Synthetic and Mechanistic Studies in Ruthenium-catalyzed Olefin Metathesis

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Abstract

Ruthenium-catalyzed olefin metathesis is now an invaluable tool in organic synthesis. However, routes to the dominant metathesis catalysts, the second-generation Grubbs and Hoveyda catalysts ($RuCl_2(PCy_3)(H_2IMes)(=CHPh)$ and $RuCl_2(H_2IMes)[=CH(o\text{-}O^iPr)C_6H_4]$, respectively) are plagued with problems. The common reliance on in situ methods to generate the *N*-heterocyclic carbene H_2IMes severely limits stoichiometric control, and results in contamination by byproducts, some of which are readily overlooked, and some of which are difficult to remove. Both can affect batch-to-batch reproducibility in catalysis. This thesis work demonstrated that widespread perceptions of the instability of free H_2IMes are erroneous, and that the free carbene is readily handled under water-free conditions. Clean, convenient, near-quantitative routes were developed to these second-generation catalysts by ligand exchange of their first-generation counterparts $RuCl_2(PCy_3)_2(=CHPh)$, $RuCl_2(PCy_3)[=CH(o\text{-}O^iPr)C_6H_4]$ with free H_2IMes, with sequestration of the liberated phosphine by an ion-exchange resin. A second focus was examination of a much-debated hypothesis in olefin metathesis: that is, the extent to which the high productivity of the Hoveyda catalysts reflects re-uptake of the styrenyl ether functionality released in the initial cycle of metathesis. Current evidence for and against this "boomerang" hypothesis is critically examined, and new approaches to examining its operation are described. Specifically, the rate of decomposition, vs. re-uptake, is examined for the active species $RuCl_2(PCy_3)(=CH_2)$, and background exchange of the parent catalyst with free styrenyl ether is measured by use of a ^{13}C-labelled styrenyl ether. These studies confirm the relevance of the boomerang mechanism for first-generation Hoveyda catalysts.

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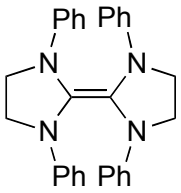
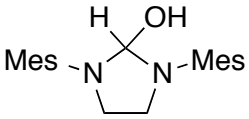
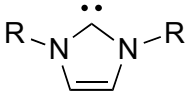
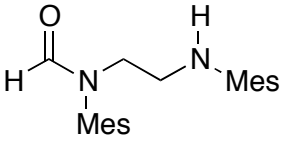
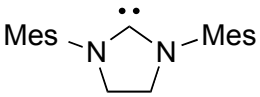
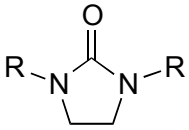
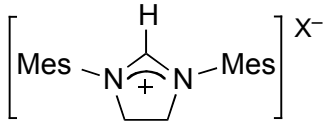
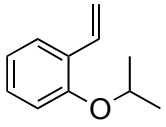
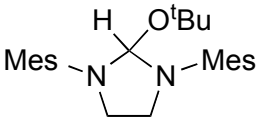
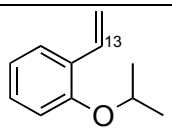
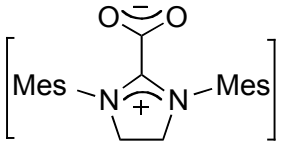
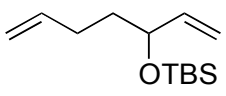
List of Abbreviations

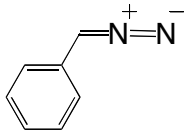
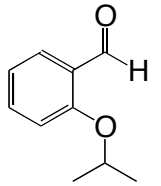
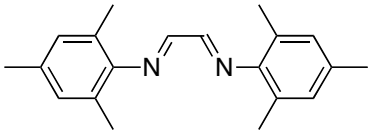
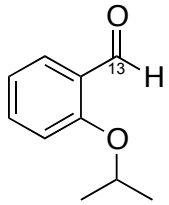
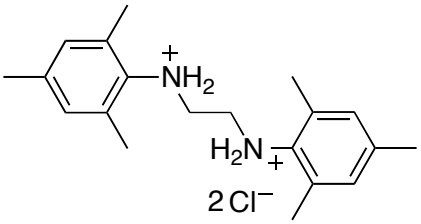
Ad	Adamantyl
ADMET	Acyclic diene metathesis
ARCM	Asymmetric ring closing metathesis
Cat	Catalyst
Cf.	Compare
CM	Cross metathesis
DeDAM	Diethyl diallylmalonate
DMF	*N,N*-Dimethylformamide
E.g.	For example
Equiv	Equivalents
EtOAc	Ethyl acetate
EYCM	Enyne cross metathesis
H_2IMes	1,3-bis-(2,4,6-trimethylphenyl)imidazolin-2-ylidene
[H_2IMes(H)](Cl)	*N,N'*-bis(mesityl)imidazolinium chloride
[H_2IMes(H)](BF_4)	*N,N'*-bis(mesityl)imidazolinium tetrafluoroborate
[H_2IMes(H)](HCO_3)	*N,N'*-bis(mesityl)imidazolinium hydrogen carbonate
H_2I*t*Bu	1,3-bis-(tert-butyl)imidazolin-2-ylidene
Hr	Hour
Hz	Hertz
IAd	*N,N'*-diadamantylimidazol-2-ylidene
IMe	1,3-dimethylimidazol-2-ylidene
IMes	1,3-bis-(2,4,6-trimethylphenyl)imidazol-2-ylidene
I*t*Bu	1,3-bis-(tert-butyl)imidazol-2-ylidene
MAS	Magic Angle Spinning
Mes	Mesityl
Min	Minutes
NHC	*N*-heterocyclic carbene
NMR	Nuclear magnetic resonance
P	Product
ppm	Parts per million (Hz/MHz); chemical shift

py	Pyridine
R	Substrate
RCM	Ring closing metathesis
RCEYM	Ring closing enyne metathesis
ROM/CM	Ring opening metathesis/cross metathesis
ROMP	Ring opening metathesis polymerization
RT	Room temperature
THF	Tetrahydrofuran
TMB	1,3,5-Trimethoxybenzene

List of Compounds

Organic Compounds

#	Compound	#	Compound
1		**7**	
2	 **a**: R = Ad **b**: R = Mes	**8**	
3		**9**	 **a**: R = Et **b**: R = Allyl **c**: R = Benzyl
4	 **a**: X = BF_4 **b**: X = Cl **c**: X = HCO_3	**10**	
5		**10***	
6		**11**	

12		**15**	
13		**15***	
14			

Ru Complexes

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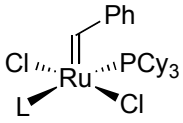
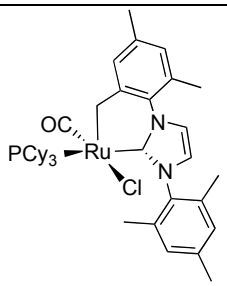
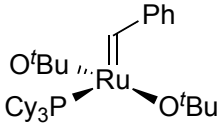
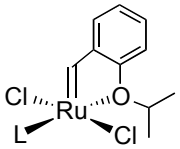
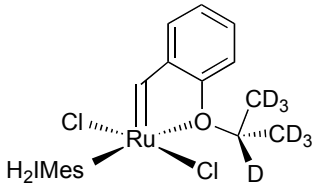
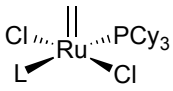
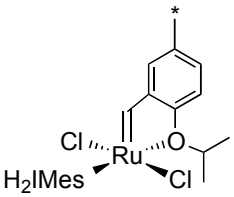
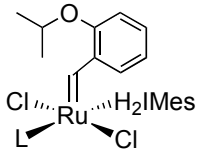
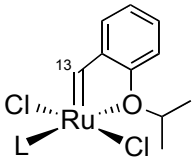
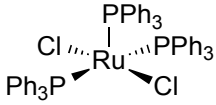
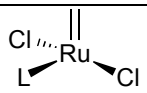
Ru-1	 **a:** L = PCy_3 **b:** L = IMes **c:** L = H_2IMes	**Ru-3**	
Ru-2		**Ru-4**	 **a:** L = PCy_3 **b:** L = H_2IMes

Ru-4b^{D}		**Ru-6**	 **a:** L = PCy_3 **b:** L = H_2IMes
Ru-4b^{F}		**Ru-7**	 **a:** PCy_{3-} **b:** H_2IMes
Ru-4*	 **a:** L = PCy_3 **b:** L = H_2IMes	**Ru-8**	
Ru-5	 **a:** L = PCy_3 **b:** L = H_2IMes		

1 Introduction

1.1 The Advent of Catalysis

Catalysts are of central importance to our everyday lives. Over 90% of chemical processes require at least one catalytic transformation,[1] including in the production of foodstuffs, synthetic fibres, plastics, dyes and perfumes.[2-8] In 1909, Willhelm Ostwald won the Nobel Prize in Chemistry for his work in catalysis and research involving the fundamental principles governing chemical equilibrium and rates of reaction. He defined catalysis as a "chemical acceleration brought about by the presence of substances that do not appear in the reaction product."[9] According to Ostwald, addition of a catalyst to a chemical process lowers the activation energy barrier and accelerates the reaction by providing an alternate, lower energy pathway, while itself remaining unchanged (Figure 1.1). For obvious reasons, the discovery and implementation of catalysts in processes have revolutionized industrial chemistry by allowing facile, low energy routes to important materials. As early as 1811, acid catalysts were used to aid in the transformation of sugars into dextrin (Kirchhoff, 1811-1814), while specific iron catalysts, proposed by Fritz Haber in 1909, still remain the major industrial route to ammonia from gaseous nitrogen and hydrogen.

The development of effective catalysts continues to represent an important area of research: Development and use of catalysts is one of the 12 principles of green chemistry.[10,11] By accelerating the reaction, lowering the energy barrier and minimizing the production of undesired by-products, high yields can be achieved at markedly lower economic and environmental costs. Additionally, the growing importance of catalysis is showcased in the Nobel Prize-winning research of Ziegler and Natta for their work in polymerization (1963), Wilkinson and Fischer (1973) for the development of organometallic "sandwich" complexes,

Knowles, Noyori and Sharpless (2001) for their work in asymmetric hydrogenation and oxidation, Grubbs, Schrock and Chauvin (2005) for their work in olefin metathesis, and Heck, Negishi and Suzuki (2010) for their work in cross-coupling reactions.[12]

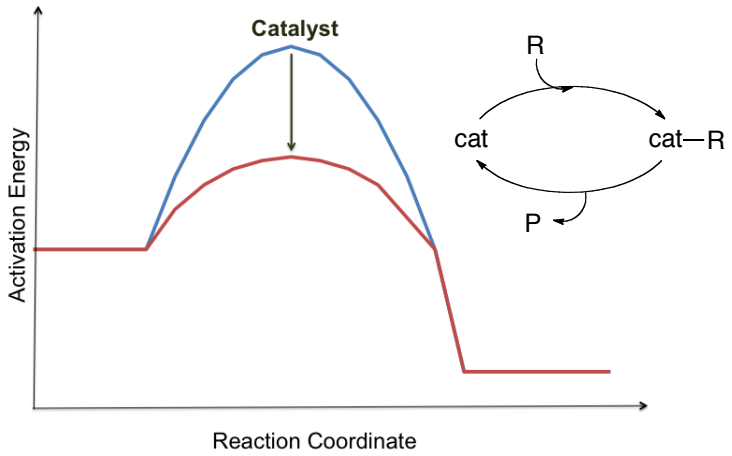


Figure 1.1 The effect of a catalyst on the activation energy barrier of a chemical reaction. (R = starting material; P = product).

Traditionally, industrial processes make use of heterogeneous catalysts in both product synthesis and in the purification of gaseous by-products from power plants.[13] While these types of catalyst are easily separated from the product and regenerated/reused following a chemical transformation, reactions only take place at the catalyst surface, often necessitating high catalyst loadings and harsh reaction conditions. Additionally, poor catalyst selectivity towards complex substrates often limits their application in specialized reactions (e.g. pharmaceuticals, tissue engineering).

The necessity for a higher level of selectivity during catalysis has led to a growing interest in homogeneous transition metal catalysts.[2,13-18] When compared with heterogeneous catalysts (which require surface contact), dissolution of a homogeneous catalyst in the

reaction medium allows increased catalytic activity at lower concentrations and under mild reaction conditions.[13,19] One of the biggest advantages also lies in the unprecedented selectivity provided by these types of complexes. Here, tuning of catalyst activity is achieved simply by modification of the ligands in the metal coordination sphere.[2,19] This is key to processes involved in the synthesis of pharmaceuticals, vitamins, agrochemicals, flavours and fragrances.

A major disadvantage of homogeneous catalysis, however, lies in the separation and recycling of residual catalyst. Purification of the complex and its associated decomposition products by extraction or distillation is quite costly, and efficient separation techniques are also crucial in terms of product purity. The European Agency for the Evaluation of Medicinal Products, for example, allows a combined upper limit of 5 ppm for platinoid metals (Pt, Pd, Ru, Ir, Rh, Os) - 0.5 ppm for pregnant women - in orally administered drugs.[20] The synthesis of biologically active molecules which meet these requirements has, however, been successfully achieved in catalytic asymmetric hydrogenation (e.g. metolachlor), addition (e.g. ABT-546, HCV polymerase inhibitor 3082), and oxidation (e.g. *s*-esameprazole) reactions.[2] More recently, the development of robust and selective ruthenium metathesis catalysts for application in the pharmaceutical industry has been a strong area of focus.[2,5,21,22]

1.2 Olefin Metathesis

1.2.1 Historical Development

Olefin metathesis is a metal-mediated process involving scission and formation of carbon-carbon double bonds. It is an extremely versatile process that has found widespread

application in various olefin-based transformations including cross metathesis (CM), ring closing metathesis (RCM), ring opening metathesis (ROM), ring closing enyne metathesis (RCEYM), ring opening metathesis polymerisation (ROMP) and acyclic diene metathesis polymerisation (ADMET).

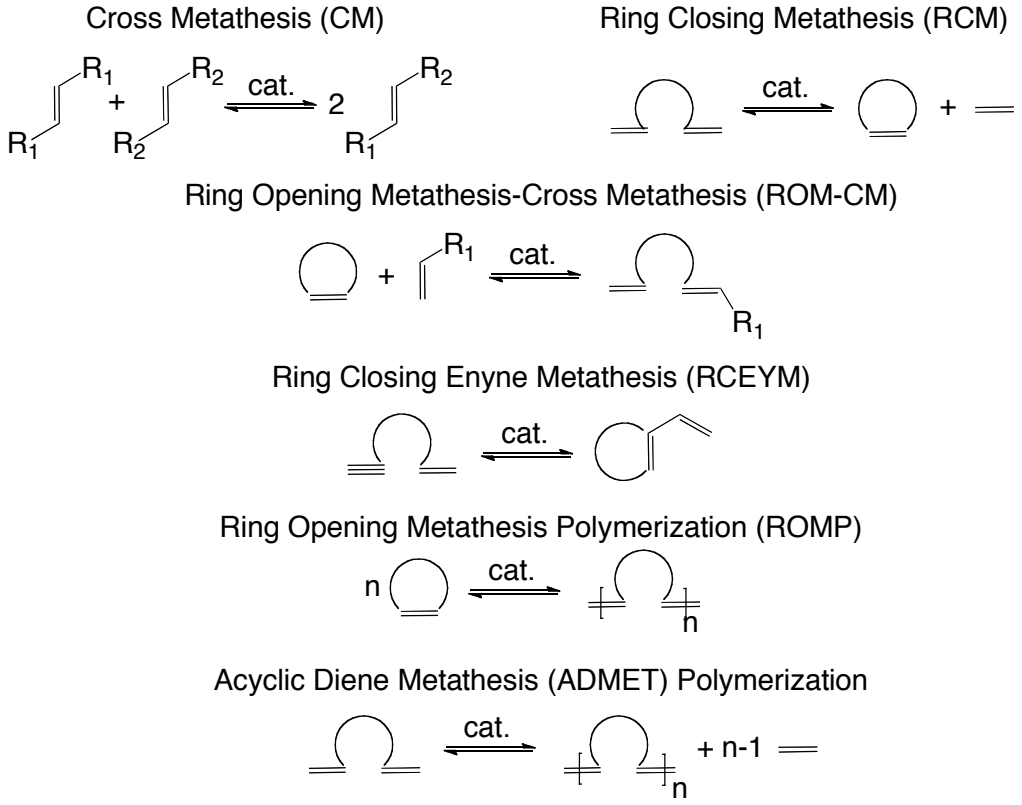


Figure 1.2 Common metathesis reactions.

Discovery of this process has had a profound effect in chemistry, both in academia and in industry. Compared with traditional carbon-carbon bond forming processes, olefin metathesis can provide access to a variety of functional groups using fewer synthetic steps under mild reaction conditions, with high selectivity towards olefins.[2,5,13,19,23] At present, heterogeneous metathesis catalysts are applied in the SHOP process (conversion of ethylene

into mixed olefins for detergent production), the Philips tri-olefin process (conversion of propylene to ethylene and 2-butene), and in the ring-opening metathesis polymerization (ROMP) of cyclooctene (Vestanomer®), norbornene (Norsonex®) and dicyclopentadiene (Metton® and Telene®).[5,19] It should be noted that the homogenous ruthenium catalysts that now dominate olefin metathesis in academia (see below) are not yet used in any industrial process on stream.

Olefin metathesis was first recognized in late 1956 when Eleuterio, a researcher at DuPont, experimentally confirmed that a feed of propylene gas passed through a molybdenum-on-aluminum catalyst bed resulted in an off-gas composed of propylene, ethylene, and 1-butene.[24] Earlier that year, a second DuPont chemist, Nicholas Merckling, observed ROMP of norbornene using a disordered $TiCl_4$ catalyst. In both cases, while it was clear that new carbon-carbon bonds were being formed, the mechanism of action puzzled researchers for many years. The first hypothesis came in 1967 when Calderon, a researcher at Goodyear Tire & Rubber, proposed that these products resulted from the cleavage and reformation of C=C double bonds to form a new olefinic product.[25] This study led Calderon to coin the term "olefin metathesis."

