, D. G.; Garber, S. B.; Kataoka, O.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 12502–12508.
- (30) Bieniek, M.; Michrowska, A.; Usanov, D. L.; Grela, K. *Chem. Eur. J.* **2008**, *14*, 806–818.
- (31) Vorfalt, T.; Wannowius, K. J.; Thiel, V.; Plenio, H. *Chem. Eur. J.* **2010**, *16*, 12312–12315.
- (32) Maechling, S.; Zaja, M.; Blechert, S. *Adv. Synth. Catal.* **2005**, *347*, 1413–1422.
- (33) Núñez-Zarur, F.; Solans-Monfort, X.; Pleixats, R.; Rodríguez-Santiago, L.; Sodupe, M. *Chem. Eur. J.* **2013**, *19*, 14553–14565.
- (34) Dunne, A. M.; Mix, S.; Blechert, S. *Tetrahedron Lett.* **2003**, *44*, 2733–2736.
- (35) Wakamatsu, H.; Blechert, S.; *Angew. Chem.* **2002**, 832–834; *Angew. Chem. Int. Ed.* **2002**, *41*, 794–796.
- (36) Wakamatsu, H.; Blechert, S. *Angew. Chem. Int. Ed.* **2002**, *41*, 2403–2405.
- (37) Grela, K.; Harutyunyan, S.; Michrowska, A. *Angew. Chem. Int. Ed.* **2002**, *41*, 4038–4040.
- (38) Michrowska, A.; Bujok, R.; Harutyunyan, S.; Sashuk, V.; Dolgonos, G.; Grela, K. *J. Am. Chem. Soc.* **2004**, *126*, 9318–9325.
- (39) Grela, K.; Kim, M. *Eur. J. Org. Chem.* **2003**, 963–966.
- (40) Gulajski, L.; Michrowska, A.; Bujok, R.; Grela, K. *J. Mol. Catal. A* **2006**, *254*, 118–123.
- (41) Zaja, M.; Connon, S. J.; Dunne, A. M.; Rivard, M.; Buschmann, N.; Jiricek, J.; Blechert, S. *Tetrahedron* **2003**, *59*, 6545–6558.
- (42) Rix, D.; Caijo, F.; Laurent, I.; Boeda, F.; Clavier, H.; Nolan, S. P.; Mauduit, M. *J. Org. Chem.* **2008**, *73*, 4225–4228.
- (43) Connon, S. J.; Rivard, M.; Zaja, M.; Blechert, S. *Adv. Synth. Catal.* **2003**, *345*, 572–575.

- (44) Buschmann, N.; Wakamatsu, H.; Blechert, S. *Synlett* **2004**, 667–670.
- (45) van Rensburg, W. J.; Steynberg, P. J.; Meyer, W. H.; Kirk, M. M.; Forman, G. S. *J. Am. Chem. Soc.* **2004**, *126*, 14332–14333.
- (46) Marciniak, B.; Rogalski, S.; Potrzebowski, M. J.; Pietraszuk, C. *ChemCatChem* **2011**, *3*, 904–910.
- (47) The concentration of **11*** in these experiments is 1 mM. Plenio and co-workers reported that **Ru-2b** reacts with styrene via a dissociative pathway at low styrene concentrations, although an interchange-associative component emerged at 20–300 mM (UV/Vis; 30 °C; 0.1 mM **Ru-2b** in toluene). See: Thiel, V.; Hendann, M.; Wannowius, K.-J. r.; Plenio, H. *J. Am. Chem. Soc.* **2012**, *134*, 1104–1114.
- (48) 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.
- (49) van Lierop, B. J.; Reckling, A. M.; Lummiss, J. A. M.; Fogg, D. E. *ChemCatChem* **2012**, *4*, 2020–2025.
- (50) Bujok, R.; Bieniek, M.; Masnyk, M.; Michrowska, A.; Sarosiek, A.; Stepowska, H.; Arlt, D.; Grela, K. *J. Org. Chem.* **2004**, *69*, 6894–6896.
- (51) Monsaert, S. F.; Verpoort, F. W. C. Process for preparation of ruthenium-based carbene catalysts with chelating alkylidene ligands. WO Patent App. WO 2011/091980 A1; CA+ 383210.
- (52) Bieniek, M.; Michrowska, A.; Gulajski, L.; Grela, K. *Organometallics* **2007**, *26*, 1096–1099.
- (53) Sauvage, X.; Demonceau, A.; Delaude, L. *Adv. Synth. Catal.* **2009**, *351*, 2031–2038.
- (54) Ashworth, I. W.; Nelson, J. D.; Percy, J. M. *Dalton Trans.* **2013**, *42*, 4110–4113.
- (55) Reckling, A. Synthetic and Mechanistic Studies in Ruthenium-Catalyzed Olefin Metathesis. M.Sc. Dissertation, University of Ottawa, Ottawa, ON, 2012.
- (56) Sanford, M. S.; Ulman, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 749–750.
- (57) Monfette, S.; Fogg, D. E. *Chem. Rev.* **2009**, *109*, 3783–3816.
- (58) Ritter, T.; Hejl, A.; Wenzel, A. G.; Funk, T. W.; Grubbs, R. H. *Organometallics* **2006**, *25*, 5740–5745.
- (59) Monfette, S.; Eyholzer, M.; Roberge, D. M.; Fogg, D. E. *Chem. Eur. J.* **2010**, *16*, 11720–11725.
- (60) Lysenko, Z.; Maughon, B. R.; Mokhtar-Zadeh, T.; Tulchinsky, M. L. *J. Organomet. Chem.* **2006**, *691*, 5197–5203.
- (61) 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.
- (62) Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 7202–7207.
- (63) van der Eide, E. F.; Romero, P. E.; Piers, W. E. *J. Am. Chem. Soc.* **2008**, *130*, 4485–4491.
- (64) Lee, L.-S.; Ou, H.-J.; Hsu, H.-L. *Fluid Phase Equilib.* **2005**, *231*, 221–230.
- (65) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783–3784.
- (66) Ulman, M.; Belderrain, T. R.; Grubbs, R. H. *Tetrahedron Lett.* **2000**, *41*, 4689–4693.

4 Ruthenium-Arylthiolate Catalysts in Z-Selective Macrocyclization

4.1 Introduction

At the forefront of selectivity challenges in olefin metathesis is control over the geometric isomer present in molecular olefin products. *E/Z* mixtures are normally obtained, limiting the efficacy of metathesis methodologies in organic synthesis in general, and particularly in exploitation of renewable feedstocks (for example, elaboration of seed-oil derived fatty acids into pheromone targets,¹ where *E/Z* selectivity is essential to function). A recent breakthrough in Group 6 catalysis led to the first examples of highly *Z*-selective olefin metathesis. Schrock and Hoveyda²⁻⁴ described a range of molybdenum and tungsten monoaryloxide-pyrrolide (MAP) complexes (Figure 4.1), with three different ligands of widely varying size present. The success of these MAP catalysts is due to the steric bulk and flexibility of the monodentate aryloxide ligand compared to the imido substituent (Scheme 4.1).^{4,5} In addition, the flexibility of the monodentate aryloxide ligand, compared to its bidentate analogues, allows the alkylidene complex to adapt to structural strains imposed during catalysis.⁵

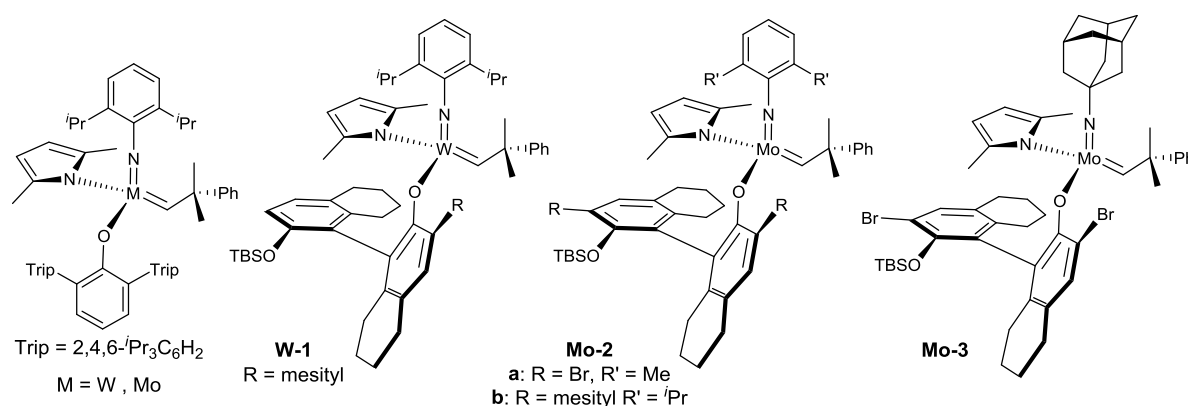
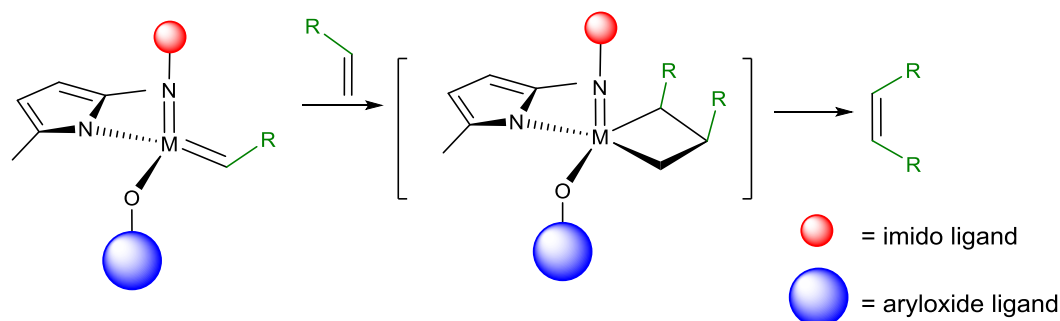


Figure 4.1 Representative molybdenum and tungsten monoaryloxide-pyrrolide (MAP) complexes. TBS = *t*-butyldimethylsilyl.



Scheme 4.1 Rationale for Z-selectivity of molybdenum and tungsten catalysts.

The MAP catalysts have been employed in a wide variety of metathesis reactions, including ROCM,⁴ ROMP,⁶ homocoupling of terminal olefins,⁷ and some demanding CM⁵ and RCM⁸ reactions. Notwithstanding this success, Group 6 catalysts are highly sensitive to trace air and water, making them difficult to handle.⁸⁻¹¹ This disadvantage has led to an interest in developing functional-group-tolerant catalysts that could enable the efficient production of Z-olefins.¹² The greater ease of handling expected for ruthenium metathesis catalysts could facilitate more widespread uptake of this methodology.