The first mechanistic explanation of olefin metathesis was presented in 1968, when Calderon proposed the formation of a cyclobutane intermediate complexed to a metal (Scheme 1.1a).[26] This report was further advanced by Pettit, who suggested the presence of a tetramethylene species (Scheme 1.1b).[27] It was Chauvin, however, in 1971 who proposed the currently accepted [2+2] cycloaddition mechanism, whereby metathesis is initiated by a metal carbene to form a metallocyclobutane intermediate, which subsequently breaks apart to produce a new olefin and a new metal carbene species (Scheme 1.1c).[28] Later work by Katz[29,30] and Schrock[31] provided support for this mechanism using W-based metal carbenes

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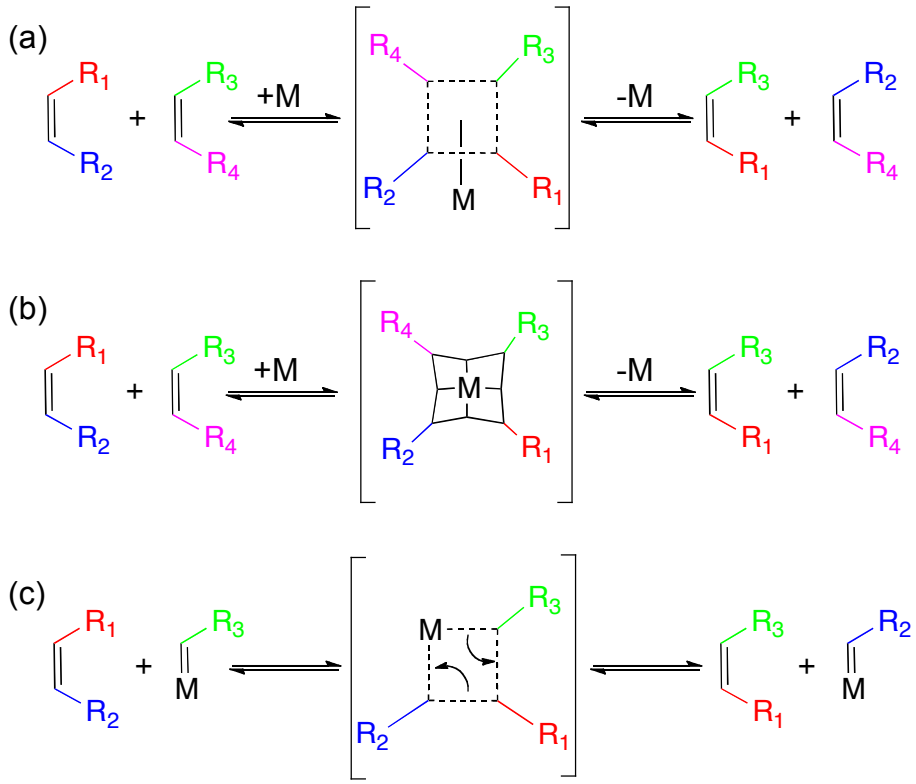
to mediate the polymerization of cyclic olefins and acetylene,[32] and showing that metal carbynes undergo olefin metathesis with acetylene.[33]



Scheme 1.1 Metathesis mechanism as proposed by a) Calderon, b) Pettit and c) Chauvin.

The observations and results described above led to several advances in the field, particularly by Schrock at MIT who first investigated metathesis catalysts of Ta and Nb.[34-37] He then moved towards the development of highly active and selective group 6 Mo and W alkylidene complexes,[38-42] which have proven highly effective in olefin metathesis, particularly in polymerization.[43-53] While Schrock catalysts provide high substrate selectivity, their oxophilicity presents a major drawback in that they undergo rapid decomposition in the presence of trace amounts of air or water.

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1.2.2 The Advent of Ru Metathesis Catalysts

A call for more robust metathesis catalysts with increased functional group tolerance led to the development of ruthenium metathesis catalysts by Grubbs in 1992.[54] As a "soft" late metal, Ru is significantly less oxophilic than the competing group 6 catalysts developed by Schrock. The reduced sensitivity of the Grubbs catalysts toward water, oxygen and heat has led to widespread uptake of olefin metathesis in organic synthesis, and to studies aimed at the potential production of biologically active molecules in an industrial setting.[2,5,13,18,55,56] Targets of particular interest include the anticancer agent Epothilone A, the Merck anti-inflammatory drug candidate NK-1, Pladienolide D, Elatol, BILN 2061 and (-)-Cyanthwigin F (Figure 1.3).

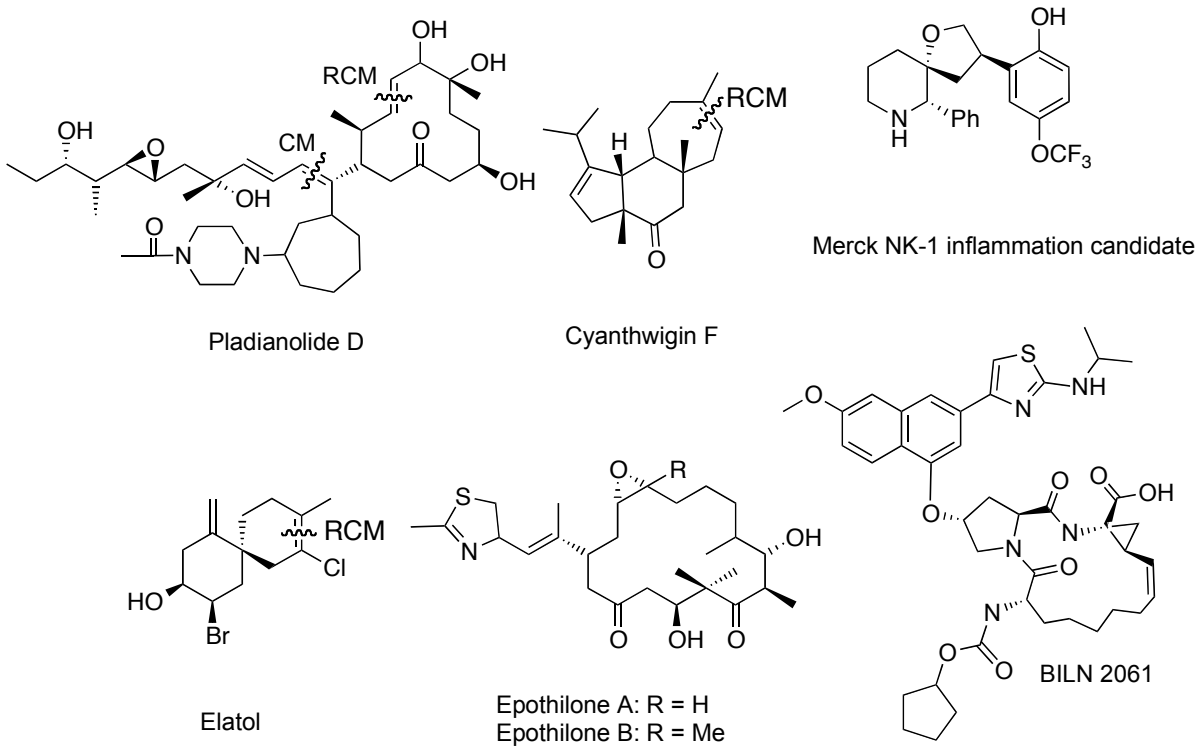

Figure 1.3 Pharmaceutical compounds synthesized using metathesis.

Although the Grubbs Ru systems are significantly more robust to atmospheric water and oxygen when compared with the Schrock group 6 catalysts, functional groups such as alcohols, aldehydes, and particularly alkoxides still prove problematic.[57-59] Much effort is directed at designing more selective Ru catalysts, with the aim of combining high selectivity with robustness.[60,61] These efforts are of particular interest for the development of low-cost, efficient routes to active pharmaceutical ingredients (API), while simultaneously decreasing the number of synthetic steps. This is an important function in a sector where the average number of steps required to synthesize an API is 12.[2]

1.2.3 Mechanism of Ru-catalyzed Olefin Metathesis

Also crucial to the advancement of this field was a conceptual understanding of catalyst mechanism. The accepted dissociative mechanism for a Grubbs-type catalyst is outlined in Scheme 1.2.[62-64] The rate-limiting step involves dissociation of a ligand, L, most commonly PCy_3, resulting in the formation of an active 14 e^- alkylidene species. The resulting vacant site on the metal center allows the coordination of an olefin, which undergoes [2+2] cycloaddition to form a metallocyclobutane intermediate. Collapse of this intermediate generates a new olefinic product and ethylene gas, while regenerating an active methylidene species. Both the metallocyclobutane and methylidene are short-lived and extremely difficult to detect, however, recent work by Piers[64,65] has allowed for the detection of the metallocyclobutane through low-temperature NMR studies.

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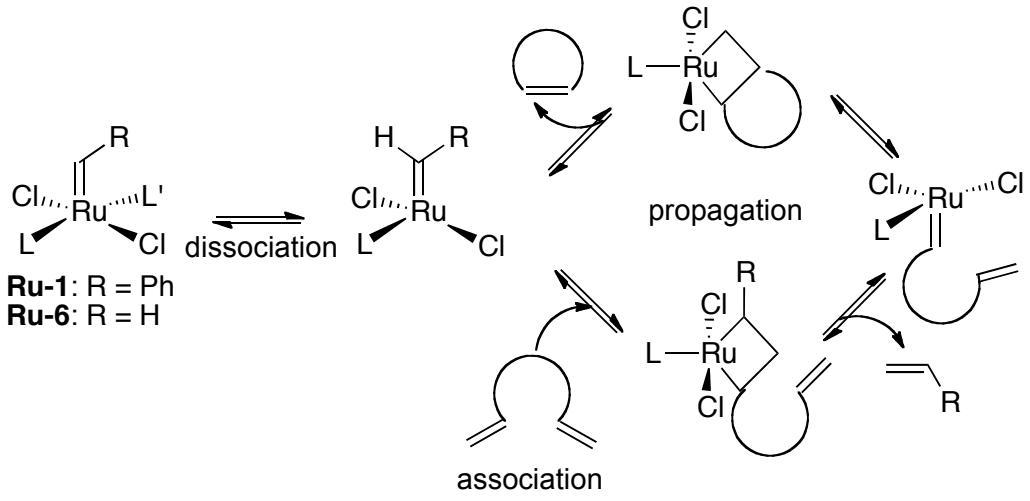

Scheme 1.2 Dissociative mechanism for Grubbs catalysts. Shown for RCM. **Ru-1** = Grubbs precatalyst. **Ru-6** = resting (L associated) and active (L dissociated) methylidene species.

While many derivations of the Grubbs catalyst have been synthesized, the four-coordinate methylidene active species remains identical in almost all cases. In each case, ligand substitution on the metal center affects only the activation efficiency and catalyst selectivity. For example, the Piers catalyst, itself a 14-electron species, is capable of carrying out metathesis at 0 °C, with activity comparable to second-generation Grubbs catalyst **Ru-1c** at 35 °C.[67]

Particular mechanistic interest also lies in the termination step of the catalyst cycle. While it is well-known that the active methylidene species is unstable and prone to deactivation,[68] Hoveyda-type catalysts, developed in 1998,[69] are of keen interest as potentially recyclable homogeneous catalysts. In this example, it has been postulated that the chelating =CHR group re-associates with the active species following metathesis. This will be discussed in more detail in Chapter 4. Such stabilization could be invaluable for reducing costs in the industrial context, in particular.

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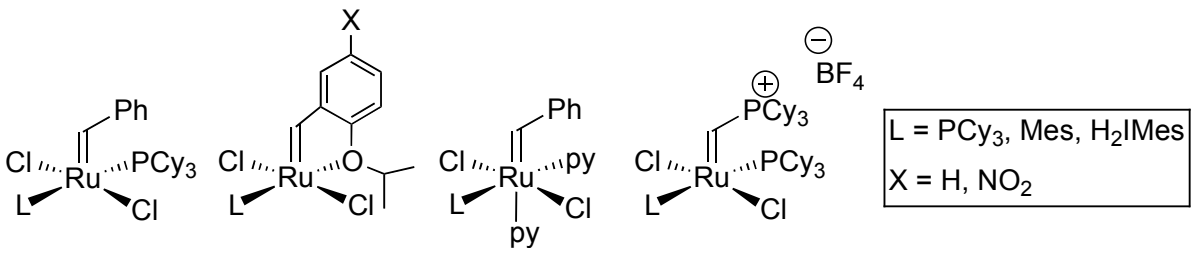

Figure 1.4 Some common Ru metathesis catalysts.

1.3 Scope of Thesis Work

The development of robust, clean routes to important Ru metathesis catalysts, and a clear understanding of potential catalyst stabilization mechanisms, are of great importance from a chemical and economic perspective. Experimental procedures used in this thesis work appear in Chapter 2. Chapter 3 presents a clean, efficient route to the important second-generation metathesis catalyst **Ru-1c**. This chapter also examines the behaviour and stability of the important *N*-heterocyclic carbene ligand, H_2IMes, used in these syntheses. Chapter 4 takes a critical approach to examination of the evidence for the so-called boomerang hypothesis for recapture of the Hoveyda catalyst by released styrenyl ether. New methods to probe this mechanism are developed, including direct examination of the four-coordinate active catalyst, and examination of a ^{13}C labelled precatalyst. Finally, conclusions and suggestions for future work appear in Chapter 5.

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2 Experimental Procedures

2.1 General Procedures

2.1.1 Reaction Conditions

Reactions were carried out under house N_2 (cryogenic boil-off, Linde) in an MBraun glovebox, or under argon or nitrogen (BOC gas, industrial grade) using standard double-manifold Schlenk techniques,[1] unless otherwise noted. The Ar and N_2 streams were dried by passage through a column of activated (blue) Drierite. Glassware was oven-dried at 150 ˚C prior to use, 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]

2.1.2 Materials

The following compounds were synthesized according to literature procedures: $RuCl_2(PPh_3)_3$ **Ru-8**,[3] *N*-tosylhydrazone,[4] and 1,3-bis(mesityl)imidazolinium hydrogen carbonate **4c**,[5] and 1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene **3**.[6]

Hydrated ruthenium chloride and tricyclohexylphosphine (97%) were purchased from Strem Chemicals. The following chemicals were purchased from Aldrich: 2-Iodopropane (99%), 4-toluenesulfonehydrazine (97%), 2,4,6-trimethylaniline (98%), glyoxal (40 wt% in water), 2-propenylphenol (98%), $LiAlH_4$ (95%), *n*-butyllithium (2.5 M in hexanes), potassium *tert*-butoxide (95%), potassium hydride (30 wt% in mineral oil), sodium hydride (95%), 1,3,5-trimethoxybenzene (>99%), ferrocene (98%; purified by sublimation by Carolyn Higman of the Fogg research group), sodium hydroxide pellets (97%), potassium hydroxide pellets (>85%), copper(I) chloride (97%), formic acid (>95%), hydrogen chloride (4 M in dioxane),

Amberlyst-15, dry dimethyl formamide (>99.5%), and potassium hydrogen carbonate (>99.5%). 2-Isopropoxybromobenzene (97%) was obtained from Alfa Aesar. Triethylorthoformate (98%) and methyl triphenylphosphonium bromide (98%) were obtained from Acros Organics. Dimethylformamide (^{13}C-carbonyl) was purchased from Cambridge Isotopes.

2.1.3 Solvents

Dry, oxygen-free benzene, toluene, hexanes, dichloromethane, tetrahydrofuran and diethyl ether (HPLC grade, Fisher Scientifics) were obtained using a Glass Contour or Anhydrous Engineering solvent purification system, and stored over Linde 4 Å molecular sieves in the glovebox. Other solvents were purified and degassed by standard distillation:[7] pyridine from CaH_2, methanol from fresh-cut sodium; pentane from sodium and benzophenone. All solvents were stored over Linde 4 Å molecular sieves in the glovebox under N_2. MeOH was stored over 3 Å molecular sieves in the glovebox under N_2.

2.1.4 Deuterated Solvents

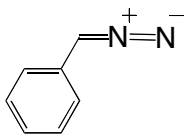
Deuterated solvents were purchased from Cambridge Isotope Laboratories Ltd. or from Aldrich, and used as received for NMR analysis of air-stable species. For oxygen- or moisture-sensitive compounds, ampoules of C_6D_6, toluene-d_8 and THF-d_8 were opened inside the glovebox and stored over Linde 4 Å molecular sieves; $CDCl_3$ was distilled from CaH_2 and stored over Linde 4 Å molecular sieves inside the glovebox. To prevent contamination of the NMR solvents, the glovebox atmosphere was purged to remove solvent vapors prior to opening these storage vessels.

2.1.5 NMR Analysis

^{1}H (300, 400 or 500 MHz), ^{13}C (75 or 125 MHz) and ^{31}P (121 MHz) NMR spectra were recorded on Bruker Avance-300, Avance-400 or Avance-500 spectrometers at 23 ˚C. Chemical shifts for ^{1}H and ^{13}C are reported relative to tetramethylsilane at 0 ppm, ^{31}P NMR spectra to 85% H_3PO_4 at 0 ppm. Spectra of organometallic compounds were measured under anaerobic conditions in NMR tubes equipped with J-Young valves or screw-thread NMR tubes with PTFE/silicon septum caps.