Design strategies. Critical to design of a Z-selective ruthenium metathesis catalyst is control over the geometry of the key retro-addition step. This requires higher steric pressure on one face of the trigonal bipyramidal metallacyclobutane (**MCB**) intermediate. No such control is attainable in the Grubbs catalysts themselves, which contains chloride ligands in the two axial sites (Figure 4.2a), thus favouring the thermodynamically preferred *E*-olefin product. We reasoned that replacing one of the chloride ligands with a bulky monodentate ligand, such as an aryloxy or arylthiolate, should give a metallacyclobutane intermediate with the desired geometry (Figure 4.2b). The differential steric pressure on the metallacyclobutane is expected to favour a syn orientation of the R groups, generating the *Z*-olefin as the major product. One of the catalysts chosen for study was arylthiolate complex **Ru-9** reported by Jensen,¹³ a variant on aryloxy catalysts originally reported by our group,¹⁴ which we hoped would benefit from faster initiation. This complex will be described in more detail below.

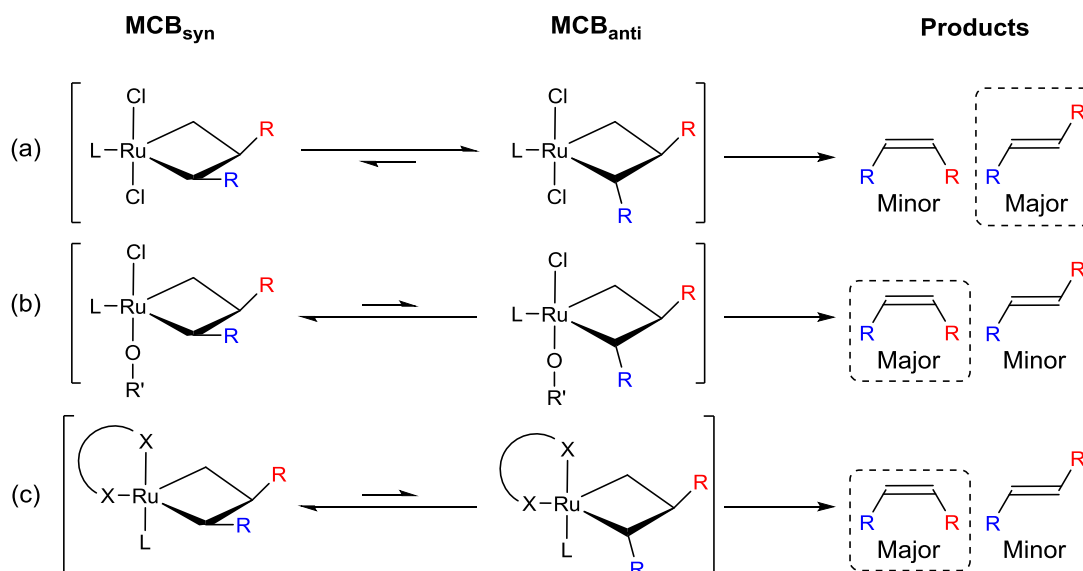


Figure 4.2 Metallacyclobutane symmetry and product selectivity. (a) Grubbs catalysts; (b) monoaryloxide catalysts; (c) (thio)catecholate catalysts.

Considered as an alternative strategy was replacement of both chloride ligands with a bidentate dianionic ligand (Figure 4.2c). While the *cis*-dianionic geometry is plagued by low initiation efficiency, this could similarly enable access to a *Z*-selective catalyst. While this work was in progress, however, an upsurge took place in the reports on ruthenium *Z*-selective olefin metathesis catalysts (see e.g. Figure 4.3).^{13,15-18} In particular, Hoveyda and co-workers¹⁶ demonstrated the success of this second strategy, employing catecholate or *o*-dithiolate ligands (Figure 4.3a, **Ru-17** and **Ru-18**) to achieve excellent *Z*-selectivities in ROMP and ROCM. The *o*-dithiolate catalyst **Ru-18** was shown to enable >98% *Z*-selectivity in ROMP of norbornene at very low catalyst loadings (86% yield in 1 h at 0.002 mol% Ru). This selection of reactions that are driven by release of ring strain from norbornene substrates points toward the expected difficulties with initiation efficiency noted above. Given this, the discussion below will focus on the first strategy outlined, and the level of selectivity attainable on incorporation of an arylthiolate ligand. First, however, a note is in order about the importance of assessing selectivity at high conversions.

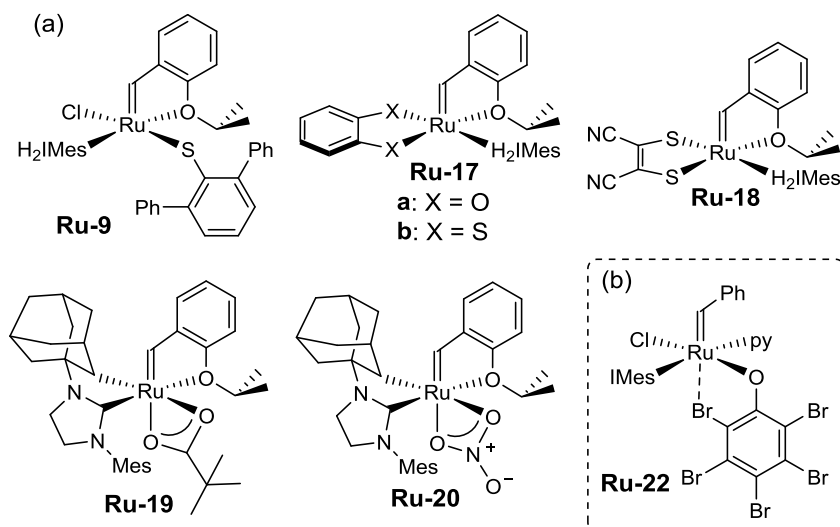


Figure 4.3 (a) State-of-the-art Z-selective ruthenium metathesis catalysts. (b) Ruthenium-aryloxy catalyst that effects RCM macrocyclization with minimal oligomerization.

Selectivity and conversions. As noted above, most metathesis reactions generate the thermodynamically preferred trans-isomer (*E*-olefin) as the major product. Selective formation of kinetic *Z*-olefin products is a challenge because of the equilibrium nature of metathesis reactions. Isomerization of kinetically generated *Z*-olefins to thermodynamically favoured *E*-olefins is typically problematic, especially at the last stages of a process.^{16,19} As a corollary, catalyst selectivity for *Z*-olefin products is relevant only at synthetically useful yields. For synthetically non-trivial substrates, bearing in mind the waste associated with product purification, a reasonable arbitrary figure can be set at >95% conversion. This issue, though widely recognized, is frequently unacknowledged, and many researchers still report *Z*-selectivities at intermediate or even low conversions. The validity of such data is particularly questionable for ruthenium catalysts, which are particularly prone to olefin isomerization over time. The problem is not confined to ruthenium catalysts, however: eroded selectivity at high conversions is also found for the Group 6 catalysts, though it is often unclear whether this is due to isomerization or metathesis equilibria. An example is the homocoupling of 1-octene **28** with the MAP catalyst **W-1** shown in Figure 4.4.⁷ More drastic losses of stereoselectivity were reported during the same reaction on use of Grubbs' chelating **Ru-19**¹⁹ and Jensen's monothiolate **Ru-9**¹⁴ (Figure 4.4). For **Ru-9**, Proton Sponge (1,8-

bis(dimethylamino)naphthalene, 2.5 mol%) was found to increase catalyst activity while reducing isomerization,¹³ perhaps by preventing the formation of ruthenium hydrides. However, despite attempts to optimize reactions via changes in concentration and temperature, or removal of ethylene, lower Z-selectivities were found at high conversions.

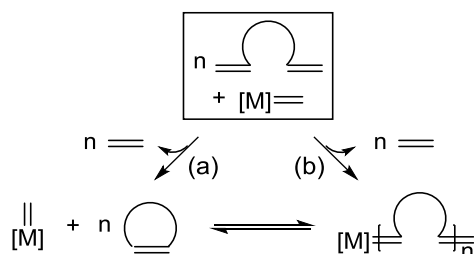
28

catalyst (mol%)	T (°C)	solvent	t (h)	% conversion	% Z-olefin
W-1 ^a (4)	22	C ₆ D ₆	0.5 (2)	38 (72)	93 (72)
Ru-19 ^b (2)	60	THF	3 (6)	83 (97)	80 (68)
Ru-9 ^c (5)	40	THF	3 (10)	67 (>99)	66 (23)

^a Prepared *in situ* ^b Static vacuum ^c 2.5 mol% Proton Sponge

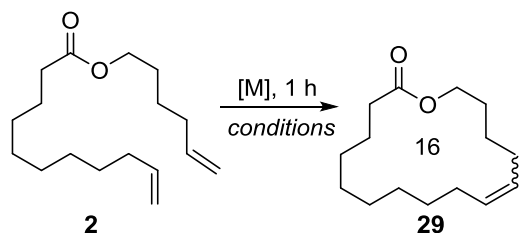
Figure 4.4 Homocoupling of 1-octene **28** showing loss of stereoselectivity over time.^{7,13,19}

Selectivity in RCM macrocyclization. Designing catalysts that can give access to macrocycles containing a Z-olefin is of keen interest in pharmaceutical chemistry, where a number of such products exhibit preferred modes of action.^{8,20,21} Without control of stereoselectivity, especially at the late stages of a multistep synthesis, impaired yields can drastically affect production costs and process viability. Our group²² has previously shown that in RCM macrocyclization, Ru-NHC catalysts of the Grubbs class do not operate via direct RCM, as commonly supposed (see Scheme 4.2, path a). Instead, they exhibit a strong kinetic bias toward oligomerization, and liberate the RCM products via backbiting (Scheme 4.2, path b). High dilutions are essential to shift the ring-chain equilibrium in favour of the RCM products, and to minimize the proportion of oligomers present. When performing a RCM macrocyclization reaction, concentration is thus a key parameter. As well, sufficient time is required for the reaction to reach equilibrium.^{22,24,25}



Scheme 4.2 RCM equilibria presuming irreversible loss of ethylene. (a) Direct RCM. (b) Oligomerization-backbiting pathway.