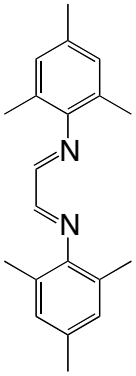
2.2 Synthesis of Ligands

2.2.1 Phenyl diazomethane, 12



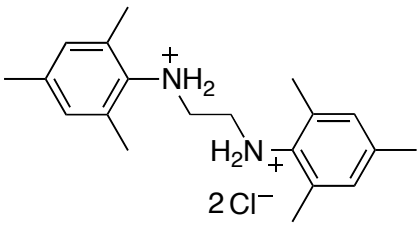
Reaction carried out in air. The isolated product was kept for a maximum of 3 h before use. Synthesis of phenyl diazomethane **12** was performed according to a modified procedure described by Creary.[4] KOH was employed in place of Na as a base for ease of handling. A 500 mL round-bottom flask was loaded with *N*-tosylhydrazone (18.35 g, 70.00 mmol) and triethylene glycol (150 mL). The suspension was warmed to 70 ˚C, and dissolution of **12** afforded a pale yellow solution. Following addition of a solution of KOH (7.51 g, 140 mmol) in water (30 mL), an immediate color change to red was observed. The solution was stirred at 70 ˚C for 10 min and distilled water (60 mL) was then added to give an orange solution with white precipitate. The product was extracted with hexanes (3 × 70 mL) and the combined organic fractions were washed with brine (1 x 100 mL), dried ($MgSO_4$), filtered and concentrated under vacuum to afford phenyl diazomethane **12** as a thick red oil. *Note: exposure to vacuum should be minimized to avoid loss of volatile **12***. Yield: 2.81g (36%). Compound **12** was used as is, without analysis for purity.

2.2.2 Glyoxal-bis-(2,4,6-trimethylphenyl)imine, 13



Reaction carried out in air. Synthesis of imine **13** was performed according to a modified procedure described by Arduengo.[8] The literature route employed heat, which was substituted by use of an acid catalyst at room temperature. A 250 mL round-bottom flask was loaded with 2,4,6-trimethylaniline (20.1 g, 150 mmol) methanol (80 mL), glyoxal (11 mL, 40% solution in water, 70 mmol) and 2 drops of formic acid as a catalyst. A yellow precipitate formed within one minute; stirring was continued for 24 h at room temperature. The yellow product was collected by filtration using a 200 mL Buchner funnel and then washed with methanol (500 mL) until washings were colorless. The product was dried under vacuum to give glyoxal-bis-(2,4,6-trimethylphenyl)imine **13** as a fluffy yellow solid. Yield: 16.9 g (80%). ^{1}H NMR data was consistent with reported values.[6] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.08 (s, 2H, NC*H*C*H*N), 6.89 (s, 4H, Mes C*H*), 2.27 (s, 6H, Mes C$H_{3(p)}$), 2.14 (s, 12H, Mes C$H_{3(o)}$).

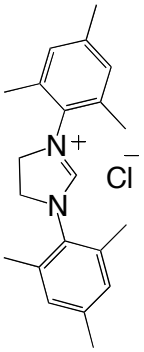
2.2.3 *N,N'*-bis(mesityl)ethylenediamine dihydrochloride, 14



Reaction carried out in air. The known compound **14** was prepared by a variation of the literature route reported by Arduengo.[8] The reported procedure employed $NaBH_4$ as a reducing agent and was heated at reflux, modified to employ $LiAlH_4$ and room temperature. A yellow solution of glyoxal-bis-(2,4,6-trimethylphenyl)imine **13** (3.92 g, 13.4 mmol) in dry THF (42 mL) was cooled to 0 ˚C. $LiAlH_4$ (2.1 g, 5.4 mmol) was then added in ca. 0.5 g portions, every 5 min. The mixture was warmed to room temperature and stirred for 24 h, then cooled to 0 ˚C. MeOH (3 mL),

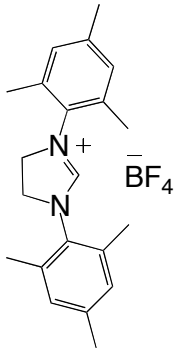
followed by distilled water (3 mL) were added dropwise. The resulting slurry was stirred for 30 min, then filtered and washed with Et_2O (3 x 50 mL). The filtrate was reduced to a minimum volume under vacuum and diluted with Et_2O (50 mL). HCl (4 M solution in dioxane, 8.9 mL, 3.6 mmol) was added dropwise and the mixture was stirred for 2 hours. The product was collected by filtration, washed with dichloromethane (3 x 20 mL) and hexanes (3 x 20 mL) and dried under vacuum for 12 h to yield a white powder. Yield 3.5 g (70 %). ^{1}H NMR data agree with the values reported.[6] ^{1}H NMR (D_2O, 300 MHz): δ 7.04 (s, 4H, Mes C*H*), 3.75 (s, 4H, NCH_2), 2.28 (s, 6H, Mes C$H_{3(p)}$), 2.24 (s, 12H, Mes C$H_{3(o)}$).

2.2.4 *N,N'*-bis(mesityl)imidazolinium chloride ([H_2IMes(H)](Cl)), 4b



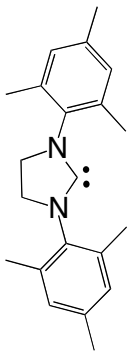
Reaction carried out in air. Synthesis of known compound **4b** was performed according to literature procedure.[8] A suspension of *N,N'*-bis(mesityl)ethylenediamine dihydrochloride **14** (2.12 g, 5.70 mmol) and formic acid (1 drop), in triethylorthoformate (20 mL, 0.25 mol) was heated at 140 ˚C for 4 h. The resulting beige precipitate was collected by filtration, washed with hexanes (3 x 5 mL) and Et_2O (3 x 5 mL), then dried under vacuum for 12 h to yield a white powder. Yield 1.6 g (84%). ^{1}H NMR data agree with the values reported.[6] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.38 (s, 1H, N=C*H*), 6.90 (s, 4H, Mes C*H*), 4.54 (s, 4H, NCH_2CH_2N), 2.36 (s, 12H, Mes C$H_{3(o)}$), 2.24 (s, 6H, Mes C$H_{3(p)}$).

2.2.5 *N,N'*-Bis(mesityl)imidazolinium tetrafluoroborate ([H_2IMes(H)](BF_4)), 4a



Reaction carried out in air. H_2IMes(H)](Cl) **4b** (4.9 g, 14 mmol) was suspended in distilled H_2O (320 mL) and stirred for 40 min. Residual salts were filtered off and HBF_4 (2.5 mL of a 48% wt solution in H_2O, 19 mmol) was then added to the filtrate, resulting in the formation of a white precipitate. The reaction was stirred for a further 15 min, after which the solid was filtered off and washed with hexanes (3 x 20 mL) and diethyl ether (3 x 20 mL). [H_2IMes(H)](BF_4) was dried under vacuum for 12 h to yield a bright fluffy white powder. Yield 4.7 g (83%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.90 (s, 1H, N=C*H*), 6.99 (s, 4H, Mes C*H*), 4.54 (s, 4H, NCH_2CH_2N), 2.36 (s, 12H, Mes C$H_{3(o)}$), 2.31 (s, 6H, Mes C$H_{3(p)}$).

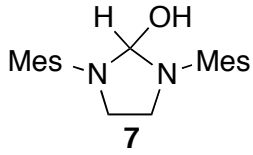
2.2.6 1,3-Bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene (H_2IMes), 3



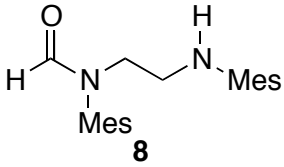
The known compound **x** was prepared by a variation of the literature route reported by Arduengo. The reported route used [H_2IMes(H)](Cl) **4b** as a precursor salt and KH as a base, which were substituted for [H_2IMes(H)](BF_4) **4a** and NaH. A 50 mL round-bottom flask was loaded with [H_2IMes(H)](BF_4) **4a** (0.35g, 0.88 mmol), tetrahydrofuran (12 mL) and sodium hydride (56 mg, 2.3 mmol). The solution was stirred at room temperature for 24 h, and the solvent then removed *in vacuo*. The yellow residue was dissolved in benzene (10 mL), filtered through Celite and dried under vacuum for 6 h to give H_2IMes **3** as a white solid. Residual impurities could be removed via recrystallization from hexanes at -35 °C. Yield: 0.194 g (72%). ^{1}H NMR data agree with the values reported.[6] ^{1}H NMR (C_6D_6, 300 MHz): δ 6.84 (s,

4H, Mes C*H*), 3.27 (s, 4H, NCH_2CH_2N), 2.31 (s, 12H, Mes $CH_{3(o)}$), 2.16 (s, 6H, Mes $CH_{3(p)}$).

2.2.7 Hydrolysis of H_2IMes: formation of H_2IMes(H)(OH) (1,3-dimesitylimidazolidin-2-ol, 7 and HC(O)N(Mes)CH_2CH_2NHMes (*N,N′*-dimesityl-*N*-formylethylenediamine), 8



7

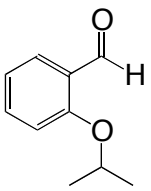


8

In the glovebox, a J-Young NMR tube was loaded with H_2IMes **3** (21 mg, 70 μmol), TMB (11 mg, 6.5 μmol) and C_6D_6 (0.8 mL), and a ^{1}H NMR spectrum was acquired to establish initial integration ratios. The sample was returned to the glovebox and treated with degassed H_2O (1.3 μL, 70 μmol). Spectra were acquired every 30 min for 12 h. No signals for H_2IMes **3** remained at 5 min, at which point the dominant species present was H_2IMes(H)(OH) **7**. After 6 h, only formamide **8** was present, as a mixture of *E* and *Z* isomers. ^{1}H NMR (C_6D_6, 300 MHz) data for H_2IMes(H)(OH) **7**: δ 6.83 (s, 4H, Mes C*H*), 5.73 (s, 1H, C*H*(OH)), 3.56 (m, 2H, CH_2), 3.11 (m, 2H, CH_2), 2.38 (s, 12H, Mes C$H_{3(o)}$), 2.04 (s, 6H, Mes C$H_{3(p)}$), OH unassigned, owing to exchange with **8**. ^{13}C NMR characterization and microanalysis were impeded by transformation into **8** over the time-scale of analysis. ^{1}H NMR values are in excellent agreement with data reported for the methoxy analogue.[9] ^{1}H NMR data for HC(O)N(Mes)CH_2CH_2NHMes **8**. *E* isomer (major, 90%): ^{1}H NMR (500 MHz, C_6D_6): δ 7.94 (s, 1H, C*H*O), 6.76 (s, 2H, Mes C*H*), 6.59 (s, 2H, Mes C*H*), 3.62 (t, $^3J_{HH}$ = 6.7 Hz, 2H, CH_2), 3.57 (s, 1H, CH_2N*H*), 3.07 (t, $^3J_{HH}$ = 6.7 Hz, 2H, CH_2), 2.21 (s, 6H, CH_3), 2.16 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 1.93 (s, 6H, CH_3). *Z* isomer (minor, 10%): ^{1}H NMR (500 MHz, C_6D_6): δ 8.07 (s, 1H, C*H*O), 6.73 (s, 2H, Mes C*H*), 6.71 (s, 2H, Mes C*H*), 3.14 (m, 2H, CH_2; overlaps with corresponding signal for *E*-isomer), 2.86 (t, $^3J_{HH}$ = 7.0 Hz, 2H, CH_2), 2.15 (s, 3H, CH_3),

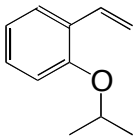
2.07 (s, 3H, C*H*$_3$), 2.05 (s, 6H, C*H*$_3$), 2.00 (s, 3H, C*H*$_3$); N*H* not observed. NMR data for **8** in $CDCl_3$ agree with values reported.[10]

2.2.8 2-Isopropoxybenzaldehyde, 15



Synthesis of 2-isopropoxybenzaldehyde **15** was performed according to a literature route reported by Marciniec. In the literature route, DMF (^{13}C-carbonyl) was used, which is substituted for anhydrous DMF in this procedure. [11] In the glovebox, a 100 mL Schlenk tube was loaded with *n*-butyllithium (2.5 M in hexanes, 1.36 mL, 3.4 mmol) in diethyl ether (12 mL). The resulting solution was cooled to 0 ˚C, and 2-isopropoxybromobenzene (0.55 mL, 3.4 mmol) was added dropwise. The resulting white precipitate suspended in a yellow solution was brought to room temperature and stirred for 2 hours. The reaction was then cooled to -78 ˚C and dry dimethylformamide (0.27 mL, 3.4 mmol) added dropwise via syringe. The suspension was warmed to room temperature and quenched with saturated NH_4Cl (15 mL). The product was extracted with diethyl ether (3 x 15 mL) and the combined organic layers were washed with brine (1 x 30 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield isopropoxybenzaldehyde **15** as a light yellow liquid. The crude product was used *as is* in the preparation of **10**. Yield: 0.89 g (>99%). Crude ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.49 (s, 1H, C*H*O), 7.82 (dd, J_{HH} = 7.9 Hz, J_{HH} = 1.8 Hz, 1H, ArC*H*), 7.52 (dt, J_{HH} = 7.7 Hz, J_{HH} = 1.5 Hz, 1H, ArC*H*), 6.98 (m, 2H, ArC*H*), 4.68 (septet, J_{HH} = 6.1 Hz , 1H, OC*H*$(CH_3)_2$), 1.40 (d, J_{HH} = 6.1 Hz, 6H, OCH$(CH_3)_2$). This same procedure was used in the preparation of ^{13}C-labelled analogue **15***, whereby ^{13}C-labelled DMF was employed. The labelled benzaldehyde **15*** was used as is, without purification.

2.2.9 2-Isopropoxystyrene, 10

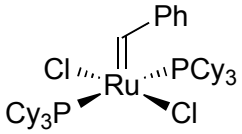


Synthesis of 2-isopropoxystyrene **10** was performed according to a modified literature route reported by Marciniec.[11] In the literature route, 1.2 equivalents of Wittig reagent were used, which was substituted for 2 equivalents in this procedure. In the glovebox, methyl triphenylphosphonium bromide (1.47 g, 4.10 mmol) was loaded into a 100 mL Schlenk tube and suspended in tetrahydrofuran (20 mL). The white suspension was cooled to 0 ˚C and *n*-butyllithium (2.5 M in hexanes; 1.7 mL, 4.1 mmol) was added slowly via syringe. The resultant cloudy red solution was stirred at 0 ˚C for 30 minutes, then brought to room temperature and stirred for an additional 1.5 hours. Crude 2-isopropoxybenzaldehyde **15** (3.4 mmol) was added dropwise to the clear red solution and the resulting orange solution then stirred under Ar for 18 hrs. The reaction was quenched with distilled H_2O (4 mL) yielding a yellow solution, and the THF was removed in vacuo. The product was extracted with diethyl ether (4 x 15 mL) and the combined organic layers were washed with brine (1 x 30 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a deep yellow oil. The crude product was purified by flash column chromatography (SiO_2; 1:49; ethyl acetate: pentane) to yield 2-isopropoxystyrene **10** as a pale yellow liquid. Yield: 390 mg (70%). ^{1}H NMR data is consistent with literature values. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.48 (dd, J_{HH} = 7.6 Hz, J_{HH} = 1.5 Hz, 1H, ArC*H*), 7.20 (t, J_{HH} = 7.8 Hz, 1H, ArC*H*), 7.07 (dd, J_{HH} = 17.8 Hz, J_{HH} = 1.9 Hz, 1H, C*H*=CH_2), 6.91 (m, 2H, ArC*H*), 5.73 (dd, J_{HH} = 17.9 Hz, J_{HH} = 1.5 Hz, 1H, *trans*-CH_2=CH), 5.23 (dd, J_{HH} = 11.1 Hz, J_{HH} = 1.5 Hz, 1H, *cis*-CH_2=CH), 4.54 (septet, J_{HH} = 6 Hz, 1H, OC*H*(CH_3)$_2$), 1.36 (d, J_{HH} = 6.0 Hz, 6H, OCH(CH_3)$_2$). This procedure was also used in the preparation of ^{13}C-labelled analogue **10*,** whereby **15*** was used in place of **15**. Yield: 340 mg (61%). ^{1}H NMR data consistent with literature values.[11] ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.49 (m, 1H, Ar), 7.38-

7.29 (ddd, J_{HH}= 17.8 Hz, J_{HH} = 11.1 Hz , J_{CH} = 156.6 Hz, 1H, ^{13}CH=CH_2), 5.74 (ddd, J_{HH} = 17.9 Hz, J_{HH} = 16.6 Hz, $^{2}J_{CH}$ = 3.4 Hz, 1H, *trans*-CH_2=CH), 5.24 (dd, J_{HH} = 11.3 Hz, J_{HH} = 1.5 Hz, 1H, *cis*-CH_2=CH), 4.13 (septet, J_{HH} = 6.1 Hz, 1H, OCH(CH_3)$_2$), 1.36 (dd, J_{HH} = 6.0 Hz, J_{HH} = 0.5 Hz, 1H, OCH(CH_3)$_2$).

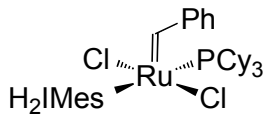
2.3 Synthesis of Ru Complexes

2.3.1 $RuCl_2(CH=Ph)(PCy_3)_2$, Ru-1a



In the glovebox, a 3-necked 500 mL round-bottom flask was loaded with $RuCl_2(PPh_3)_3$ **Ru-8** (7.06 g, 7.40 mmol) and CH_2Cl_2 (200 mL). The brown solution was removed to a Schlenk manifold and cooled to –78 ˚C. A solution of **13** (1.79 g, 15.00 mmol) in hexanes (20 mL) was slowly added by cannula creating a color change to green-brown. The solution was stirred at –78 ˚C for an additional 20 min and then warmed to 0 ˚C. A colorless solution of tricyclohexyl phosphine (4.71 g, 17.00 mmol) in toluene (50 mL) was added by cannula and the reaction was stirred for a further 30 minutes. The solution was then warmed to room temperature and stirring continued for 2 h, affording a gradual color change to dark red-purple. The volatiles were removed under vacuum and the resulting dark red-purple residue was suspended in methanol (300 mL) in the glovebox. The purple solid was filtered, washed with cold acetone (4 x 20 mL) and dried under reduced pressure. Yield: 4.3 g (71%). Spectroscopic values match those reported.[12] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 19.99 (s, 1H, CHPh), 8.44 (d, 2H, J_{HH} = 7.5 Hz ArC$H_{(o)}$), 7.54 (m, 1H, ArC$H_{(p)}$), 7.33 (m, 1H, ArC$H_{(m)}$), (m, 2.62 – 1.20, 66H, PCy_3). $^{31}P\{^{1}H\}$ NMR (C_6D_6, 300 MHz): δ 36.9 (s, PCy$_3$).

2.3.2 $RuCl_2(H_2IMes)(PCy_3)(=CHPh)$, Ru-1c



a) A 100 mL round-bottom flask was loaded with **Ru-1a** (710 mg, 860 μmol) and benzene (15 mL). A solution of H_2IMes **3** (284 mg, 930 μmol) in benzene (5 mL) was then added to the purple solution, affording a near immediate color change to red. The solution was stirred at room temperature for 2.5 h, at which point the volatiles were removed under reduced pressure. The foamy red residue was then washed with hexanes (2 x 4 mL) at –78 ˚C to afford **Ru-1c** as a red-pink solid. Yield: 642 mg (88%). Spectroscopic values match those reported.[13] ^{1}H NMR (C_6D_6, 300 MHz): δ 19.64 (s, 1H, Ru=C*H*Ph), 7.14-6.94 (m, 9H, Ph, Mes C*H*), 3.30-3.18 (m, 4H, CH_2CH_2), 2.85-1.12 (m, 51H, Mes CH_3, PCy_3). $^{31}P\{^1H\}$ NMR (C_6D_6, 300 MHz): δ 30.3 ppm (s, PCy_3).

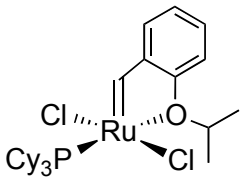
b) In the glovebox, a 20 mL scintillation vial was loaded with **Ru-1a** (243 mg, 300 μmol) and THF (3 mL). A solution of H_2IMes **3** (95 mg, 0.31 mmol) in THF (1.5 mL) was then added, affording a near immediate color change to red. The solution was stirred at room temperature for 30 minutes, and Amberlyst-15 resin (251 mg, 118 μmol) was added. Stirring was continued for an additional hour, and the resin then filtered off and rinsed with THF (5 x 1 mL). The combined filtrate was stripped of solvent to afford **Ru-1c** as a red-pink solid. Yield: 248 mg (99%) Spectroscopic values match those reported.[13]

c) Attempted Synthesis from H_2IMes(H)(HCO_3) **4c**:

In the glovebox, a 50 mL Schlenk flask was loaded with **Ru-1a** (79.8 mg, 97.0 μmol), TMB (5.0 mg, 30 μmol) and dry THF (4.5 mL). Following acquisition of a time zero spectrum, [H_2IMes(H)](HCO_3) **4c** (38.0 mg, 103 μmol) was added to the purple solution, and the resulting suspension was heated at 60 °C for 5 h under a flow of Ar, undergoing a color

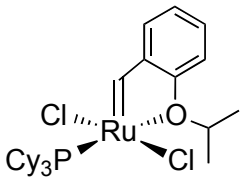
change from purple to brown. The solvent was removed in vacuo and ^{1}H NMR analysis of the brown solid showed a product : starting material ratio of 58% : 9%, with 33% decomposition as gauged by integration against a TMB internal standard.

2.3.3 Attempted Synthesis of $RuCl_2(PCy_3)(=CH\text{-}2\text{-}O^iPrC_6H_4)$ Ru-4a in the absence of phosphine scavenger.



In the glovebox, a J-Young NMR tube was loaded with **Ru-1a** (16 mg, 20 μmol), TMB (2.0 mg, 10 μmol) and $CDCl_3$ (0.7 mL), and a ^{1}H NMR spectrum was acquired to establish initial integration ratios. The sample was returned to the glovebox and treated with 2-isopropoxystyrene **10** (7.0 mg, 40 μmol). The reaction was heated in an oil bath for 6 hours at 60 ˚C, and ^{1}H NMR spectra taken every 60 minutes. ^{1}H NMR analysis of the reaction solution after 6 hours showed a **Ru-1c**: **Ru-7a**: **Ru-1a** ratio of 67% : 9% : 8%, with 16% decomposition as gauged by integration against a TMB internal standard.

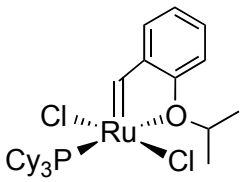
2.3.4 Synthesis of $RuCl_2(PCy_3)(=CH\text{-}2\text{-}O^iPrC_6H_4)$ Ru-4a using Amberlyst® 15.



In the glovebox, Amberlyst-15 resin (215 mg, 1.00 mmol) was added to a stirred solution of **Ru-1a** (208 mg, 250 μmol) and 2-isopropoxystyrene **10** (45 mg, 0.27 mmol) in THF (5 mL). The sealed vessel was removed to a Schlenk manifold and the reaction was heated at 50 °C with stirring for 2 h, over which time the solution turned from purple to dark brown. The reaction was cooled to room temperature, the Schlenk tube returned to the glovebox, and the resin then filtered off and rinsed with THF (5 × 1 mL). The combined filtrate was stripped of solvent and the residue was washed with cold pentane (3 × 5 mL, –35 °C) to remove the styrene co-

product. Yield of brown **Ru-4a**: 131 mg (87%). ^{1}H NMR (C_6D_6, 500 MHz): δ 17.37 (d, $^{3}J_{PH}$ = 4.7 Hz, 1H, =C*H*Ph), 7.39 (dd, J_{HH} = 7.4 Hz, J_{CH} = 1.4 Hz, 1H, ArC*H*), 7.21 (t, J_{HH} = 7.6 Hz, J_{CH} = 1.4 Hz, 1H ArC*H*), 6.75 (t, J_{HH} = 7.6 Hz, 1H, ArC*H*), 6.65 (d, J_{HH} = 8.0 Hz, 1H, ArC*H*), 4.73 (septet, J_{HH} = 6.3 Hz, J_{CH} = 1.3 Hz, 1H, C*H*(CH_3)$_2$), 2.43 (m, 3H, P*Cy*$_3$), 2.22 (m, 6H, CH(C*H*$_3$)$_2$), 1.96 (m, 6H, P*Cy*$_3$), 1.75 (m, 12H, P*Cy*$_3$) 1.57 (s, 3H, P*Cy*$_3$). ^{31}P{^{1}H} NMR (C_6D_6, 500 MHz): δ 60.4 (s, *P*Cy$_3$). This procedure was also used in the preparation of ^{13}C-labelled **Ru-4a***, whereby labelled stryenyl ether **10*** was used in replacement of **10.** Yield: 140 mg (86%). ^{1}H NMR is identical to unlabelled **Ru-4a**, except the alkylidene proton peak, which is split by ^{13}C. ^{1}H NMR (500 MHz, C_6D_6): δ 17.64-17.10 (dd, J_{CH} = 162.7 Hz, $^{3}J_{PH}$ = 162.7 Hz, 1H, =C*H*Ph).

2.3.5 Attempted synthesis of $RuCl_2(PCy_3)(=CH\text{-}2\text{-}O^{i}PrC_6H_4)$ Ru-4a from Ru-6a



In a glovebox, a 4 mL scintillation vial was loaded with **Ru-6a** (11 mg, 15 μmol), TMB (79 μL 0.105 M) and dry THF (666 μL), and a ^{1}H NMR spectrum was acquired by spiking with C_6D_6 to establish initial integration ratios. The sample was returned to the glovebox and treated with 2-isopropoxystyrene **10** (155 μL, 16.5 μmol) and Amberlyst-15 (13 mg, 0.061 mmol). Spectra were taken at 15 and 60 min, showing 18% NMR yield of **Ru-4a** and 36% decomposition of methylidene species **Ru-6a** after 60 min, as gauged against TMB internal standard. In order to expedite conversion to **Ru-4a**, the reaction was capped, taken outside the glovebox, heated at 40 °C in an aluminum heating tray, and spectra taken after 15 and 35 minutes. After 35 minutes at 40 °C, only the alkylidene signal for **Ru-4a** was visible. ^{1}H NMR analysis of the final reaction solution showed an in situ yield of 27% for **Ru-4a**, with 73% decomposition as gauged by integration against a TMB internal standard.

2.4 NMR/exchange experiments

2.4.1 Thermolysis of H_2IMes

Solid white H_2IMes **3** (10 mg, 33 μmol) and TMB (3.7 mg, 22 μmol) were dissolved in C_7D_8 (1 mL) in a J-Young NMR tube, and a ^{1}H NMR spectrum was acquired to establish initial integration ratios. The sample was then heated in the NMR probe at 80 ˚C, and analyzed periodically over 8 h. A similar experiment carried out in THF-d_8 at 60 ˚C showed no decomposition over a period of 2 weeks.

2.4.2 Ligand exchange reaction between Ru-4a* and styrenyl ether 10 at 40 °C

In a glovebox, a J-Young NMR tube was loaded with **Ru-4a*** (15 mg, 25 μmol), TMB (1.0 mg, 10 μmol) and THF-d_8 (0.5 mL), and a ^{1}H NMR spectrum was acquired to establish initial integration ratios. The sample was returned to the glovebox and treated with a solution of 2-isopropoxystyrene **10** (7.0 mg, 40 μmol) in THF-d_8 (0.1 mL). The sealed tube was removed from the glovebox and heated at 40 °C in the NMR probe, and spectra recorded every 30 min for 14 h. The sealed tube was transferred to an oil bath at 40 °C, and ^{1}H NMR spectra recorded daily until a 43:57 **Ru-4a*: Ru-4a** equilibrium was reached after 141 h (4 days). No sign of decomposition was apparent, as gauged against TMB internal standard. An identical procedure was carried out for the addition of labelled styrenyl ether **10*** to a solution of unlabelled **Ru-4a**, which reached a 46:54 equilibrium ratio after 90 h at 40 °C.

2.4.3 Ligand exchange reaction between Ru-4a* and styrenyl ether 10 at 23 °C

In a glovebox, a J-Young NMR tube was loaded with **Ru-4a*** (13 mg, 20 μmol), TMB (1.0

mg, 10 μmol) and C_6D_6 (0.7 mL), and a ^{1}H NMR spectrum was acquired to establish initial integration ratios. The sample was returned to the glovebox and treated with a solution of 2-isopropoxystyrene **10** (4.0 mg, 20 μmol) in C_6D_6 (0.1 mL). The reaction was monitored daily by ^{1}H NMR, reaching a 47:53 equilibrium value after 19 days at 23°C. No sign of decomposition was apparent, as gauged against TMB internal standard.

2.5 References

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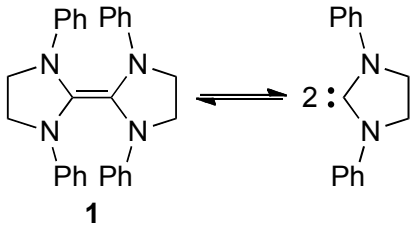
3 A Clean, High-Yield Route to the Second-generation Grubbs Catalyst

3.1 An Introduction to N-Heterocyclic Carbenes

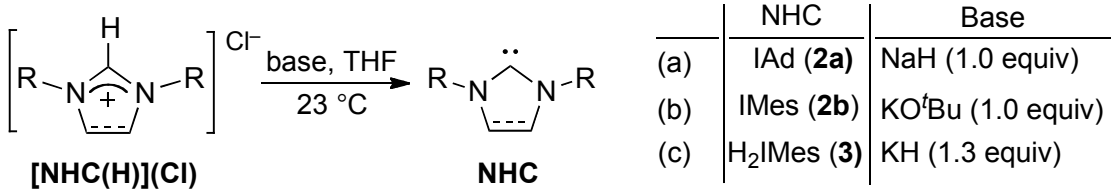
The term carbene, used to describe a class of compounds possessing two lone electrons and no formal charge at carbon, was first coined by William Doering during a nocturnal taxi ride in 1956.[1] The *N*-heterocyclic carbene (NHC) ligand class, which now plays an important role in organometallic chemistry and catalysis,[2-8] was discovered shortly afterwards, when Wanzlick reported observation of a diphenylimidazolyl carbene on thermolysis of dimeric **1** at 170 °C (Scheme 3.1).[9]



Scheme 3.1 Thermolysis of diphenylimidazolyl carbene **1**, as reported by Wanzlick.

Due to the difficulties associated with isolation of free carbene species, these developments remained of interest chiefly to specialists until 1991,[10] when Arduengo reported IAd **2a** – the first example of an *isolable* free carbene – and, in 1992, IMes **2b** (Scheme 3.2).[11] The saturated carbene H_2IMes **3**, prepared using a slightly different synthetic methodology (vide infra), was first reported in 1995.[12] These NHC ligands rapidly attracted interest for their potential as ligands in transition-metal chemistry. Like phosphine ligands, they are good σ-donors and weak π-acceptors. However, NHCs display stronger donor capacities than even alkylphosphine ligands.[13] As such, they have received much attention as alternatives to phosphines in catalytic reactions that benefit from an electron-rich metal. A

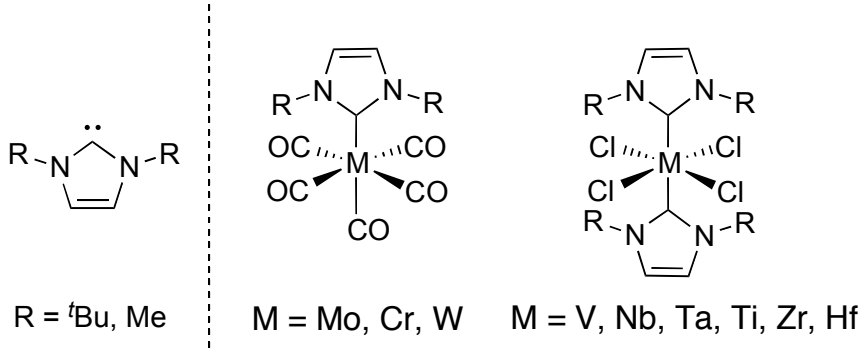
very important example of such a reaction is Ru-catalyzed olefin metathesis, as discussed below.



	NHC	Base
(a)	IAd (**2a**)	NaH (1.0 equiv)
(b)	IMes (**2b**)	KO^{t}Bu (1.0 equiv)
(c)	H_2IMes (**3**)	KH (1.3 equiv)

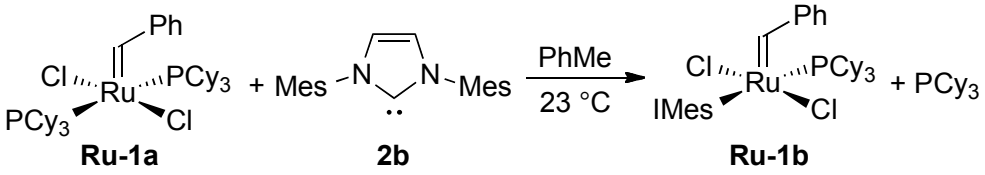
Scheme 3.2 Synthesis of (a) Iad (**2a**). (b) IMes (**2b**). (c) H_2IMes (**3**). (IAd = *N,N'*-diadamantyl imidazol-2-ylidene; IMes = 1,3-bis(mesityl)imidazol-2-ylidene; H_2IMes = 1,3-bis(mesityl)imidazolin-2-ylidene).

The Arduengo route to IMes and other aromatic NHCs was rapidly adopted by practitioners of catalysis. In particular, Herrmann made use of this high-yield synthetic methodology to prepare a host of NHC complexes (containing chiefly imidazol-2-ylidene ligands) of the group 5-6 and groups 8-10 metals (Scheme 3.3).[13-20] Among these were bis-NHC complexes that can be regarded as conceptual precursors to the powerful "second-generation" Grubbs metathesis catalyst, $RuCl_2(IMes)(PCy_3)(=CHPh)$ **Ru-1b**. The synthesis of **Ru-1b** (Scheme 3.4), reported simultaneously by the groups of Nolan[21] and Grubbs,[22] was a landmark in catalysis, and the dramatically higher reactivity of these NHC complexes relative to the parent Grubbs catalyst **Ru-1a** has transformed organic synthesis.



Scheme 3.3 Select Herrmann NHCs and transition metal complexes. [20]

The Grubbs and Nolan syntheses of **Ru-1b** are essentially identical, proceeding by ligand exchange of **Ru-1a** with free IMes at room temperature, and affording the product in up to 85% yield (Scheme 3.4).[22] A recent *Nature Protocols* publication reproduces Nolan's original synthetic routes to free IMes and **Ru-1b**.[23]

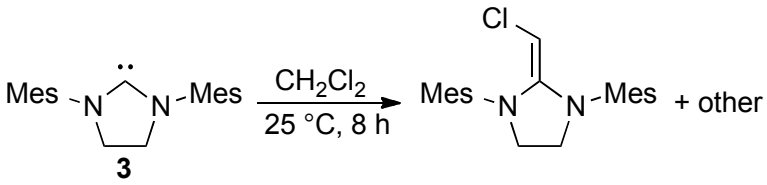


Scheme 3.4 Free-carbene route to $RuCl_2(IMes)(PCy_3)(=CHPh)$ **Ru-1b** reported by Grubbs and Nolan.