While Z-selective RCM macrocyclization has only recently been explored, important lead results were reported by Schrock and Hoveyda.⁸ Treatment of prolactone **2** with 5 mol% **Ru-1b** (Grubbs second-generation catalyst) or **Mo-1** afforded the 16-membered macrocycle **29** as predominantly the *E*-isomer (Figure 4.5). With the Mo-MAP complex **Mo-2a**, Z-selectivity increased to 70%, albeit at only 56% conversion. Values at higher conversions were not reported. On replacing the arylimido ligand with adamantylimido, (i.e. use of **Mo-3**) and optimization of the reaction conditions to reduce isomerization, stereoselectivity increased to 92%, albeit still at incomplete conversions (75%; Figure 4.5). Grubbs and co-workers²⁶ recently reported the first example of Z-selective macrocyclization via ruthenium catalysts, using chelating **Ru-20** to afford lactones with high Z-selectivity over a wide range of ring sizes. Best results were found for 16-membered lactone **29**, obtained with 84% Z-selectivity at ca. 80% conversion,²⁶ slightly lower than that obtained with the Mo-MAP complexes (Figure 4.5).⁸ The ruthenium catalyst required longer reaction times (24 h vs. 1 h) and more forcing conditions, including higher catalyst loadings and higher temperatures (Figure 4.5). Therefore, advances are still necessary for the Z-selective ruthenium catalysts to reach the success of the Mo-MAP complexes.



[M] (mol%)	solvent	T (°C)	% conversion	% yield	% Z-olefin
Ru-1b (5)	CH ₂ Cl ₂	40	75	61	21
Mo-1 (5)	toluene	22	85	60	22
Mo-2a (5)	toluene	22	56 ^c	45	70
Mo-3^a (1.2)	toluene	22	75	56	92
Ru-20^b (7.5)	DCE	60	ca. 80	72	84

^a *P* = 7.0 Torr ^b 24 h, *P* = 20 mTorr ^c Highest conversion reported

Figure 4.5 Ability of various catalysts to promote Z-selective RCM macrocyclization of **2** to form 16-membered lactone **29**.^{8,26}

The section below describes collaborative work with the Jensen group (Norway), in which we examined the Z-selectivity attainable in RCM macrocyclization by two ruthenium-monothiolate catalysts (Figure 4.6b, **Ru-9** and **Ru-10a**). The impact of substrate

concentration on product distribution and reaction rates was examined. Catalyst **Ru-9** bears a thiolate ligand along with a chloride ligand, consistent with the design strategy outlined above.¹³ Catalyst **Ru-10**, in which there is a *o*-Cl donor on the arylthiolate ligand, can be viewed as a more labile variant of **Ru-9**.¹⁵ Due to the hemilabile character of the chelating arylthiolate ligand, an equilibrium between the four- and five-coordinate species is anticipated (Figure 4.6c, **Ru-21** and **Ru-10**). Of keen interest is the possibility that the proximity of the chlorine substituent to the metal centre could protect the vulnerable active species from decomposition, and catalyst lifetime was therefore examined. Complicating comparison, however, is the fact that the two structures also differ in the NHC ligand: **Ru-10a** contains H₂IPr, vs. the H₂IMes ligand on **Ru-9**. Unfortunately, we were not able to obtain samples of the H₂IMes analogue **Ru-10b**. Both **Ru-9** and **Ru-10b** have been employed in the homocoupling of 1-octene **28** (Figure 4.6a): moderate selectivities were obtained however at relatively low conversions. Best results to date were a maximum of 81% Z-selectivity obtained for **Ru-9** at full conversion in the homocoupling of allyl acetate **30**.¹³

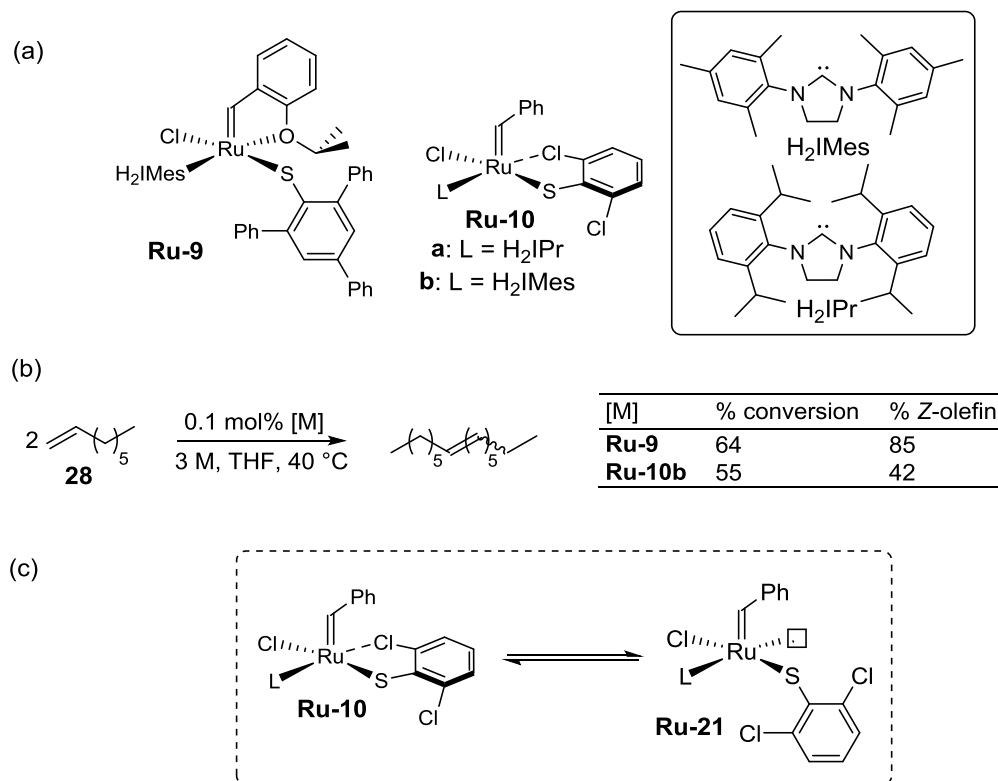


Figure 4.6 (a) Ruthenium-arylthiolate catalysts studied in this work. (b) Z-Selectivity of **Ru-9** and **Ru-10b** in homocoupling of 1-octene **28**.¹⁵ (c) Equilibrium between the

five- and four-coordinate complexes, **Ru-10** and **Ru-21** respectively, due to the hemilabile arylthiolate ligand.

Jay Conrad of this research group¹⁴ demonstrated that the perbromoaryloxide catalyst **Ru-22** (Figure 4.3b) effects highly efficient RCM of **2**, resulting in quantitative formation of the 16-membered lactone **29** within 15 min without apparent formation of oligomers. This is advantageous for Z-selective RCM macrocyclization, as oligomers are the kinetic product and recycling of these species through backbiting favours the thermodynamic product (*E*-olefin). The aryloxide catalysts are limited, however, by their tendency to decompose on prolonged reaction, and their slow initiation (a trait shared with their cis-chelating catecholate derivatives).^{23,27} Subsequent work by Sebastien Monfette of this group²⁸ demonstrated much-improved initiation efficiencies on incorporation of monodentate *N*-anionic ligands, behaviour we attribute to the lower electronegativity of nitrogen vs. oxygen. We thus considered that the lower electronegativity of the sulfur donor in **Ru-9** and **Ru-10a** could likewise facilitate catalyst initiation. An additional benefit, anticipated by analogy to the ruthenium-aryloxide catalysts, is the ease of separating the products from spent catalyst, in contrast to the Grubbs systems. Conrad and Fogg¹⁴ showed that the high polarity of the aryloxide ligand results in a high affinity for silica, enabling removal of ruthenium to ppm levels in a single chromatographic pass. In subsequent work with aryloxide and arylthiolate catalysts **Ru-17** and **Ru-18**, Hoveyda and co-workers¹⁶ reported similarly straightforward chromatographic purification. This confers added interest in **Ru-9** and **Ru-10a**, beyond the potential for Z-selective RCM macrocyclization arising from the axial dissymmetry of the metallacyclobutane intermediate, and the potential for minimal oligomerization by analogy to the aryloxide catalysts.

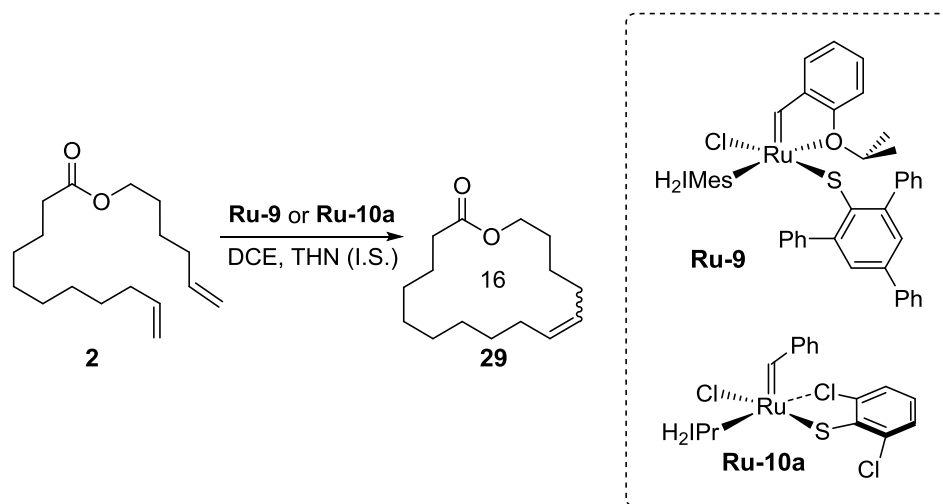
4.2 Results and discussion

4.2.1 RCM macrocyclization by **Ru-9**

4.2.1.1 Effect of concentration and temperature on rate and product distribution

As noted above, cyclization of large rings requires high dilutions.²²⁻²⁵ In this work, the ability of **Ru-9** and **Ru-10a** to generate Z-olefin macrocycles was examined: specifically, the RCM of **2** to give the 16-membered lactone **29** (Scheme 4.3). Reactions were initially performed

using conditions previously shown to be optimal for the Grubbs and Hoveyda second-generation catalysts,²² i.e. 5 mol% Ru at a substrate concentration of 5 mM. In the prior work, the solvent of choice was CH₂Cl₂ and the reactions were performed at reflux (40 °C). However, 1,2-dichloroethane (DCE) was used in the present work to permit reaction in the glovebox (sand bath). This permitted samples to be withdrawn without risk of introducing air. Reactions were analyzed by gas chromatography (GC) using 1,2,3,4-tetrahydronaphthalene (THN) as an internal standard for quantification. The proportion of oligomers, which cannot be observed by GC owing to their involatility, was determined by difference. To prevent “run-on” metathesis for samples awaiting analysis in the GC queue, the catalyst was quenched with potassium tris(pyrazolyl)borate (KTp) in the glovebox prior to analysis.



Scheme 4.3 RCM macrocyclization reaction of **2** performed with **Ru-9** and **Ru-10a**.