The corresponding free-carbene route to H_2IMes analogue **Ru-1c** is absent from the literature. Complex **Ru-1c** is normally synthesized by thermal deprotection of H_2IMes precursors in situ (see next section), reflecting the perception that free H_2IMes – unlike free IMes – is highly unstable.[24] Greater stability indeed results from the aromaticity of the imidazolium ring, as noted above. For example, Arduengo noted that H_2IMes rapidly decomposes in moist air,[12] a sensitivity attributed to hydrolysis. Consistent with this, Denk

observed hydrolysis of H_2I^tBu within min in THF at room temperature, whereas its aromatic counterpart I^tBu was stable for months.[25]

Given these trends, we were intrigued by other data from Arduengo suggesting that IMes is not invariably more stable than H_2IMes. Thus, IMes was reported to react rapidly with CH_2Cl_2, where H_2IMes was apparently stable to small amounts of CH_2Cl_2 (ca. 40 equiv in hexanes) at room temperature over 7 days.[26] (Heating at 70 °C for 15 h, however, gave a mixture of olefinic H_2IMes=CHCl and the imidazolinium chloride [H_2IMes(H)](Cl) (Scheme 3.5).[26,27] As methylene chloride is a convenient solvent in which to carry out the ruthenium chemistry described below, we re-examined the stability of H_2IMes in 2:1 CH_2Cl_2:C_6D_6 at ambient temperatures (Scheme 3.5). No H_2IMes remained after 8 h. Two products were observed, in ca. 1:1 ratio, consisting of the chlorinated olefin reported by Arduengo, and an unidentified aldehyde. In subsequent synthetic work with H_2IMes, we therefore avoided use of methylene chloride.



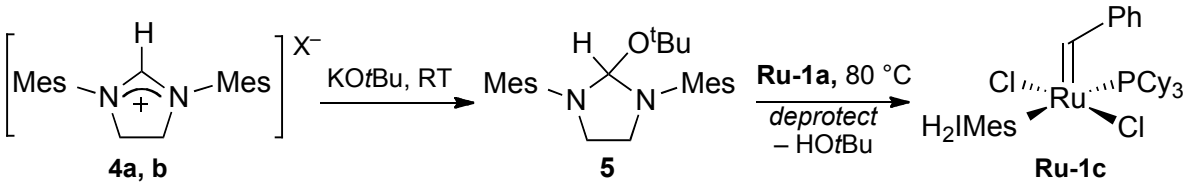
Scheme 3.5 Decomposition of H_2IMes **3** in neat CH_2Cl_2.

3.1.1 Analysis of Literature Routes to $RuCl_2(H_2IMes)(PCy_3)(=CHPh)$, Ru-1c

Deprotonation of imidazolinium salts, [H_2IMes(H)](X).

In the original synthesis of **Ru-1c**, Scholl and Grubbs treated [H_2IMes(H)](BF_4) **4a** with KO^tBu in THF at room temperature, generating alcohol adduct **5**, from which free H_2IMes was liberated upon heating (Scheme 3.6; it should be noted that under the same

conditions, the imidazolium salt liberates free IMes **2b**, rather than forming an adduct).[28] Compound **5** was not isolated: instead, the thermolysis step was carried out in the presence of the Grubbs catalyst **Ru-1a**, after diluting with benzene to improve the solubility of the ruthenium species. Complex **Ru-1a** was used as the limiting reagent (0.71 equiv vs. the starting salts) to ensure its complete conversion. The desired ligand-exchange reaction was complete after 30 min at 80 ˚C, after which **Ru-1c** was isolated in 75% yield by removing the volatiles and washing with MeOH. Subsequent reports by Trnka and Grubbs,[29] and by Furstner,[30] note that the product is impure, however, and indeed we observe large amounts of benzene-insoluble salts even after washing with MeOH (Figure 3.1).



Scheme 3.6 Synthesis of **Ru-1c** via in situ deprotection of imidazolinium salts. X = BF_4 (**4a**); Cl (**4b**).[28]

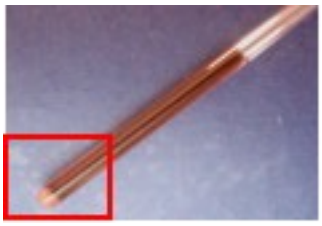
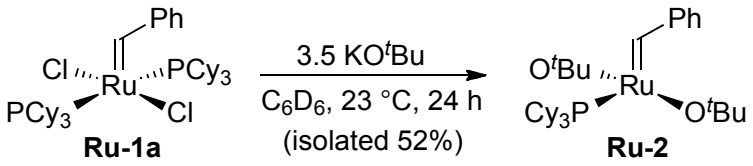


Figure 3.1 Benzene-insoluble salts present following the published route to **Ru-1c.**[28]

A subsequent workup procedure was designed to remove these salts. Thus, the reaction mixture was stripped to dryness, taken up in benzene, and filtered through Celite, after which **Ru-1c** was precipitated with MeOH and washed with MeOH and pentane.[29] However, at just 45%, the yield was very low and the product was contaminated by small

amounts of a hydridocarbonyl complex. Formation of the latter was attributed to reaction of **Ru-1c** with methanol during washing. Methoxide formed in situ may be a more likely culprit. Beach, Fogg and co-workers recently reported that **Ru-1a** - **Ru-1c** are rapidly decomposed by methoxide at room temperature,[31] whereas reaction of these species with MeOH takes place over 48 h, even in solution at higher temperatures.[29,31-34]

Use of **Ru-1a** as the limiting reagent results in a further byproduct, $Ru(O^tBu)_2(PCy_3)(=CHPh)$ **Ru-2**, formed by a competing reaction with KO^tBu (Scheme 3.7; ^1H 15.5 ppm, d, J_{HP} = 4.4 Hz; ^{31}P at 83.5 ppm).[29] Trnka and Grubbs noted that less of this byproduct was formed on using $[H_2IMes(H)](Cl)$ **4b**, relative to $[H_2IMes(H)](BF_4)$ **4a**. They were able to obtain analytically clean **Ru-1c** in 75% yield by treating $[H_2IMes(H)]Cl$ with excess KO^tBu in hexanes to liberate the carbene, then adding **Ru-1a**, and heating at 60 °C for 24 h. While **Ru-1a** was again the limiting reagent, the insolubility of all reagents other than H_2IMes in hexanes was apparently successful in limiting side-reactions. Workup involved extraction of salts from the suspension of **Ru-1c** with isopropanol-water, then hexanes, and filtration.[29] Use of potassium *tert*-amylate in hexanes resulted in similar yields.[35]

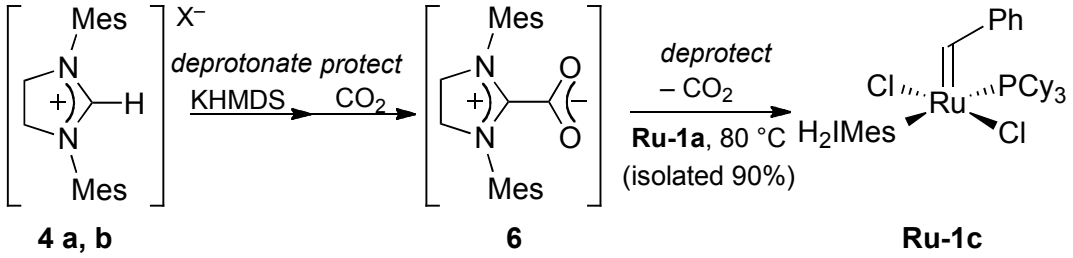


Scheme 3.7 Reaction of **Ru-1a** with KO^tBu.[36]

3.1.2 Other adducts.

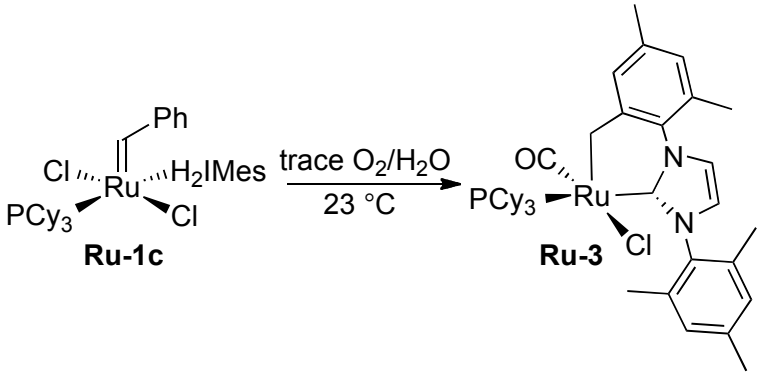
As well as the $H_2IMes(H)(O^tBu)$ adduct **5** used above, adducts of C_6F_5, CCl_3,[37] and CO_2[38] have been used to stabilize H_2IMes **3** prior to reaction with **Ru-1a**. In each case, the

free carbene is liberated by thermolysis of excess adduct in the presence of **Ru-1a** at 60-80 °C. Most interesting of these is the CO_2 adduct **6**. This compound, developed by Crabtree,[39] can be viewed as a zwitterionic carboxylate, which liberates only innocuous CO_2 on heating (Scheme 3.8). Delaude and co-workers have used it to prepare **Ru-1c** under the usual thermolytic conditions, following which column chromatography to remove the excess reagent and the PCy_3 byproduct afforded **Ru-1c** in 90% yield.



Scheme 3.8 Generation and deprotection of zwitterionic CO_2 adduct **6** to form **Ru-1c**.[38]

A common inconvenience in these reactions is the requirement for heating on a Schlenk line. Rigorous exclusion of air under these circumstances is important. The carbene itself reacts with trace water even at ambient temperatures (see section 3.2), while the Grubbs group has reported that contamination by air during Schlenk-line synthesis of **Ru-1c** can cause decomposition. Specifically, formation of **Ru-3** was described (Scheme 3.9), in which the benzylidene ligand is lost and a mesityl methyl group is activated.[29]



Scheme 3.9 Reported decomposition of **Ru-1c** on attempted synthesis in the presence of trace air.[29]

The foregoing demonstrates that in situ deprotection of H_2IMes, though widely accepted, has undesirable consequences in terms of stoichiometric control, and hence product yields and purity. This chapter asks whether such protocols are truly necessary. The ease with which H_2IMes can be handled is examined in studies of the relative susceptibility of free H_2IMes toward heat, oxygen and water, and a convenient, free-carbene route to the benchmark metathesis catalyst **Ru-1c** is developed.

3.2 Results & Discussion

3.2.1 Synthesis of free H_2IMes

Arduengo reported a yield of 72% H_2IMes **3** within 3 h at *room temperature* on treating [H_2IMes(H)](Cl) **4b** with KH. Subsequent routes have made minor modifications (Table 3.1), but without an increase in yield.[12,40-42] Two of these routes involve a "catalytic" amount of KO^{t}Bu or NaO^{t}Bu, as well as the hydride reagent.[40,42] The need for these adjuncts is not commented on, but its use may originate in an earlier report describing the synthesis of the smaller IMe ligand (IMe = 1,3-dimethylimidazol-2-ylidene), which likewise made use of

NaH and 5 mol% KO^{t}Bu.[11.] Nolan found that using NaH instead of KH required heating for 20 h at 60 ˚C, owing to the lower reactivity of the hydride relative to KH.

A disputed point in the synthesis of H_2IMes is the desirability of [H_2IMes(H)][BF_4] versus [H_2IMes(H)](Cl) as a precursor. Use of [H_2IMes(H)](BF_4) requires an additional synthetic step, and has been implicated by Grubbs in increased formation of byproducts such as Ru(O^{t}Bu)$_2$(PCy_3)(=CHPh) **Ru-2** (Scheme 3.7).[29] Likewise, Grela and co-workers have reported that even trace impurities in the tetrafluoroborate salt resulted in drastically decreased yields of **Ru-1a**.[43] In a recent *Nature Protocols* paper, however, Nolan remarks that deprotonation of HBF_4 salts is "more general and efficient," and gives cleaner products.[23] We found that clean [H_2IMes(H)](BF_4) was easily obtained by adding HBF_4 (40 wt% in H_2O) to an aqueous solution of [H_2IMes(H)](Cl). Extraction into CH_2Cl_2, as described in the Nolan protocol, was unnecessary. The tetrafluoroborate salt was obtained in 83% yield by filtering off and washing with hexanes and ether. No impurities were evident by ^{1}H NMR analysis ($CDCl_3$).

Table 3.1 Existing routes to H_2IMes**.**

Precursor	Base	Conditions[a]	Yield (%)	Ref.
[H_2IMes(H)](Cl)				
	KH (1.3 equiv)	23 °C, 3 h	72	[12]
	NaH (1.5 equiv) NaO^{t}Bu (0.01 equiv)	60 °C, 20 h	66	[42]
[H_2IMes(H)](BF_4)				
	KH (1 equiv) + KO^{t}Bu (0.2 equiv)	23 °C, 4 h	60	[40]
	K[N($SiMe_3$)$_2$] (1.0 equiv)	23 °C, 0.5 h	46	[41]
	NaH (2.5 equiv)	23 °C, 24 h	67%	This work
	NaH (2.0 equiv)	23 ˚C, 12 h	72%	BVL

[a] All reactions are carried out in THF.

In our hands, synthesis of free H_2IMes by the Arduengo procedure, in which the chloride salt was treated with a dispersion of KH in mineral oil, proceeded in ca. 65% yield (1 gram scale). On a 4.0 g scale, however, removal of residual mineral oil from the product required multiple recrystallizations. Much more convenient was use of solid NaH. We found that reaction of [H_2IMes(H)](BF_4) with NaH (2.5 equiv) in THF was slower, but considerably more convenient. Reaction was complete at room temperature within 24 h. H_2IMes was obtained as a white crystalline powder in 72% yield after filtering through Celite and recrystallizing from hexanes. Excess hydride (2.5 equiv) was used in this reaction, for convenience. In a subsequent synthesis on 3.5 g scale, Bianca van Lierop of the Fogg research group used 2 equiv NaH. Reaction was complete in 12 h, and clean H_2IMes was obtained in 67% yield after workup as before.

It should be noted that free H_2IMes has also recently become available through Strem Chemicals (2010; $164/g). As a precautionary measure, and irrespective of its source, free H_2IMes should be dissolved in benzene or hot hexanes and filtered through Celite to remove any potential contaminants prior to long-term storage under N_2.[44] We find that white, crystalline material is stable for months when stored in the glovebox.

3.2.2 Gauging the Reactivity of Free H_2IMes

Thermal Stability of H_2IMes

The thermal stability of free H_2IMes was suggested by Arduengo's finding that H_2IMes melts cleanly and shows no sign of decomposition in hexanes at boiling 69 °C, albeit for an unspecified time period.[12] Similarly, Denk has reported that H_2I^iPr, H_2IEt, and H_2IMe

were stable at 100 °C even after 12 months.[25] To confirm the stability of H_2IMes under conditions relevant to the synthesis of **Ru-1c**, we heated a sample of the free carbene at 80 °C in dry toluene-d_8 in the presence of an internal standard. No decomposition was observed over 8 h, as judged by integration against TMB (1,3,5-trimethoxybenzene). Likewise, thermolysis of H_2IMes in dry THF-d_8 at 60°C showed no signs of decomposition over a period of 2 weeks (Figure 3.2).

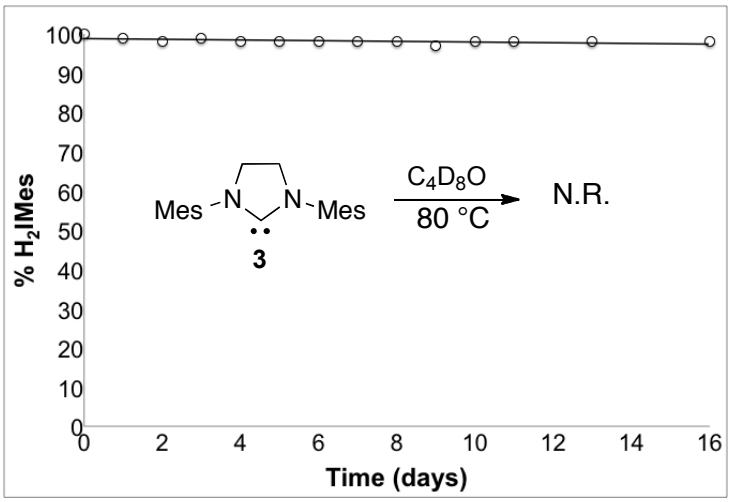


Figure 3.2 Thermolysis of H_2IMes **3** at 60 °C in dry, degassed THF-d_8. No decomposition observed by ^{1}H NMR after 16 days, as gauged against TMB internal standard.

Hydrolysis of H_2IMes

While the hydrolysis of H_2IMes has not been studied directly, Denk has reported that H_2I*t*Bu is immediately hydrolyzed by water in room-temperature THF, undergoing complete conversion to the ring-opened formamide within 30 min.[25] Work by Ying,[45] Günay,[46] and co-workers points toward a similar susceptibility to trace water for H_2*i*IPr or H_2IMes generated in situ. We confirmed this for H_2IMes in controlled hydrolysis experiments in which degassed water (1 equiv) was added to a solution of the free carbene in C_6D_6 in an N_2-filled glovebox. ^{1}H NMR analysis indicated complete loss of H_2IMes within 5 min. The principal

species present was assigned as 1,3-dimesitylimidazolidin-2-ol **7** (Scheme 3.10). Its chemical shifts are in excellent agreement with the values reported[47] for the methoxy analogue, apart from the singlet for the methine proton, which is shifted downfield (5.73 ppm, vs. 5.48 ppm). Also present are small amounts of the known[46] formamide **8**, as a 9:1 mixture of *E* and *Z* isomers (Figure 3.3). After 6 h, only **8** is evident (Figure 3.4).

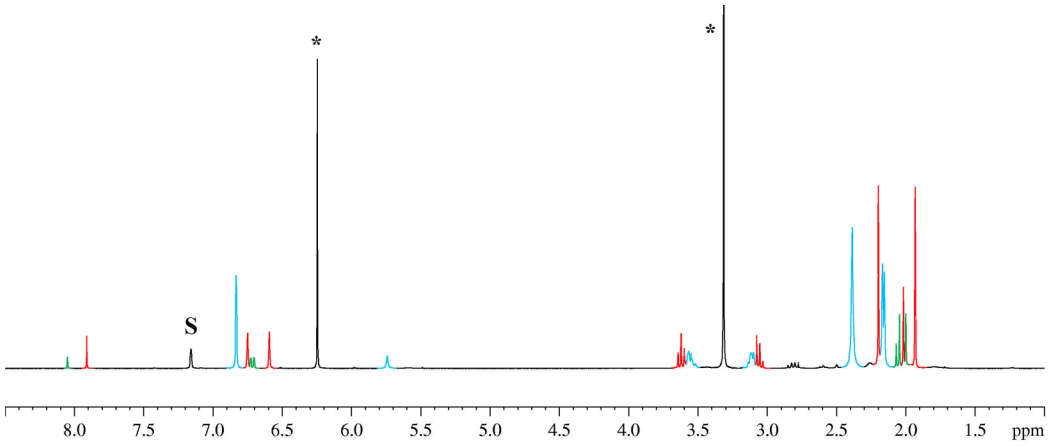


Figure 3.3 ^{1}H NMR spectrum of the reaction of H_2IMes **3** with degassed H_2O (1 equiv) in C_6D_6 (S) after 70 min (Blue = intermediate **7**. Red = *E*-formamide **8**. Green = *Z*-formamide **8**. TMB internal standard denoted by *).

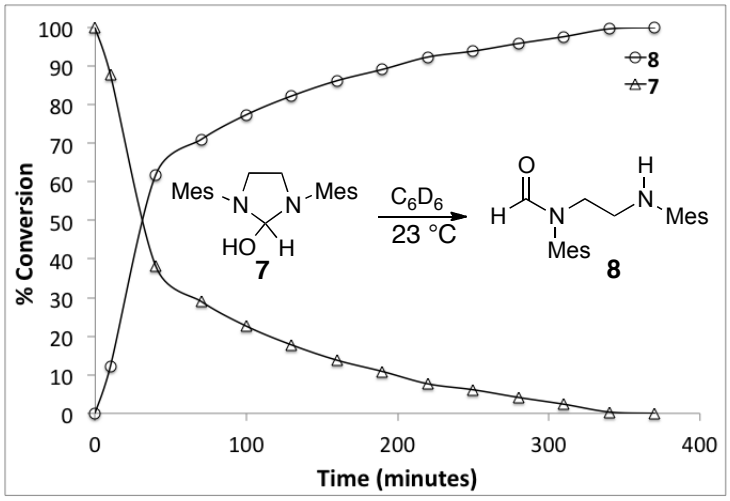
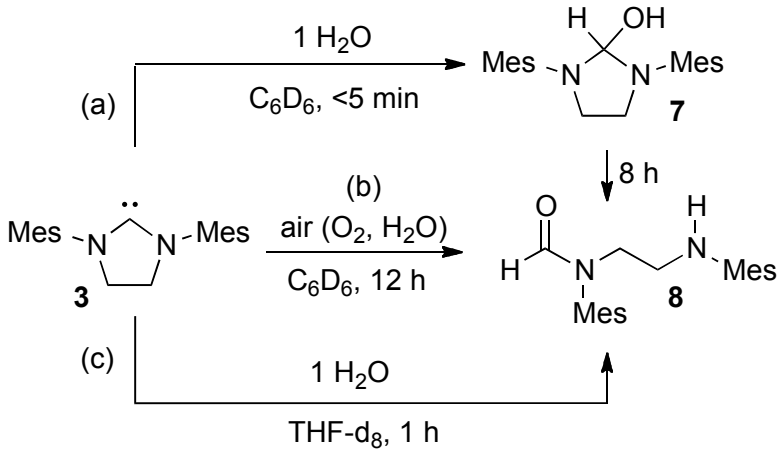


Figure 3.4 Hydrolysis of H_2IMes at 23 °C in C_6D_6 (**7** = Δ; **8** = O).

Compound **8** is likewise observed as the sole product after stirring a solution of H_2IMes in C_6D_6 in air for 12 h. No oxidation by-products were evident, consistent with Denk's suggestion that such carbenes are inert toward oxygen.[25] Finally, transformation of H_2IMes into formamide **8** is much faster in THF, with no signals for the intermediate **7** remaining after 1 h.



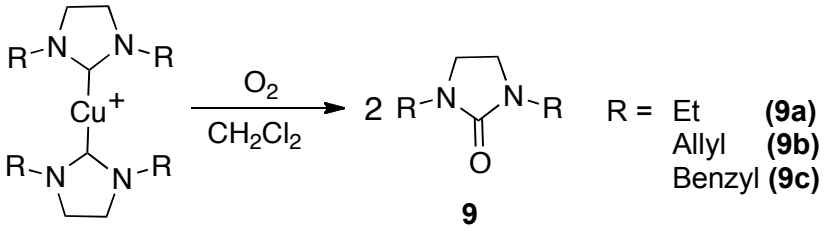
Scheme 3.10 Room-temperature hydrolysis of H_2IMes **3**. (a) By added water in C_6D_6 under N_2. (b) by atmospheric water in C_6D_6 in air. (c) by water in THF-d_8 under N_2.

Unintended hydrolysis was found on dissolving H_2IMes in a freshly opened 1 mL ampoule of toluene-d_8 (Cambridge Isotopes) for an experiment originally intended to assay the thermal stability of H_2IMes. Ca. 15% conversion to **8** was evident within 15 min at 80 °C; no further change was observed over 8 h, indicating complete consumption of the water present.

Oxidative Stability of H_2IMes.

Zero or limited reactivity of free carbenes toward oxidizing agents is implied by their common use as organocatalysts in oxidation reactions.[48-50] Consistent with this, Denk

reported that carbenes I^{t}Bu and H$_2$I^{t}Bu are completely inert towards dry oxygen, as well as the oxidizing agents CuO, Cu$_2$O and HgO.[25] Sawaki has demonstrated that singlet oxygen is sufficiently reactive toward I^{t}Bu to generate the corresponding carboxylate species, however,[51] and Liu has described formation of ketones **9a-9c** on reaction of Cu(I)-NHC derivatives with dioxygen (Scheme 3.11).[52]



Scheme 3.11 Reaction of [Cu(NHC)$_2$]$^+$ complexes with dioxygen, as reported by Liu et al. [52]

The reaction of H$_2$IMes with dry air was examined using the experimental set-up of Figure 3.5. A cylinder of compressed air (BOC; UHP grade) was plumbed into a drybox using copper tubing, and attached to a colour-indicating drying tube filled with CaSO$_4$ (Drierite). A stream of air was passed through a deep purple solution of sodium ketyl in benzene, as a gauge for dryness. The slow decolourization of the solution (to pale yellow; 7 min) was taken to indicate the absence of water. Ketyl solutions react with O$_2$, as well as water, but at a significantly reduced rate: reaction of the radical anion with even trace water induces a color change within seconds. The lines were purged for an additional 30 min, following which a sparging tube was attached, and dry air was bubbled through a solution of H$_2$IMes (0.03 M) and TMB in C$_6$D$_6$. ^{1}H NMR analysis at 30 min intervals indicated no change over a period of 2 h. After 24 h, however, the solution was orange: ca. 50% loss of the starting H$_2$IMes **3** was evident, and the hydrolysis products **7** and **8** were evident, as well as an unknown compound with aromatic and alkyl signals in a ratio of 1: 1: 1.6 ratio,

respectively.

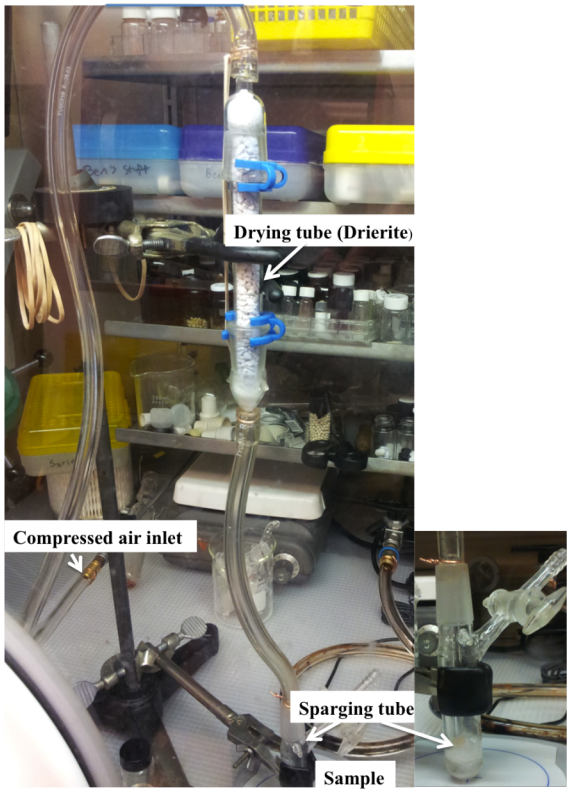


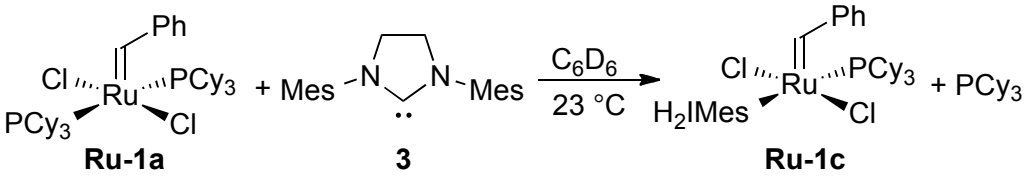
Figure 3.5 Glovebox apparatus used to sparge dry air through a solution of H_2IMes **3** in C_6D_6. All hose attachments are secured with copper wire.

This experiment was repeated on the Schlenk line: apart from 10% hydrolysis observed at the first time of interrogation (1 h), no change occurred over 24 h. These results thus tend to support the Denk statement that NHCs are inert toward normal (triplet) oxygen.

3.2.3 Free-Carbene Route to Ru-1c

With free H_2IMes in hand, the ligand-exchange reaction with **Ru-1a** was explored. The reaction was first probed on NMR scale in C_6D_6 , using 1.2 equiv H_2IMes to minimize weighing errors. Conversion to **Ru-1c** reached 99% at 90 min, and was complete at 2 h (Figure 3.6). A preparative-scale reaction (0.7 g) was then undertaken, using 1.05 equiv

H_2IMes. After 2 h at RT, NMR analysis of an aliquot indicated 5% unreacted **Ru-1a**, which disappeared over a further hour of stirring. This increase in reaction time reflects the higher concentration of the probe reaction (60 mM vs 40 mM). After washing the pink product with hexanes to extract the free phosphine, **Ru-1c** was obtained in 88% yield. The partial solubility of **Ru-1c** in hexanes, even at -78 °C, is responsible for this decrease in yield.



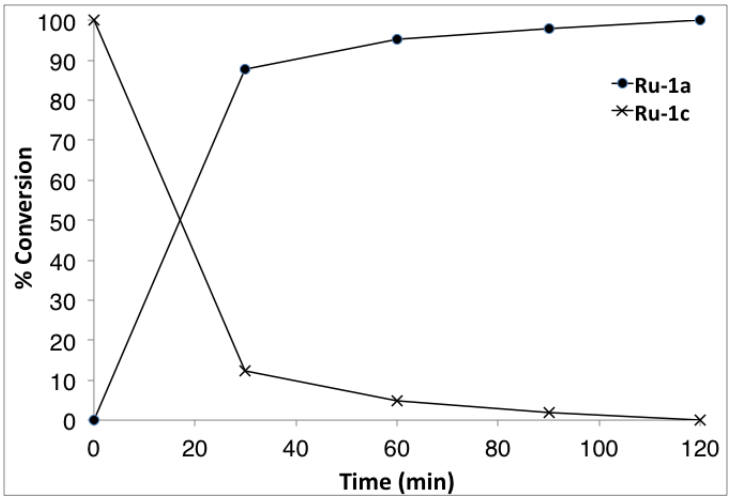


Figure 3.6 Rate profile for syntheisis of **Ru-1c** at 22 °C by ligand exchange (• = conversion to **Ru-1c**, x = conversion from **Ru-1a**; measured against a TMB internal standard).

A more convenient workup procedure, which circumvents the losses associated with extraction of PCy_3, was suggested by a recent patent by Verpoort and co-workers on indenylidene chemistry.[53] This described efficient removal of phosphine by-products using the cationic ion-exchange resin Amberlyst-15 (a divinylbenzene-crosslinked polystyrene bearing sulfonic acid groups). We therefore explored the use of Amberlyst-15 resin in this chemistry. Before use, the dry resin was heated under vacuum for 16 h. More rigorous

removal of water entrapped in the resin pores involved a subsequent swelling in THF, filtration, and re-drying the resin.

NMR experiments in which a C_6D_6 solution of **Ru-1a** was treated with H_2IMes (1.2 equiv) and 4 equiv Amberlyst-15 indicated 90% conversion to **Ru-1c** within 30 min. Removal of free PCy_3 was inefficient, however, with 0.6 equiv of the phosphine still being present. This is consistent with poor swelling of the resin in the non-polar aromatic solvent, and consequently limited accessibility of the active sites.[54] As chlorinated and polar reaction solvents promote bead swelling, the reaction was repeated in THF. A control experiment in the absence of resin indicated quantitative conversion of **Ru-1a** to **Ru-1c** within 30 min (cf. 2 h in C_6H_6; ligand exchange was earlier shown to be faster in THF).[55] Addition of 4 equiv resin after complete conversion to **Ru-1c** showed complete loss of free PCy_3 after 1 h (^{31}P NMR analysis).

Reaction on a 250 mg scale was then carried out, using 1.05 equiv H_2IMes **3**. After 30 min, Amberlyst-15 was added, and the solution was stirred to ensure efficient dispersion of the beads. (Excessively vigorous stirring should be avoided, as it can cause powdering of the resin, which is then difficult to filter off). After an hour, the resin was filtered off in the drybox and washed well with THF. The combined filtrate was evaporated to dryness, yielding clean red **Ru-1c** in 96% yield.

Despite the apparent purity of the product, it will necessarily contain the 0.05 equiv excess of H_2IMes used in the reaction. A potential solution was seen in three factors: the water content present in "off-the-shelf" Amberlyst-15 resin (up to 1.5% H_2O by weight), the high hydrolytic sensitivity of H_2IMes, particularly in THF, and the effectiveness of Amberlyst-15 at scavenging free amines, as well as phosphines. With this in mind, undried Amberlyst-15 was examined as a formamide scavenger. Addition of the resin (4 equiv) to a

stirred solution of the formamide in THF resulted in complete disappearance of **8** within 30 min, as judged by NMR analysis.

Synthesis of **Ru-1c** was then repeated using off-the-shelf resin. The isolated yield of **Ru-1c** reached 99% for reactions on both a 0.25 g and 5 g scale, and showed no sign of catalyst decomposition due to the presence of trace water during work-up. This route provides both a significantly reduced reaction time (cf. 2 h in C_6H_6), as well as a simplified work-up procedure and a dramatically increased product yield in comparison to current state of the art methods.

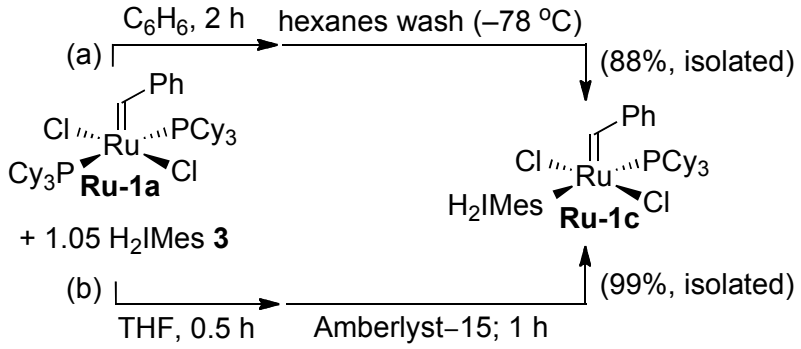
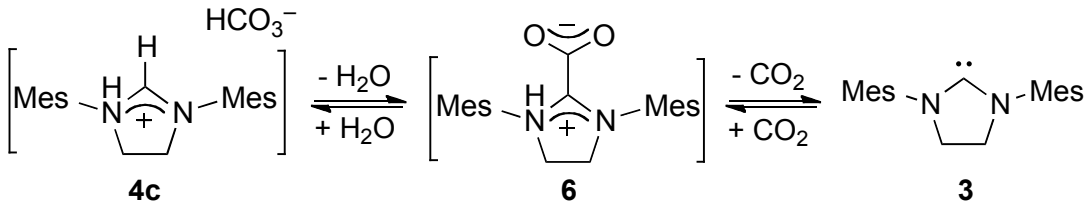


Figure 3.7 Optimized routes to **Ru-1c** where (a) PCy_3 is removed by washing with cold (-78 °C) hexanes. (b) where PCy_3 is removed through addition of Amberlyst-15 as a phosphine scavenging agent**.**

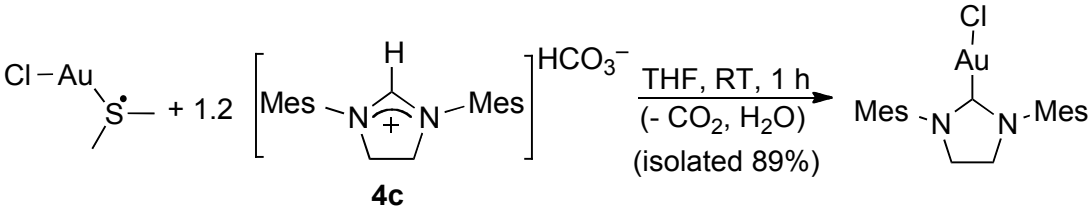
3.2.4 Potential Route to Ru-1c through [H_2IMes(H)](HCO_3) 4c

A recent study by Taton reports synthesis of the air- and water-stable carbonic acid adduct [H_2IMes(H)](CO_3) **4c**.[24] This precursor was used to prepare AuCl(H_2IMes), apparently via equilibration with the CO_2 adduct **6**, and ultimate release of H_2O, CO_2 and free H_2IMes (Scheme 3.12). Strikingly, high temperatures were apparently not required to generate the free carbene, the target reaction proceeding at RT. This offers a potentially attractive alternative route to **Ru-1c**, as the carbonate salt - unlike free H_2IMes - is both air-

and water-stable. Release of an equivalent of water carries the clear potential hazard of competing hydrolysis of the free carbene, however (see section 3.2.2): the apparent immunity of the Taton chemistry may reflect very fast uptake of H_2IMes by the gold reagent (Scheme 3.13), and/or the use of an excess of $[H_2IMes(H)](CO_3)$ (ca. 1.2 equiv).