RCM was slow with 5 mol% **Ru-9**, requiring 4 d to reach >99% conversion (Figure 4.7). At 3 d (97% conversion), 82% yield of the desired lactone was formed. However, only 23% was the Z-isomer. This is a slightly lower Z-selectivity than the Grubbs catalyst **Ru-1c** (28%).²² The ruthenium-monothiolate catalyst showed an induction period of 1 d. At this point, only 9% of the diene was consumed, after which catalyst activity significantly increased. Thus, 78% of the diene was consumed in the ensuing 24 h. Slow initiation of **Ru-9** was unexpected, given its structural resemblance to the Hoveyda catalyst **Ru-2b**. In Chapter 3,

initiation of the Hoveyda catalyst **Ru-2b** was shown to be complete within 10 min at RT during the RCM of **1**.

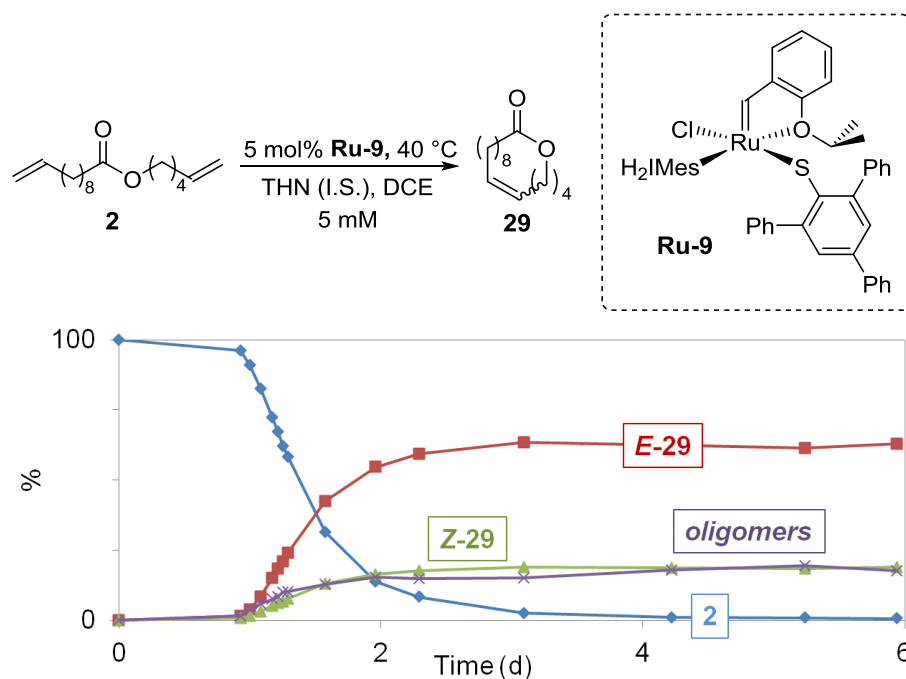


Figure 4.7 Product distribution in RCM macrocyclization of **2** with **Ru-9**. The initial diene concentration was 5 mM.

As noted above, RCM yields can be increased by using high dilutions to promote backbiting of the oligomeric species. After permitting reaction for sufficient time (6 d) to observe any changes in product distribution for the RCM of **2** by **Ru-9**, attempts were made to induce backbiting. A tenfold dilution (to 0.48 mM), however, resulted in no change in product distribution, suggesting catalyst decomposition. More surprisingly, addition of a further charge of catalyst (5 mol%) had no impact on the product distribution. This contrasts with prior work from our group, in which both Conrad²² and Monfette²³ demonstrated that with Grubbs or Hoveyda catalysts, **Ru-1b** and **Ru-2b** respectively, diluting enabled near-quantitative formation of macrocycle **29** (in the latter case, from 54% to 96%). While decomposition of **Ru-9** would obviously mean that diluting could not alter the product distribution, backbiting should have occurred once an additional catalyst charge was added. The failure of fresh catalyst to induce formation of further RCM product suggests that **Ru-9** may be incapable of effecting backbiting, at least at ca. 0.5 mM.

Given this unexpected failure, a further reaction was carried out at a relatively high initial substrate concentration (ca. 500 mM), followed by a 100-fold dilution to 5 mM to promote backbiting. This method, originally implemented by Conrad,²² could further benefit macrocyclization reactions using **Ru-9**. For the parent Hoveyda catalyst **Ru-2b**, higher olefin concentrations accelerate metathesis of sterically accessible olefins, owing to operation via an interchange-associative mechanism.^{19,29-31}

The limited solubility of **Ru-9** in DCE meant that the target RCM reaction could only be carried out at a maximum initial substrate concentration of 545 mM. Olefin consumption was indeed much faster at this concentration than at the 5 mM level described above. Conversions of 99% were reached after 10 h, and full conversion within 1 d (Figure 4.8a). As expected, oligomers dominate at this concentration: only 3% **29** was present (of which 81% was the Z-isomer). The reaction was then diluted to 5 mM to induce backbiting. Unexpectedly, the product distribution changed only slightly (16%) even over 2.5 d, with a final yield of 19% of the desired **29** (32% Z-isomer), and 81% oligomers (Figure 4.8a). To assess whether this was due to catalyst deactivation, a second catalyst charge (5 mol%) was added. No effect on the equilibrium product distribution was observed. This suggests that **Ru-9** is not kinetically competent to induce backbiting at the 1,2-disubstituted olefinic linkages in the oligomer chains, at least prior to catalyst deactivation at 40 °C. This point is explored in more detail in Section 4.2.1.2.

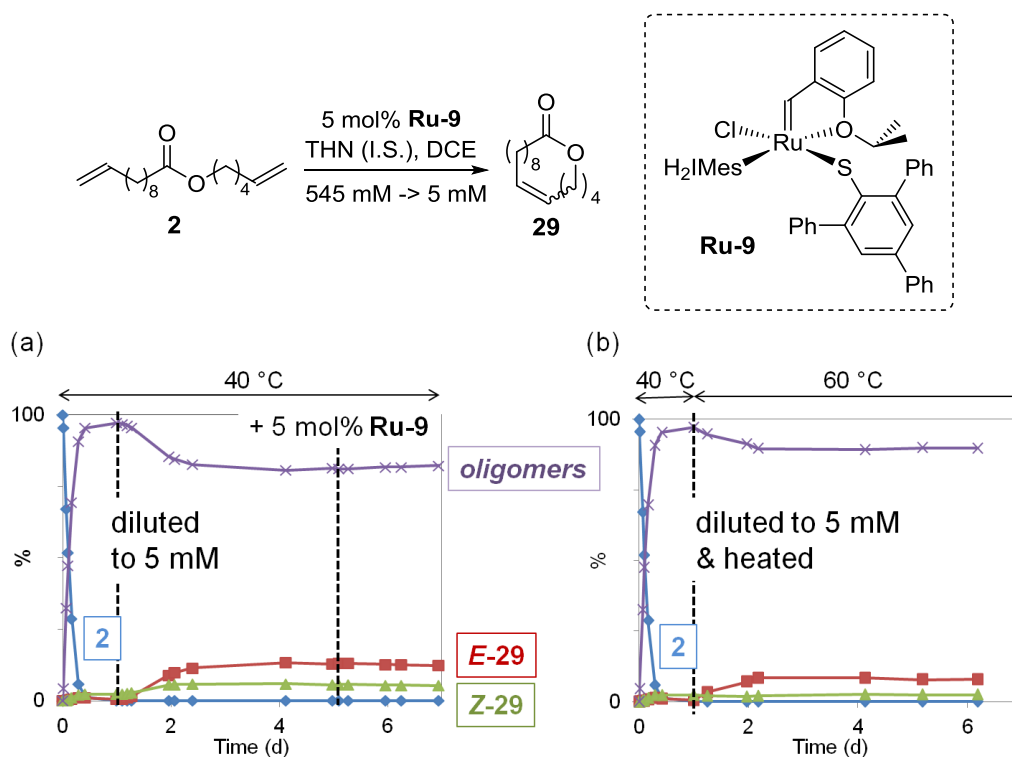


Figure 4.8 RCM macrocyclization of **2** (545 mM) using **Ru-9**. (a) At 40 °C, followed by dilution to 5 mM and addition of 5 mol% **Ru-9**. (b) At 40 °C, diluted to 5 mM and heated to 60 °C.

Grubbs and co-workers²⁶ have suggested that RCM macrocyclizations performed with chelating **Ru-20** require elevated temperatures (60 °C) to favour ring closure over oligomerization (for a detailed analysis of the effect of temperature on the ring-chain equilibrium see the review by Fogg and co-workers²⁴). Previous reports with **Ru-9** found that for the homocoupling of allyl-TMS **31**, increasing the temperature (60 °C) resulted in higher conversions while retaining Z-selectivity.¹³ We therefore examined the effect of temperature on product distribution. Once the reaction reached full conversion at 545 mM and 40 °C, an aliquot was removed, diluted to 5 mM, and heated to 60 °C. After 2 d, the yield of the 16-lactone **29** was 10%, 24% being the Z-isomer (Figure 4.8b). Oligomers accounted for 90% of the product, indicating that on increasing the temperature from 40 to 60 °C, the yield of desired product decreased. Grubbs and co-workers²⁶ previously reported lower yields for a RCM macrocyclization with chelating **Ru-20** to generate a 14-membered lactone when performed at 80 °C (vs. 60 °C). This was attributed to catalyst decomposition. Heating

accelerates decomposition of ruthenium catalysts, for example, the methyldiene resting-state species **Ru-6b** has a reported half-life of 5.7 h at 55 °C in C₆D₆.^{32,33}

The results above indicate that with **Ru-9**, the product distribution depends strongly on concentration, but that yields of the macrocycle **29** cannot be significantly improved by manipulating a concentration-dependent ring-chain equilibrium. For the RCM reaction carried out at 5 mM, the yield of **29** was 82% (Figure 4.7), compared to just 18% for the same reaction carried out at 545 mM followed by dilution to 5 mM (Figure 4.8). In addition, and regardless of initial substrate concentration, Z-selectivities were low at the end of the reaction (23% at 5 mM, vs. 31% at 545 mM). Importantly, the higher activity and >85% Z-selectivities reported in cross-metathesis reactions with **Ru-9** by Jensen and co-workers¹³ were associated with high substrate concentrations (typically 4 M), which seem essential to maintain high activity for **Ru-9**. This is obviously incompatible with the high dilutions required for macrocyclization. In addition, THF was used as a solvent, and this may enhance overall catalyst performance by coordinative stabilization (see also comments in lifetime Section 4.2.3). Ruthenium-catalyzed RCM is occasionally carried out in THF, typically where required for reasons of substrate solubility, but chlorinated or aromatic solvents are more usual.³⁴ With **Ru-20**, it may be noted that RCM macrocyclizations in THF resulted in a significant increase in oligomerization products even at 3 mM, relative to reactions in DCE.²⁶

4.2.1.2 Assessing catalyst lifetime in the presence of substrate

The data above illustrate the failure of **Ru-9** to participate in “equilibrium RCM”. Typically, when oligomers are obtained despite use of appropriate dilutions (5 mM for **2**), the problem is premature deactivation.²⁴ To assess whether this was the case for **Ru-9**, an experiment was carried out in which, once macrocyclization of **2** had stalled, the highly reactive diene diethyl diallylmalonate (DeDAM, **14**) was added to the reaction mixture. To determine if **Ru-9** was capable of cyclizing DeDAM **14** under the conditions required for the RCM macrocyclization of **2** (that is 5 mM, DCE, 40 °C), a control reaction was first carried out with **14**. The reaction was surprisingly slow, reaching 99% conversion only after 2.3 d (Figure 4.9-dashed line). This however, indicated catalyst competence. Metathesis of **2** was therefore carried out under conditions designed to minimize reaction time (545 mM, DCE, 40 °C, 5 mol% **Ru-9**; Figure 4.9). At 60 h (2.5 d), 20 equiv of DeDAM **14** (relative to Ru)

was added to the reaction mixture: this corresponds to a catalyst loading of 5 mol%, assuming zero deactivation of **Ru-9**. RCM of **14** was rapid, reaching full conversion in ca. 0.75 d (Figure 4.9-solid line). This is important in demonstrating conclusively that active catalyst is present. Also notable is the fact that the reaction occurred ca. seven times faster than the control experiment: that is, no initiation period was required. Clearly, **Ru-9** is hampered by its slow initiation, and this almost certainly accounts for the inability to “correct” the product distribution by adding a further catalyst charge.

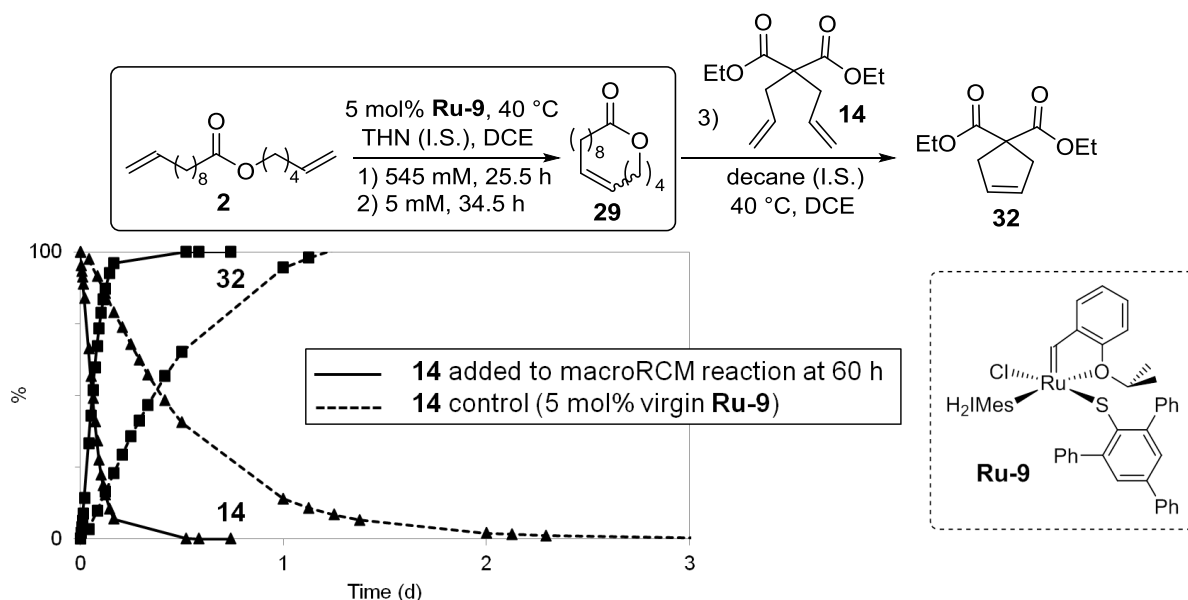


Figure 4.9 Ability of **Ru-9** to effect RCM of **14** (5 mM) into **32** with 5 mol% virgin catalyst (control, dashed line) and once substrate was added (20 equiv to Ru) to RCM macrocyclization reaction at 2.5 d (solid line).

The failure of **Ru-9** to recycle oligomers into the desired RCM product is intriguing. While the crystal structure reported by Jensen and co-workers¹³ suggests that the arylthiolate ligand in **Ru-9** does not impose significant steric congestion, the presence of two sterically demanding *o*-phenyl groups could impede access of the oligomer backbone to the metal center and thus impede efficient backbiting. An experiment was therefore performed with DeDAM **14** to assay catalyst productivity over an extended period at 40 °C. Additional **14** was added to the reaction mixture every 24 h (20 equiv, assuming no deactivation, and correcting for amounts removed in reaction aliquots). Over 4 d the reaction kinetics remained consistent proving the catalyst was still alive, active, and performing at near-original

capacity. This further supports the inference that the catalyst has not decomposed, and that the oligomers are too bulky for **Ru-9** to backbite efficiently.

After addition of **14**, the RCM macrocyclization was monitored to determine the effect (if any) on the product distribution. Little change was observed, as oligomers were still the major species (Figure 4.10). The experiment above showed **Ru-9** was still active; therefore, at 3.25 d an additional 20 equiv of **2** (relative to Ru, assuming no deactivation) was added. Much slower consumption of substrate ensued, as expected given the lower substrate concentration (5 mM vs. an initial 545 mM). Conversions of 97% were reached in 3 d with an RCM yield of 68% (Figure 4.10) compared to the reaction in Figure 4.7, which reached an 82% yield (3 d). The lower yield (68%) was attributed to minor amounts of catalyst deactivation resulting in a catalyst loading of <5 mol%. However, even after 6 d, **Ru-9** was still active and capable of turning over the bulky, less reactive macrocycle **2** (compared to DeDAM **14**).

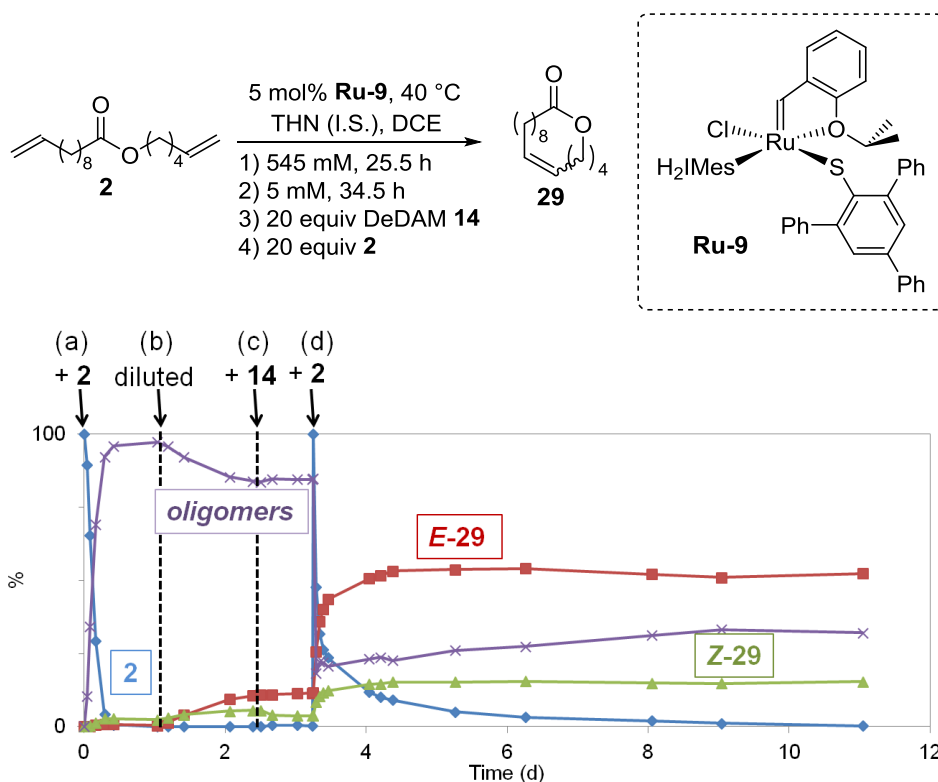


Figure 4.10 Product distribution in the RCM macrocyclization of **2**. Conditions: (a) 5 mol% **Ru-9** at an initial diene concentration of 545 mM, (b) diluted to 5 mM, (c) added 20 equiv DeDAM **14**, (d) added an additional 20 equiv of **2**.

4.2.2 RCM macrocyclization using *o*-dichloroarylthiolate catalyst **Ru-10a**

4.2.2.1 Effect of concentration on rate and product distribution

Initial RCM macrocyclization reactions with **Ru-10a** were performed under the same conditions as with **Ru-9** (Figure 4.11). At a substrate concentration of 5 mM, the reaction reached 98% conversion in about 1.5 d. The final RCM yield was 61%, with 23% of the *Z*-isomer. **Ru-10a** had the same *Z*-selectivity as **Ru-9** but at a lower RCM yield (61% vs. 82% for **Ru-9**). As with **Ru-9**, dilution of the reaction mixture to 0.5 mM, as well as an additional charge of catalyst caused no change in the product distribution. However, for both catalysts the arylthiolate ligand assisted, to a small extent and only at low conversions, to direct RCM with less formation of oligomeric species than the parent Grubbs and Hoveyda complexes, **Ru-1b** and **Ru-2b** respectively (at 5 mM).²³ The difference between the RCM of **2** with **Ru-9** and **Ru-10a** was the time required to reach maximum conversion. With **Ru-10a**, after only 1 d, the reaction reached 97% conversion, whereas with **Ru-9** it took 3 d to reach the same conversion. Unlike **Ru-9**, no initiation period for **Ru-10a** was observed. The chlorine substituent in **Ru-10a** acts as a dissociating ligand that is a weak donor compared to other classical ligands (ex. phosphines). Therefore, **Ru-10a** can initiate rapidly, forming the desired four-coordinate species **Ru-21** available for coordination of an olefin. In a private communication, the Jensen group suggested that **Ru-10a** initiates very rapidly, even at 0 °C.³⁵