Scheme 3.12 Generation of free H_2IMes **3** from $[H_2IMes(H)](HCO_3)$ **4c**, as reported by Taton.[24]



Scheme 3.13 Room-temperature synthesis of $AuCl(H_2IMes)$ from $[H_2IMes(H)](HCO_3)$ **4c**, as reported by Taton.[24]

To gauge the relevance of this methodology to the synthesis of **Ru-1c**, we explored use of the Taton salt at the reaction stoichiometry employed in the free-carbene route of Section **3.2.3**. Addition of 1.05 equiv $[H_2IMes(H)](CO_3)$ **4c** to a solution of **Ru-1a** and TMB in THF resulted in <5% conversion to **Ru-1c** after 3 h at room temperature (cf. complete conversion after 30 min when using H_2IMes). Consistent with the Delaude chemistry,[38] heat was found to be required to liberate the carbene. Over 2 h at 60 °C, the solution changed colour from purple to brown (rather than the deep red of **Ru-1c** noted above. At 5 h, conversion from **Ru-1a** to **Ru-1c** remained incomplete: 58% **Ru-1c** was present, along with

9% unconverted **Ru-1a**. More concerning is the loss of 33% of integration in the alkylidene region of the ^{1}H NMR spectrum, vs. TMB internal standard, indicative of side-reactions or of catalyst decomposition. The $^{31}P\{^{1}H\}$ NMR spectrum revealed, in addition to the expected singlets for **Ru-1c** and **Ru-1a** (30.4 and 34.7 ppm, respectively), unassigned signals at 27.6, 97.5, 102.2 and 104.4 ppm. We suspect that the release of an equivalent of H_2O during carbene generation effected hydrolysis of free H_2IMes: some of the side-reactions reflect the thermal instability of **Ru-1a**, but we do not exclude the possibility that the formamide product may contribute to side-reactions

Given the extreme sensitivity of free H_2IMes to hydrolysis, particularly at elevated temperatures, the fact that nearly 60% carbene uptake is observed is notable. The equilibrium between free H_2IMes **3** and its H_2IMes(CO_2) **6** and [H_2IMes(H)](CO_3) **4c** congeners, which are stable to air and moisture, may provide some protection for free H_2IMes against H_2O. For synthetic purposes, however, this route does not compare with that based on use of isolated free H_2IMes, as outlined in Section 3.2.3.

3.3 Conclusions

The foregoing demonstrates that free H_2IMes is a useful, readily handled reagent for organometallic synthesis. While the sensitivity of this species to hydrolysis means that it must be handled using dry solvents, and that atmospheric moisture must be excluded, we find it no more difficult to work with than (e.g.) PCy_3 or transition-metal hydrides. Use of free H_2IMes in ligand exchange reactions enables clean, convenient access to the important second-generation catalyst **Ru-1c**. Freedom from the need for thermolytic release of the free carbene adds greatly to the purity of the product, as no byproducts are generated other than

the displaced PCy_3. As well, it means that reaction can be conveniently carried out in the glovebox, eliminating the potential for air-exposure and decomposition previously reported in the literature for Schlenk-line synthesis of **Ru-1a**. Finally, use of Amberlyst-15 resin as a phosphine scavenger enables quantitative recovery of the Ru product, with no workup being required other than filtration of the resin and evaporation of the solvent. These advances are likely to be advantageous not only in the present context, but also for the synthesis of saturated NHC complexes of other transition metals, for purposes beyond olefin metathesis.

3.4 References

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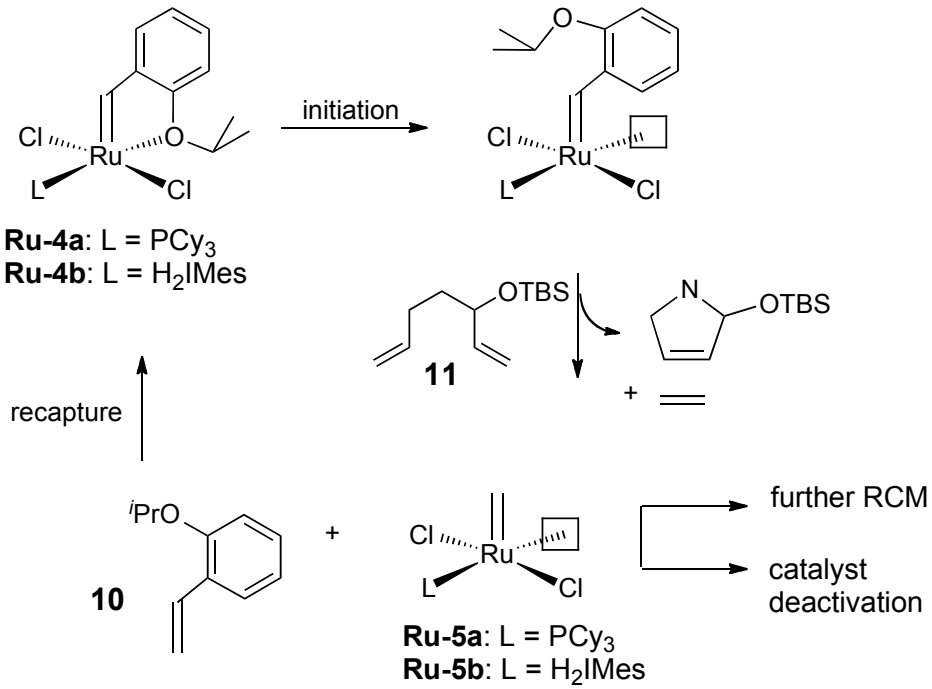
4 Probing the Boomerang Hypothesis in Olefin Metathesis

4.1 Introduction

Since the synthesis of first-generation Grubbs catalyst **Ru-1a** in 1996,[1] a host of Ru metathesis catalysts have been developed.[2-8] A particularly important example is the Hoveyda catalyst **Ru-4** (Scheme 4.1), now of major importance for challenging applications in "green metathesis" chemistry, involving cross-metathesis of oleate esters.[9-13]

Hoveyda catalysts initiate very slowly, relative to **Ru-1a** and even its second-generation derivative **Ru-1c**,[2] owing to the stability of the five-membered chelate ring. A topic of continuing debate is the extent to which the styrenyl ether **10**, once released from the catalyst in the first cycle of metathesis, can recapture the active catalyst, methylidene **Ru-5**.[14-16] This is of great interest because recapture of the highly active four-coordinate species, if competitive with deactivation, could be an important mechanism for prolonging catalyst lifetime.

In early studies using **Ru-4a** in RCM of silyloxy **11**, Hoveyda noted that up to 95% of the initial catalyst charge could be isolated by chromatography after catalysis. To account for this, he proposed that the free styrenyl ether can effectively recoordinate the catalyst post-metathesis. This was entitled a boomerang, or "release-return," mechanism (Scheme 4.1).[2] In this analysis, rate-limiting initiation and metathesis liberates four-coordinate **Ru-5a**. This species can continue to react with diene to form additional RCM product and ethylene, decompose, or re-associate the styrenyl ether to regenerate the original precatalyst. The latter can be separated from metathesis or decomposition products via chromatography on silica gel.[2] (A striking feature of the Hoveyda catalysts is their resistance to decomposition by water and oxygen, a function of their low turnon efficiency).



Scheme 4.1 Boomerang, or release-return, mechanism, as proposed by Hoveyda for RCM.[2]

An alternative explanation, however, is that the catalyst charge recovered by chromatography does not represent recaptured **Ru-5a**, but virgin catalyst that did not initiate to begin with. The high catalyst loading used (5 mol%), in conjunction with the high reactivity of the RCM substrate, increases the probability that a very small percentage of the Hoveyda catalyst was activated. Nevertheless, this idea attracted widespread attention, and several studies aimed at investigating the validity of the boomerang mechanism were subsequently published.[17-22]

4.2 Literature Studies Aimed at Probing the Boomerang Mechanism

In the first direct examination of the boomerang mechanism, Hoveyda undertook crossover studies involving three different catalysts anchored to independent, pelletized sol-gel glass supports (Figure 4.1).[22] As depicted in Scheme 4.2, Pellet A (bearing a deuterium-

labelled catalyst; 2 equiv) was charged to a flask along with Pellets B and C (bearing **Ru-1c** and its 1,6-diphenyl analogue, respectively; 1 equiv each). RCM was carried out at a total catalyst loading of 10 mol%. Following metathesis, Pellet A was removed, rinsed to remove any free catalyst (CH_2Cl_2), and heated with 2-isopropoxystyrene to cleave the catalyst from the glass support. ^{1}H NMR analysis indicated a total of ca. 2% of catalysts **B** and **C** (as gauged from the diagnostic alkylidene and alkyl signals: A: 19.43 ppm , B: 16.45 ppm, C: 4.18 ppm). As such species can only be formed by recapture of the unlabelled catalysts from solution, Hoveyda took this as positive evidence for operation of the boomerang mechanism.

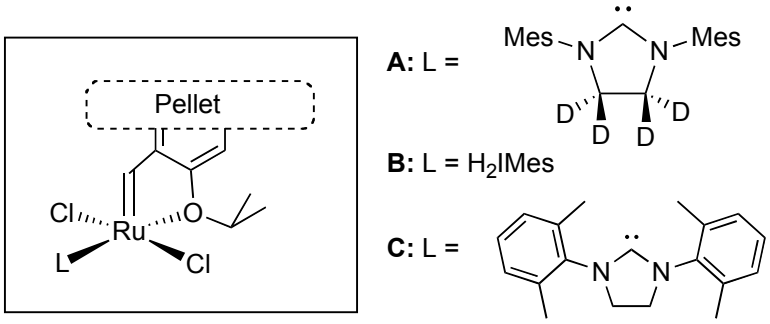
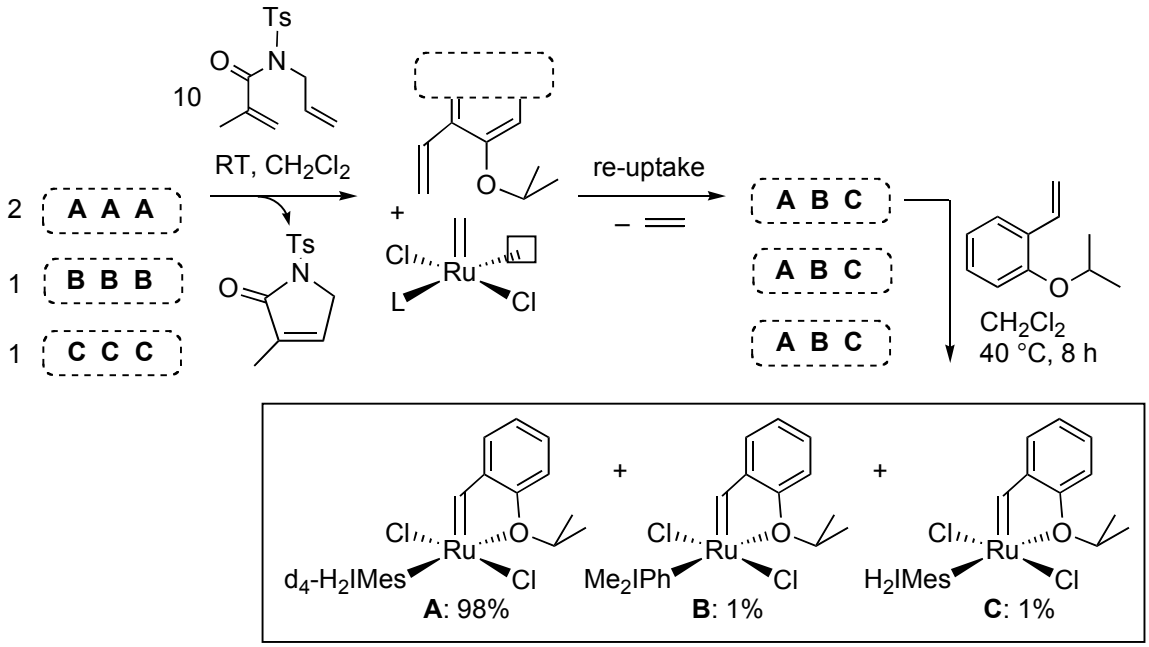


Figure 4.1 Supported catalysts investigated in the crossover study of Scheme 4.2.[22]

The high catalyst loadings used in this study, and the consequently low catalyst initiation, undoubtedly contributes to the very small proportion of the crossover product. The fact that crossover is seen at all at these loadings is highly suggestive, but the very small absolute numbers (2%, vs. a figure of 0% for no reuptake) means that the evidence is not conclusive. As well, this system is perturbed relative to the actual homogeneous catalyst. In particular, it is not clear that the behaviour of the glass-supported catalysts, with presumably increased steric congestion at Ru, will necessarily reproduce that of the free catalyst.

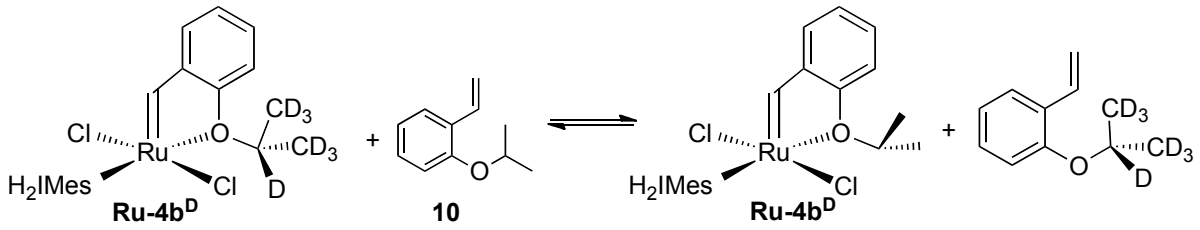


Scheme 4.2 Crossover study designed by Hoveyda to probe the boomerang hypothesis.[22] Complex C corresponds to **Ru-4b**.

Grela and co-workers likewise used deuterium labelling to investigate the boomerang hypothesis.[20] In a control experiment, deuterated **Ru-4b** (**Ru-4b^{D}**) was allowed to reach equilibrium with one equivalent of the protio-styrenyl ether in a sealed NMR tube at 25 °C (20 mM in CD_2Cl_2; Scheme 4.3a). ^{1}H NMR analysis indicated 2% exchange after 1 h, increasing to 50% over 48 h (i.e. a 1:1 mixture of **Ru-4b** and **Ru-4b^{D}**, as judged by integration of the methine septet for the free and bound styrenyl ether). RCM was then carried out under the same conditions, using **Ru-4b^{D}** in the presence of added 2-isopropoxystyrene (5 mol % each; Scheme 4.3b).

Reaction was complete after 1 h, and the catalyst was recovered in 85% yield by chromatography. ^{1}H NMR analysis indicated 41% loss of the deuterium label, a figure reached only after 24 h in the absence of substrate (Scheme 4.3a). This was taken as

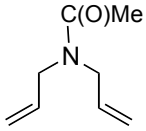
evidence for re-uptake of styrenyl ether by four-coordinate **Ru-5b**. Both the added styrenyl ether and entrapped ethylene will contribute to higher initiation. A more fundamental issue is the absence of an internal standard to quantify exchange, vs. "washing out" of the deuterated tag. This could potentially occur via C-D activation of the pendant isopropoxy tag, or by catalyst deactivation. Blechert has reported significant decomposition of this catalyst at room temperature over several hours in CD_2Cl_2.[23]



(a) No substrate

time (h)	% **Ru-4b^D**	% **Ru-4b**
0	100	0
1	98	2
2	94	6
24	**61**	**39**
48	50	50

(b) 20



time (h)	% **Ru-4b^D**	% **Ru-4b**
0	100	0
1	59	41

Scheme 4.3 Equilibrium between **Ru-4b^D** and **10** (20 mM in CD_2Cl_2; 25 ˚C).[20] (a) Control experiment in the absence of RCM substrate; (b) exchange in the presence of *N,N*-diallylacetamide. A higher proportion of equilibration between labelled and unlabelled species in (b), vs. (a), is taken as support for the boomerang hypothesis (but see text).

A mechanistic study by Plenio provides the most conclusive experimental evidence to date against the boomerang mechanism. This study sought to measure re-uptake of a styrenyl ether tagged with a dansyl fluorophore (dansyl denoted by * in Figure 4.2). Dansyl

fluorescence is quenched for the bound ligand, but release of the tagged styrenyl ether via metathesis permits emission. Consistent with this, a control experiment showed low fluorescence for the tagged complex **Ru-4b^{F}** in solution. This value increased very slowly over time. (The origin of this background fluorescence, and the reason for its slow increase, were not discussed: as it is negligible with respect to the signal resulting from RCM, however, it was disregarded).

Plenio reasoned that the fluorescence levels attained during diene RCM should decrease once the substrate was completely consumed, owing to re-uptake of the dansyl-tagged styrenyl ether (Figure 4.2a). Accordingly, fluorescence was monitored during RCM of diethyl diallylmalonate (DeDAM) in a quartz cuvette (5 mol % **Ru-4b^{F}**, toluene, 40 °C; it is unclear whether the reaction was stirred). A rapid increase in intensity was observed, reaching a plateau approximately ten times higher than the background level after 2 h. This remained constant over the next 18 h (Figure 4.2b). The same total fluorescence was seen for three different catalyst loadings. This was taken as evidence for quantitative catalyst initiation (though see below), and hence complete release of the styrenyl ether: because no fluorescence quenching was observed following metathesis, it was concluded that no re-uptake of styrenyl ether occurred.