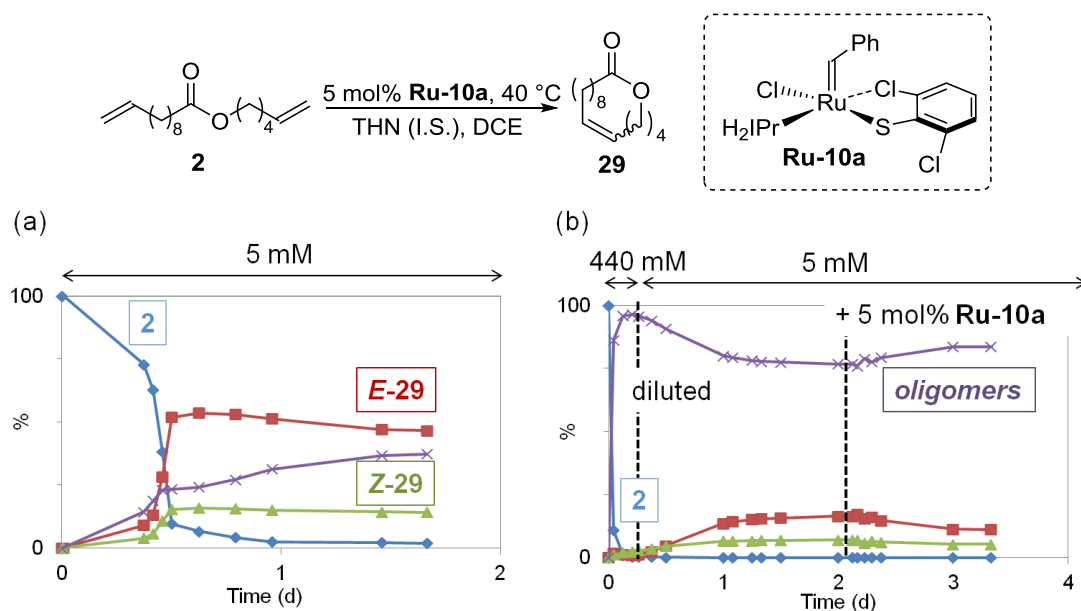


Figure 4.11 Product distribution of RCM macrocyclization of **2** with 5 mol% **Ru-10a** at an initial diene concentration of (a) 5 mM or, (b) 440 mM, diluted to 5 mM and additional catalyst charge of 5 mol% **Ru-10a**.

As noted above, oligomerization at an initial substrate concentration of 100 mM, then diluting to 5 mM to induce backbiting, enabled efficient RCM of **2** by Grubbs catalyst **Ru-1b**.²² While this strategy was unsuccessful for **Ru-9**, it was explored with **Ru-10a**. The initial substrate concentration used was 440 mM (limited by catalyst solubility in DCE). As expected, diene consumption was faster, taking 3 h to reach 99% conversion, vs 1.5 d at 5 mM (Figure 4.11b). In comparison, 10 h was required to reach 99% conversion with **Ru-9** at 545 mM. Therefore, regardless of initial substrate concentration (ca. 5 mM or 500 mM), the RCM macrocyclization was about three times faster when performed with **Ru-10a**. For both catalysts, the RCM macrocyclization (performed at ca. 500 mM) showed several similarities in product distribution (Figure 4.8a vs. Figure 4.11b). Prior to dilution, at 99% conversion, the *Z*-isomer dominated (69% with both **Ru-10a** and **Ru-9**), however the RCM yield was extremely low (3%). Upon dilution to 5 mM, yields increased to 19-23% lactone but with diminished *Z*-selectivity (30-32%). Oligomers dominated at every point during the reaction, and while dilution induced backbiting, it did not occur to the desired extent. For **Ru-10a**, backbiting could have been compromised by the presence of the bulky NHC ligand H₂IPr. In addition, fresh catalyst had little to no effect on product distribution for both catalysts.

4.2.2.2 Effect of lower catalyst loading and temperature

Catalyst **Ru-10a** showed better activity and faster initiation than **Ru-9**. Therefore, the catalyst loading was decreased. As expected, at 1 mol% **Ru-10a**, the reaction was slower, taking 10 d to reach 89% conversion (Figure 4.12a). However, the reaction did not reach full conversion likely because of catalyst deactivation. At the end of the reaction, the RCM yield was ca. 15% lower than that attainable at 5 mol% Ru (48% vs. 61%). However, the Z-selectivity of the reaction was similar (26% vs. 23% at 5 mol%).

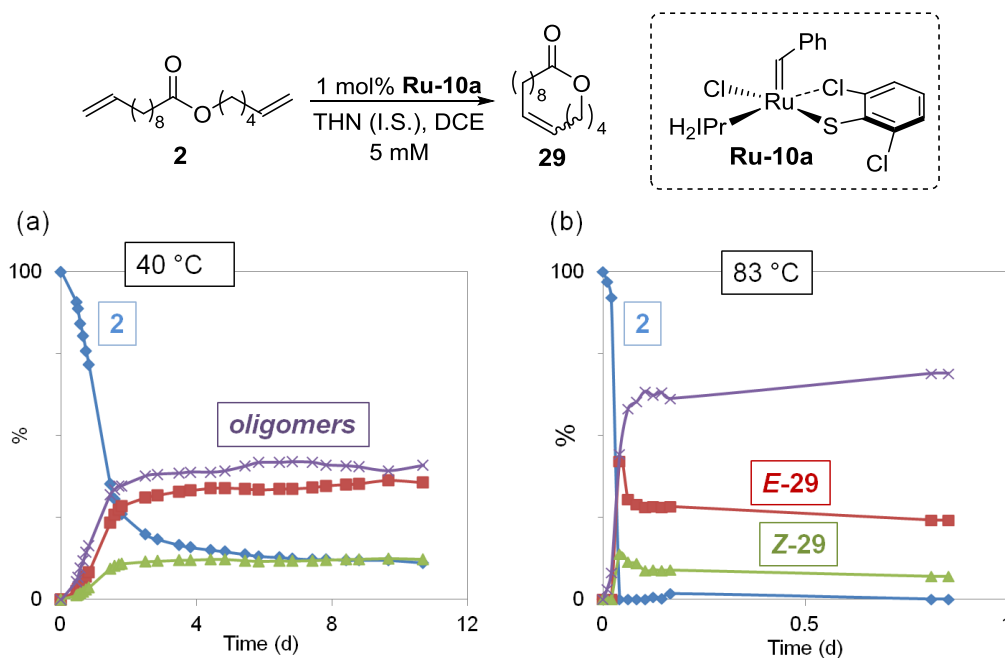


Figure 4.12 Effect of temperature on RCM macrocyclization of **2**. Conditions: 1 mol% **Ru-10a** in DCE at (a) 40 °C or, (b) reflux (83 °C).

For RCM macrocyclizations performed with Grubbs catalyst **Ru-1b**, higher temperatures can help drive cyclization when oligomers are formed.^{24,36} In addition, a study by Danishefsky and co-workers³⁷ using **Ru-1b** showed that upon increasing the temperature (40 °C to 80 °C), the yields of the “cyclomonomer” improved and the reaction time decreased significantly. RCM macrocyclization using **Ru-10a** was therefore carried out in DCE at reflux (Figure 4.12b). The reaction proceeded to full conversion in 1 h, compared to only 89% conversion after 10 d when performed at 40 °C. However, RCM yield was only 31% (29% being the Z-isomer), vs. 48% when performed at 40 °C. Again, oligomers dominated the product mixture (79% yield). The lower RCM yield was attributed to deactivation of the

catalyst before backbiting was complete. As noted above, elevated temperatures accelerate catalyst deactivation; lower RCM yields were also found at higher temperatures with **Ru-9**.

4.2.3 Stability of **Ru-9** in the absence of substrate

If a catalyst is not long-lived, the oligomerization-backbiting equilibrium will be arrested, and RCM yields can be adversely affected.²⁴ That is, premature catalyst deactivation results in oligomers that cannot be recycled, affecting the yield of the reaction. The thermal stability of the precatalysts in the reaction solvent DCE, was therefore explored, in the absence of substrate. To assess catalyst lifetime, in the ¹H NMR spectrum the alkylidene signal for the precatalyst was integrated vs. dimethyl terephthalate as an internal standard. Jensen and co-workers¹³ previously reported that solutions of **Ru-9** in CD₂Cl₂ at RT can be stored under argon for a few days without sign of decomposition. More surprisingly, negligible decomposition of **Ru-9** was reported after 24 h in THF at 60 °C.

In the presence of acids or quinones, these workers observed evolution of small amounts of the Hoveyda catalyst **Ru-2b** by ¹H NMR analysis.¹³ Decomposition of **Ru-9** may occur through an anionic exchange reaction.³⁵ This pathway appears to be enhanced with use of chlorinated solvents CHCl₃ and CH₂Cl₂. In addition, Jensen's homocoupling reactions with **Ru-9** employ a Proton Sponge, thought to prolong catalyst lifetime.¹³ The Proton Sponge helps to inhibit catalyst decomposition producing less Hoveyda catalyst **Ru-2b**. Without the presence of a Proton Sponge and with use of chlorinated solvent DCE, this pathway is likely to be promoted, increasing the rate that **Ru-2b** is formed (Figure 4.13). Precatalyst **Ru-9** was very stable in solution, with only 28% decomposition observed after 4 weeks in DCE at 40 °C. Minimal decomposition was observed, until after 3 d when a small signal for Hoveyda catalyst **Ru-2b** (16.38 ppm) was evident (Figure 4.13). ¹H NMR analysis of an authentic sample of **Ru-2b** in DCE confirmed this signal. After 4 weeks, 21% of **Ru-2b** was present and no hydride species were observed.

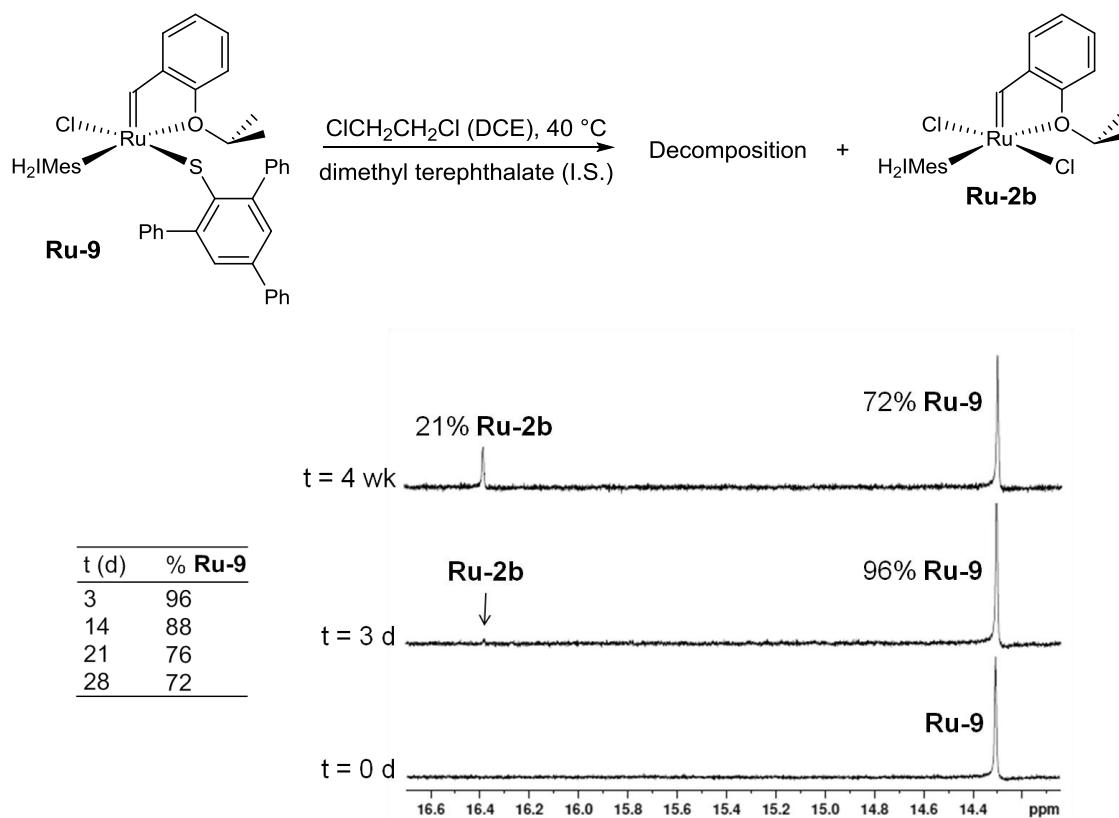


Figure 4.13 Examining the solution stability of **Ru-9** in DCE at 40 °C over time.

The majority of the catalytic activity observed when the RCM of **2** is performed at 5 mM, with **Ru-9**, occurs after 1 d (Section 4.2.1.1). While this could reflect slow initiation for **Ru-9**, Jensen and co-workers^{13,35} believe that at low substrate concentrations, **Ru-9** is essentially inactive. The activity observed at later stages of catalysis could be thus be due to traces of **Ru-2b** formed during decomposition of **Ru-9**, due to the use of chlorinated solvent (DCE) as noted above.³⁵ Hoveyda catalyst **Ru-2b** is not a Z-selective catalyst, which could explain the loss in Z-selectivity as the reaction proceeds. This was most relevant for reactions performed at a higher substrate concentration (ca. 500 mM), where high Z-selectivities (although at very low RCM yields) were observed early in the reaction, which deteriorated over time. In the thermolysis of **Ru-9** (DCE, 40 °C), after 3 d, only 2% of **Ru-2b** was observed which, in the presence of substrate, would correlate to 0.1 mol%. The Hoveyda catalyst **Ru-2b** is an extremely active catalyst and can perform at incredibly low catalyst loadings in a variety of olefin metathesis reactions.³⁸⁻⁴⁰

4.2.4 Stability of Ru-10a in the absence of substrate

For complex **Ru-10a**, a second alkylidene signal was evident (δ_{H} 17.43 ppm) after 4.5 h in DCE at 40 °C. The catalyst was less stable than **Ru-9**, with no alkylidene signal remaining after 24 h (Figure 4.14). This species also initiates rapidly. Fast initiation is consistent with the lability of the dative chloride, but the relatively short lifetime in solution suggests that this ligand does not exert the protective effect originally anticipated. The bulk of the H₂IPr ligand combined with the lability of the dative chloride could allow the catalyst to be prone to C-H bond activation. Thus, rapid turn-on did not translate into rapid conversion of substrate into RCM product: instead, competing deactivation accounts for the failure to see increased RCM yields upon diluting reactions from 5 mM to 0.5 mM (Section 4.2.2.1). The more unexpected failure of fresh **Ru-10a** to improve RCM yields (this having resulted only in an increase in oligomer) indicates that metathesis of the internal olefins in the oligomers is slower than deactivation for this catalyst.

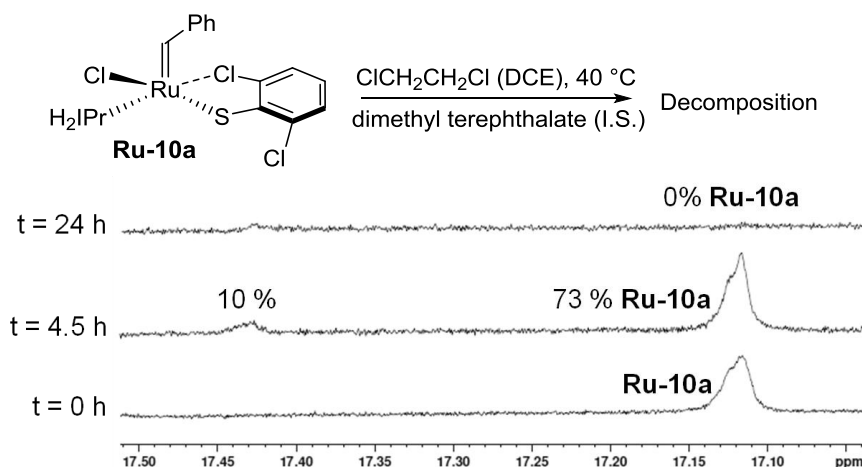


Figure 4.14 ¹H NMR spectra for decomposition of **Ru-10a** in DCE at 40 °C over time. (The poor peaks shapes are due to analysis in protio-DCE, which limits the efficacy of shimming).

On repeating the thermolysis study in CD₂Cl₂ in a sealed J. Young NMR tube at 35 °C, a dramatic increase in the lifetime of **Ru-10a** was observed (Figure 4.15a). After 1 d, 95% of **Ru-10a** was still present, as compared to 0% after the same period in DCE at 40 °C. The ¹H NMR spectrum indicates multiple decomposition products (2-6 new signals between 9-18

ppm; Figure 4.15b). This suggests that **Ru-10a** decomposes by very different pathways in CD_2Cl_2 vs. DCE, despite the similar polarities of these chlorinated solvents.

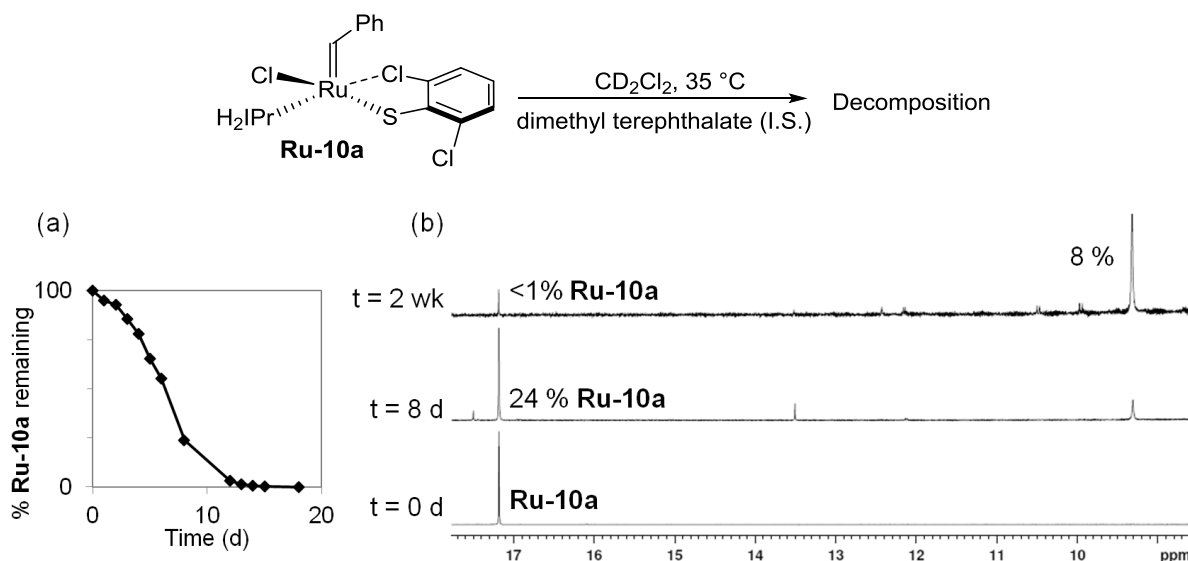


Figure 4.15 Thermolysis of **Ru-10a** in CD_2Cl_2 at 35 °C. (a) Rate curve of the decomposition of **Ru-10a**. (b) ^1H NMR spectra showing decomposition products.

4.3 Conclusions

This chapter described a study of the ability of two ruthenium-monothiolate catalysts, **Ru-9** and **Ru-10a**, to effect Z-selective RCM macrocyclization. These catalysts had not previously been employed in RCM, and the information gained is valuable to improving their design (see Chapter 5). The arylthiolate ligand is shown to behave differently from the aryloxy ligand:¹⁴ specifically, it does not promote RCM in preference to oligomerization. The Z-selectivity observed for **Ru-9** in less challenging contexts was not maintained in macrocyclization. With use of **Ru-9**, observed catalytic activity could be attributed to the Hoveyda catalyst **Ru-2b**, which is not Z-selective. Formation of this species increases in a chlorinated solvent such as DCE. Both **Ru-9** and **Ru-10a** were not capable of backbiting effectively to liberate macrocycles from the oligomeric species, even at appropriate dilutions with a fresh catalyst charge. For **Ru-9**, the catalyst was found to be remarkably long lived, in the presence or absence of substrate. Thermolysis experiments (DCE, 40 °C), in the absence of substrate showed 72% **Ru-9** present after 4 weeks. In the presence of substrate, minimal catalyst deactivation was observed over 6 d, as the catalyst was capable of turning over both

2 and **14** multiple times, at near-original capacity. **Ru-10a** was less stable in the absence of substrate, indicating the *o*-Cl group on the arylthiolate is too labile to effectively stabilize the catalyst. However, **Ru-10a** was able to perform the RCM macrocyclization at a lower catalyst loading (1 mol%). Although the reaction proceeded rather slowly reaching incomplete conversion, after 6 d diene was still being consumed.

In terms of experimental design, other avenues that could potentially improve yields and Z-selectivity include carrying out catalysis under reduced pressure.^{5,8,19} Active removal of ethylene from solution has been shown to be more effective than use of inert atmosphere or sparging with argon.²⁶ Use of THF as the solvent in the RCM macrocyclization could also be beneficial due to its coordinating ability. It may increase catalyst solubility permitting higher substrate concentrations, as **Ru-9** is believed to be essentially inactive at low concentrations. This should enable faster consumption of substrate, as well as increase the activity resulting from **Ru-9**, permitting higher Z-selectivity. Lastly, eliminating the use of a chlorinated solvent and/or addition of a Proton Sponge could ensure diminished activity of the decomposition pathway of **Ru-9** into Hoveyda catalyst **Ru-2b** and possibly even inhibit it altogether.

Dramatic increases in selectivity are required to reach the current state-of-the-art ruthenium Z-selective catalysts. Although use of THF, and therefore higher substrate concentrations, would be beneficial for these catalysts, this will cause an increase in the proportion of oligomers. If use of the ruthenium-arylthiolate catalysts could limit oligomerization, these reaction conditions would be advantageous. At earlier conversions, using **Ru-9** and **Ru-10a**, less oligomers were produced than when the RCM macrocyclization was performed with parent Grubbs and Hoveyda complexes, **Ru-1b** and **Ru-2b** respectively (at 5 mM).²³ The problem with the ruthenium-monothiolate catalysts was their inefficient backbiting; however if overcome these could be very useful catalysts. The arylthiolate ligand was chosen to apply steric pressure on the metallocyclobutane, to generate the desired Z-product. However, it was known that if the ligand was too bulky, catalyst activity might be compromised. Future work could entail designing a similar catalyst that is slightly less bulky to allow recycling of the oligomers into the desired RCM product.

4.4 References

- (1) Pederson, R. L.; Fellows, I. M.; Ung, T. A.; Ishihara, H.; Hajela, S. P. *Adv. Synth. Catal.* **2002**, *344*, 728–735.
- (2) Malcolmson, S. J.; Meek, S. J.; Sattely, E. S.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2008**, *456*, 933–937.
- (3) Sattely, E. S.; Meek, S. J.; Malcolmson, S. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 943–953.
- (4) Ibrahim, I.; Yu, M.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3844–3845.
- (5) Meek, S. J.; O'Brien, R. V.; Llaveria, J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *479*, 461–466.
- (6) Flook, M. M.; Jiang, A. J.; Schrock, R. R.; Muller, P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 7962–7963.
- (7) Jiang, A. J.; Zhao, Y.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 16630–16631.
- (8) Yu, M.; Wang, C.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *479*, 88–93.
- (9) Schrock, R. R. *Angew. Chem. Int. Ed.* **2006**, *45*, 3748–3759.
- (10) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29.
- (11) Armstrong, S. K. *J. Chem. Soc., Perkin Trans.* **1998**, 371–388.
- (12) Teo, P.; Grubbs, R. H. *Organometallics* **2010**, *29*, 6045–6050.
- (13) Occhipinti, G.; Hansen, F. R.; Törnroos, K. W.; Jensen, V. R. *J. Am. Chem. Soc.* **2013**, *135*, 3331–3334.
- (14) Conrad, J. C.; Parnas, H. H.; Snelgrove, J. L.; Fogg, D. E. *J. Am. Chem. Soc.* **2005**, *127*, 11882–11883.
- (15) Jensen, V. R.; Occhipinti, G.; Hansen, F. R. Novel Olefin Metathesis Catalysts. WO 2012/032131 A1, 2012.
- (16) Khan, R. K. M.; Torker, S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2013**, *135*, 10258–10261.
- (17) Keitz, B. K.; Endo, K.; Patel, P. R.; Herbert, M. B.; Grubbs, R. H. *J. Am. Chem. Soc.* **2012**, *134*, 693–699.
- (18) Endo, K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2011**, *133*, 8525–8527.
- (19) Keitz, B. K.; Endo, K.; Herbert, M. B.; Grubbs, R. H. *J. Am. Chem. Soc.* **2011**, *133*, 9686–9688.
- (20) Wang, C.; Haefner, F.; Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2013**, *52*, 1939–1943.
- (21) Höfle, G.; Bedorf, N.; Steinmetz, H.; Schomburg, D.; Gerth, K.; Reichenbach, H. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1567–1569.
- (22) 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.
- (23) Monfette, S. Exploration of Ligand Effects, Substrate Effects and Reactor Effects on Macrocyclization via Ring-Closing Metathesis: A Rational Approach to Efficient Cyclization. Ph.D. Dissertation, University of Ottawa, Ottawa, ON, 2010.
- (24) Monfette, S.; Fogg, D. E. *Chem. Rev.* **2009**, *109*, 3783–3816.
- (25) Monfette, S.; Crane, A. K.; Duarte Silva, J. A.; Facey, G. A.; dos Santos, E. N.; Araujo, M. H.; Fogg, D. E. *Inorg. Chim. Acta* **2010**, *363*, 481–486.

- (26) Marx, V. M.; Herbert, M. B.; Keitz, B. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2013**, *135*, 94–97.
- (27) Monfette, S.; Camm, K. D.; Gorelsky, S. I.; Fogg, D. E. *Organometallics* **2009**, *28*, 944–946.
- (28) Monfette, S.; Marleau-Gillette, S.; Conrad, J. C.; McDonald, R.; Fogg, D. E. *Dalton Trans.* **2012**, *41*, 14476–14479.
- (29) Vorfalt, T.; Wannowius, K. J.; Plenio, H. *Angew. Chem. Int. Ed.* **2010**, *49*, 5533–5536.
- (30) Thiel, V.; Hendann, M.; Wannowius, K.-J. r.; Plenio, H. *J. Am. Chem. Soc.* **2012**, *134*, 1104–1114.
- (31) Ashworth, I. W.; Hillier, I. H.; Nelson, D. J.; Percy, J. M.; Vincent, M. A. *Chem. Comm.* **2011**, *47*, 5428–5430.
- (32) Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 7202–7207.
- (33) Hong, S. H.; Wenzel, A. G.; Salguero, T. T.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2007**, *129*, 7961–7968.
- (34) van Lierop, B. J.; Lummiss, J. A. M.; Fogg, D. E., Ring-Closing Metathesis: A How-To Guide. In *Olefin Metathesis-Theory and Practice*, Grela, K., Ed. Wiley: Weinheim, 2014.
- (35) Occhipinti, G.; Jensen, V. R. University of Bergen, Bergen, NO. Personal communication, 2013.
- (36) Lee, C. W.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 2145–2147.
- (37) Yamamoto, K.; Biswas, K.; Gaul, C.; Danishefsky, S. J. *Tetrahedron Lett.* **2003**, *44*, 3297–3299.
- (38) Rogalski, S.; Pietraszuk, C.; Marciniak, B. *J. Organomet. Chem.* **2009**, *694*, 3918–3922.
- (39) Kong, J.; Chen, C.-y.; Balsells-Padros, J.; Cao, Y.; Dunn, R. F.; Dolman, S. J.; Janey, J.; Li, H.; Zacuto, M. J. *J. Org. Chem.* **2012**, *77*, 3820–3828.
- (40) Miao, X.; Malacea, R.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Green Chem.* **2011**, *13*, 2911–2919.

5. Conclusions and Future Directions

The research presented in this thesis focused on gaining a greater insight into ruthenium metathesis catalysts, with the intention of clarifying the origin of catalyst performance. Chapter 3 described an investigation into the much debated release-return mechanism in the well-known Hoveyda catalyst, **Ru-2b**. With the aid of a ^{13}C -labeled styrenyl ether ligand **11***, uptake of this moiety by the four-coordinate methyldiene **Ru-5b** was shown to occur rapidly during both RCM and CM reactions. Operation of the boomerang mechanism in **Ru-2b** has major implications towards catalyst lifetime, which ultimately impacts catalyst loadings. This insight is important in showing some of the basis for the excellent performance of this catalyst in industrial contexts, and points toward the value of this aspect of catalyst design. The latter may be important in development of new catalysts for more demanding olefin metathesis reactions, where decomposition plays a major limiting role. In the future, studying the boomerang mechanism in more complex metathesis reactions is suggested. This includes CM of a “deep internal” olefin (for example methyl oleate), and RCM of macrocycles. In addition, studying the homocoupling of a simple internal olefin would allow a more detailed investigation of the ability of the styrenyl ether **11** to be recaptured by other active species. Also of keen interest is the potential re-uptake of the styrenyl ether **11** by the enoic carbene during acrylate CM.

Reactions of **Ru-2b** and **11*** demonstrated the relatively fast initiation of **Ru-2b** when compared to **Ru-2a**. This is opposite to the trend observed in the Grubbs systems, where **Ru-1a** has much faster initiation efficiency than **Ru-1b**. Uncovering the reason for this reversed trend, could provide further information relating to catalyst handling. For example, continuous slow-addition of a rapidly initiating catalyst avoids a reservoir of active species that is available for bimolecular decomposition. More interesting could be a comparison of the rates of initiation of second-generation Grubbs and Hoveyda catalysts, **Ru-1b** and **Ru-2b** respectively, which to the best of my knowledge, has never been examined. Hoveyda catalysts are commonly viewed as being rather slow to turn-on compared to the Grubbs' systems, due to less facile dissociation of the smaller styrenyl ether ligand **11** (compared to PCy_3). This thesis study suggests that this may not be the case, and further investigation into the factors which contribute to initiation of these two key metathesis catalysts, is warranted.

Chapter 5. Conclusions and Future Directions

A direct comparison with an appropriate substrate would be required, since initiation of **Ru-1b** proceeds by a dissociative mechanism: depending on the substrate, **Ru-2b** can proceed by a dissociative or interchange-associative mechanism.

Chapter 4 of this thesis investigated two novel catalysts and their ability to affect Z-selective RCM macrocyclization of **2**. While ruthenium-monothiolate complexes, **Ru-9** and **Ru-10a**, did not show promising activity in this type of metathesis transformation, valuable information was gained that may help to improve catalyst design. During RCM, the desired Z-selectivity was not obtained at the highest possible conversion, nor did the arylthiolate ligand help to limit the amount of undesired oligomers: both catalysts were unable to efficiently backbite the 1,2-disubstituted olefins generated during primary metathesis, which is believed to be a result of steric congestion. Ongoing work is aimed at examining the hypothesis that the efficiency of backbiting is sterically controlled, and at examining the impact of equilibrium metathesis on Z-selectivity.

List of Contributions

Manuscripts published or submitted:

- 1- Bates, J.M.; Lummiss, J.A.M.; Bailey, G.A.; Fogg, D.E., *ACS Catal.* **2014**, submitted.
- 2- Beach, N.J.; Lummiss, J.A.M.; Bates, J.M.; Fogg, D.E., *Organometallics* **2012**, *31*, 2349-2356.

Poster presentations:

- A- Bates, J.M.; Fogg, D.E. *Toward Value-Added Arylpropenes from Renewable Resources*. 95th Canadian Chemistry Conference and Exhibition (CSC), Calgary, AB, May 26-30, 2012.
- B- Bates, J.M.; Fogg, D.E. *Toward Value-Added Arylpropenes from Renewable Resources*. Ottawa-Carleton Chemical Institute (OCCI) Day, Ottawa, ON, May 18, 2012.