A puzzling aspect of this experiment lies in the disconnect between the 40-min timescale required for complete RCM, versus the 2 h required to reach maximum fluorescence intensity (at 40 min, fluorescence is ca. 65% of the level ultimately attained). This point, though not addressed in the paper, tends to suggest that catalyst initiation is *not* complete during RCM: that is, release of the dansyl tag continues after RCM is complete. We suspect that this sustained increase in fluorescence intensity reflects secondary

metathesis: that is, cross-metathesis between the tagged complex **Ru-4b^{F}** and the ethylene byproduct of RCM (or indeed the dansyl tag itself), as shown in Figure 4.3. While a balloon was attached to the cuvette to permit release of ethylene, the continued increase in fluorescence – which is difficult to account for by any means other than continued initiation of **Ru-4b^{F}** after RCM is complete – suggests that this precaution was insufficient. This is a concern because increases in fluorescence associated with continued release of the dansyl tag post-RCM would mask any decrease in fluorescence associated with styrenyl ether re-uptake.

A major weakness in this study thus lies in the assumption of quantitative initiation of the precatalyst. This does not take into account the very high reactivity of the four-coordinate active species, and the notoriously low initiation efficiency of the Hoveyda catalysts (as confirmed most clearly in ROMP experiments).[24] An appropriately rigorous measure of total initiation would have involved measuring fluorescence intensity of the dansyl tag itself, and using this to quantify the amount of free styrenyl ether. Calibration was also attempted by reacting the tagged **Ru-4b^{F}** with a large excess of ethyl vinyl ether (up to 5000 equiv). The resulting fluorescence intensity was ca. 3x larger than that observed in RCM, tending to confirm incomplete initiation during the latter experiments. This control experiment assumes complete initiation, the very process that the experiment is designed to probe.

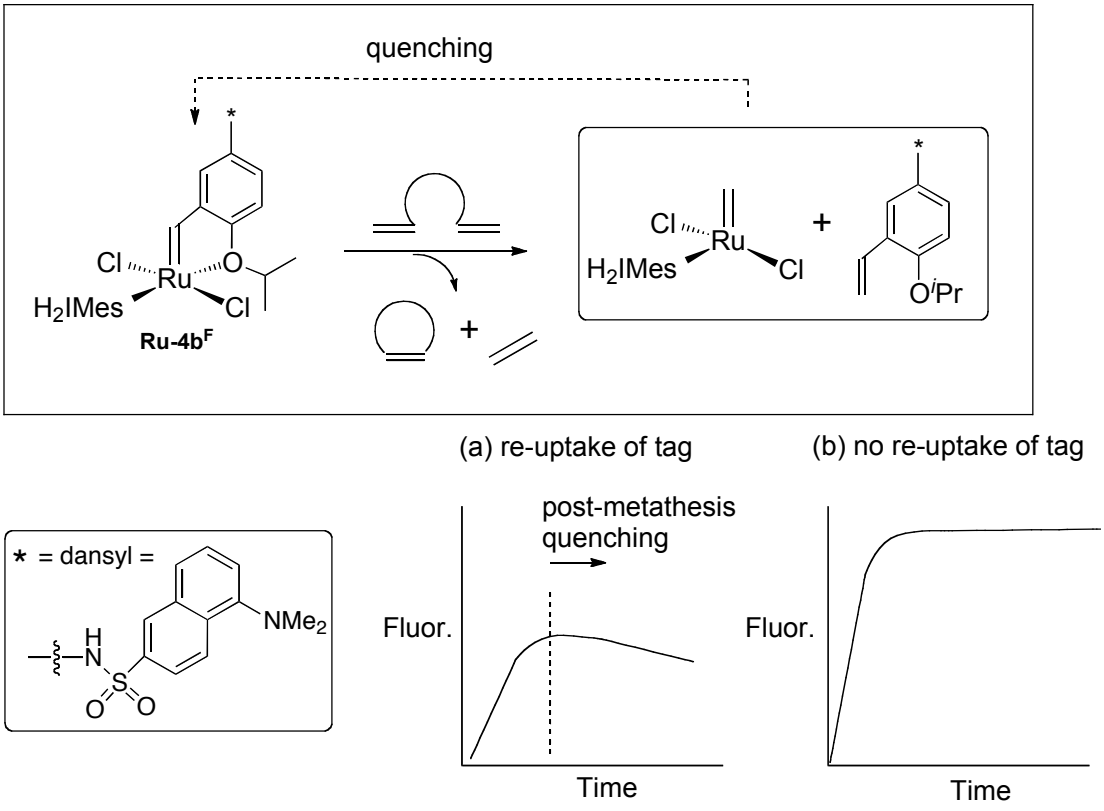


Figure 4.2 Conceptual framework depicting assumptions in the Plenio study. (a) Expected behaviour if re-uptake of the dansyl-tagged styrenyl ether is significant. (b) No recapture of the dansyl tag. Note that total fluorescence is lower in (a), reflecting competing re-uptake of styrenyl ether during RCM**.**

It should also be recognized that in this experiment, the dansyl tag may perturb the system. That is, the tagged styrenyl ether is not identical to the styrenyl ether itself. Indeed, RCM experiments comparing the tagged catalyst **Ru-4b^{F}** and the parent Hoveyda catalyst indicate a ca. 15% difference in conversions at the early stages of reaction (ca. 5 min), presumably reflecting differences in rates of initiation. A need thus exists for a study in which no such perturbation arises.

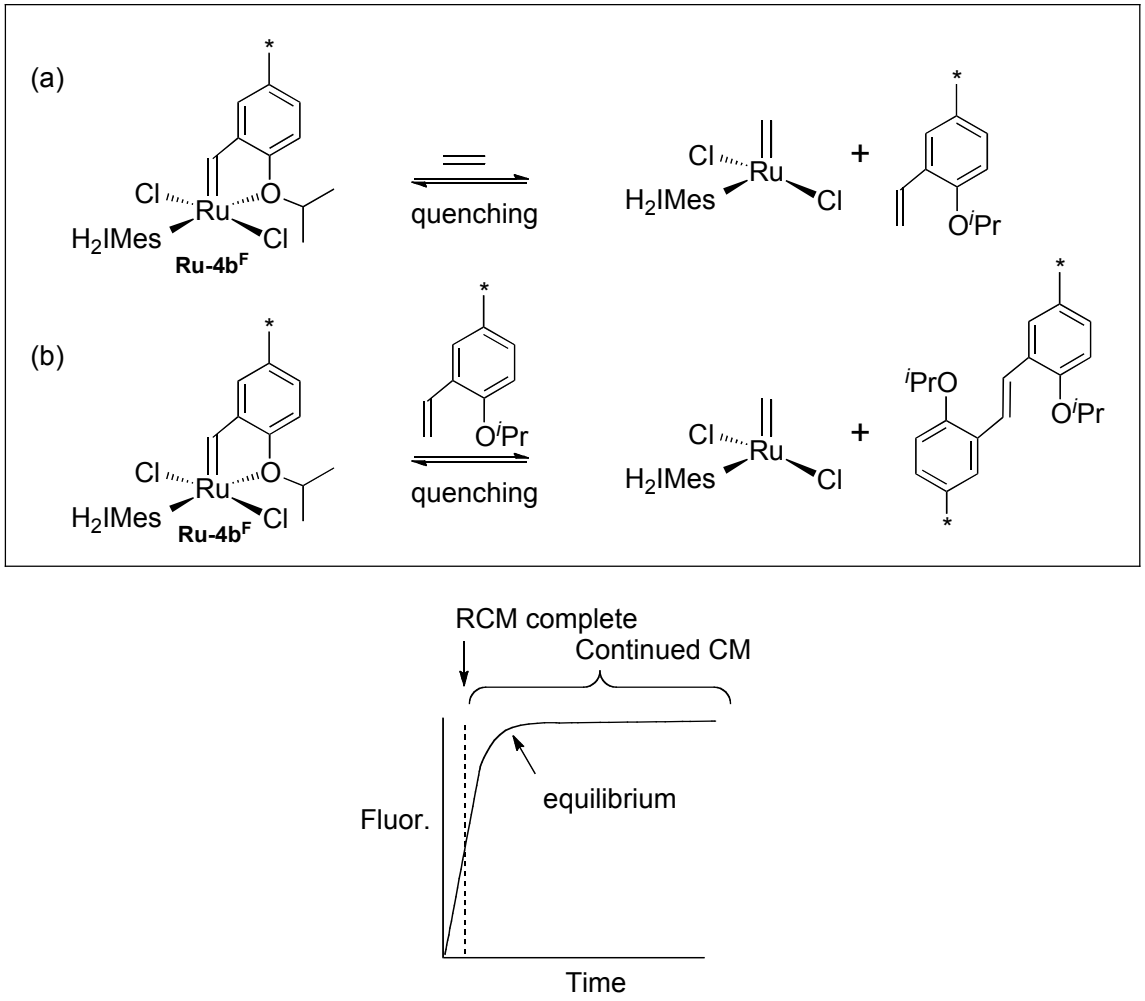


Figure 4.3 Alternative analysis of the Plenio data, which would account for the sustained fluorescence observed following complete RCM. Potential cross-metathesis (CM) reactions of **Ru-4b^{F}**: (a) with ethylene; (b) with the styrenyl ether, to liberate a doubly-tagged stilbenoid.

In a parallel study in the same paper, an analogous catalyst containing a *p*-fluorinated styrenyl ether was used to effect RCM of DeDAM. The ^{19}F NMR spectrum was measured after 4 h, at which point the only species reportedly observable was the free fluorinated styrenyl ether. This was taken as further evidence for complete initiation, without re-uptake.

The absence of a signal for the precatalyst is indeed consistent with complete initiation, but it is unclear whether this again reflects "run-on" metathesis with trapped ethylene, with which the styrenyl ether does not effectively compete. As a more minor point, the dominant signal in the NMR spectrum provided is due to C_6F_6 (presumably added as an internal standard): the relative height of the singlet for free *p*-fluorostyrenyl ether is only ca. 5%, while the somewhat high signal-to-noise ratio means that additional signals may be lost in the baseline.[17] Finally, the electronic perturbation of the styrenyl ether is a weakness here, as in the study above.

The foregoing describes in detail evidence both for and against the boomerang mechanism. A general weakness, however, is the ambiguity introduced by perturbations to the system, as noted in the individual studies above. As well, we saw the need to explicitly separate the question of initiation efficiency from the question of re-uptake efficiency. The experiments described in this chapter were designed to answer these questions.

4.3 Uptake of Styrenyl Ether 10 by Ru-5a, Ru-6a

Central to the boomerang hypothesis is facile re-uptake of free styrenyl ether by **Ru-5a,** the four-coordinate Ru-methylidene that functions as the active catalyst in CM or RCM of terminal olefins. The difficulty in measuring the rate of re-uptake lies in the low initiation efficiency of **Ru-4a**, which translates into unobservably low concentrations of **Ru-5a**. Use of higher temperature to drive initiation is hampered by decomposition. Even for phosphine-stabilized **Ru-6a**, the half-life for decomposition at 55 °C in C_6D_6 is 40 min (23 mM).[25]

To overcome this problem, we sought to generate **Ru-4a** in situ from **Ru-6a**, in the presence of styrenyl ether **10**, by using Amberlyst-15 to scavenge the PCy_3 ligand. Synthesis

of the first-generation Grubbs methylidene **Ru-6a** was originally reported by Grubbs,[1] and recently improved in purity by Lummiss and Fogg.[26]

The experiment was carried out with first-generation methylidene **Ru-6a** in THF (0.9 mL) in the presence of 1.1 equiv of styrenyl ether **10** and 4 equiv of Amberlyst-15. These reactions were carried out in a loosely-capped 4 mL vial in the glovebox with vigorous stirring, in order to promote loss of any ethylene evolved in the reaction. Loss of **Ru-6a** and uptake of styrenyl ether were quantified by integrating the ^{1}H NMR singlet for **Ru-6a** (19.35 ppm in THF) and the doublet for **Ru-4a** (17.36 ppm; d, $^3J_{HP}$ = 4.7 Hz) vs. the aromatic protons of TMB; any difference is assigned to decomposition. Background decomposition was measured in a parallel control experiment without styrenyl ether present.

In the experiment with **10** present, ca. 10% conversion to **Ru-4a** was observed after 15 min at RT in C_6D_6 in the glovebox, with no trace of free PCy_3. The four-coordinate intermediate **Ru-5a** is not observed. After 1 h, conversion to **Ru-4a** reached 40%, with 55% decomposition. In the absence of styrenyl ether **10**, decomposition was 17% after 15 min and 66% after 1 h at RT.

The samples were tightly sealed and removed from the glovebox at 75 min, and heated at 40 °C in an aluminum block. The styrenyl ether-containing sample showed 20% remaining **Ru-6a** and 25% **Ru-4a** after 15 min. At 35 min, no further **Ru-6a** was evident, and the proportion of **Ru-4a** reached 27%. The control experiment with no styrenyl ether showed 95% decomposition after removal from the glovebox and heating at 40 °C for 15 min. The longer lifetime of the four-coordinate methylidene complex in the presence of **10** necessarily reflects re-uptake of the styrenyl ether. Thus, the difference in the two experiments, as depicted in Figure 4.5, reflects the extent to which the styrenyl ether can

"rescue" the four-coordinate methylidene species. This is the first example showing substantial re-uptake (27%) of free styrenyl ether by the *active* methylidene species

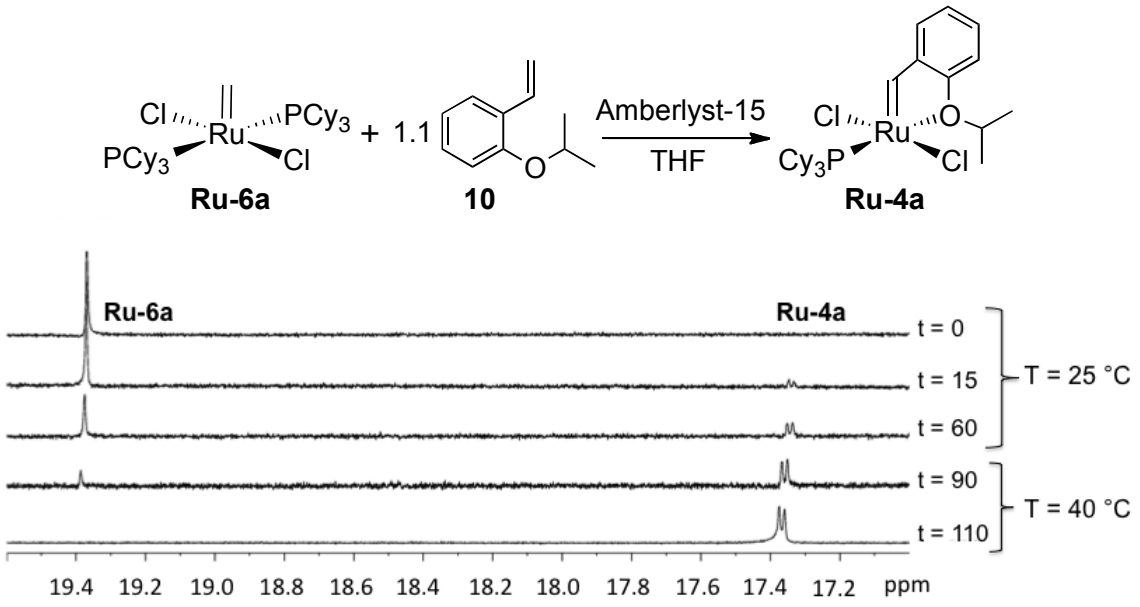


Figure 4.4 ^{1}H NMR spectra showing reaction of methylidene **Ru-6a** with styrenyl ether **10** (1.1 equiv) in the presence of Amberlyst-15 in THF. Aliquots from the reaction solution were removed and diluted with C_6D_6 for NMR analysis. Heated at 40 °C from t = 75 min.

While the number of data-points at 25 ˚C is too small for any but qualitative assessment, a plot of the natural logarithm of Figure 4.5 vs. time suggests first-order rate of decomposition (Figure 4.6). While more detailed studies (and a more rigorous kinetic analysis) are required, these data provide the first insights suggesting that decomposition of **Ru-5a** occurs via a unimolecular pathway, at least in the absence of substrate. The corresponding ^{31}P{1H} NMR spectrum is shown in Figure 4.7.

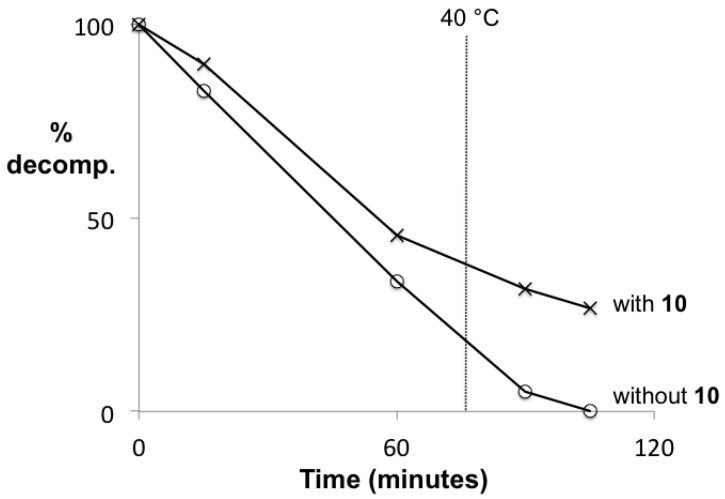


Figure 4.5 Decomposition of the species from Figure 4.4 in the presence of Amberlyst-15 (4 equiv) in THF at 25 ˚C. (x = in the presence of **10**; **O** = control experiment). Dotted line shows the time-point at which the temperature was raised to 40 °C (75 min).

Of interest, unimolecular decomposition has been suggested previously for the first- and second-generation methylidene complexes $RuCl_2(L)(PCy_3)(=CH_2)$ – **Ru-6a** and **Ru-6b**.[25,27,28] The kinetics for the latter were complicated by PCy_3-mediated attack on the methylidene moiety and (ultimately) formation of $[CH_3PCy_3]Cl$ and a diruthenium product.[25,28] Phosphine-mediated decomposition is obviously precluded for the Hoveyda catalysts, however.

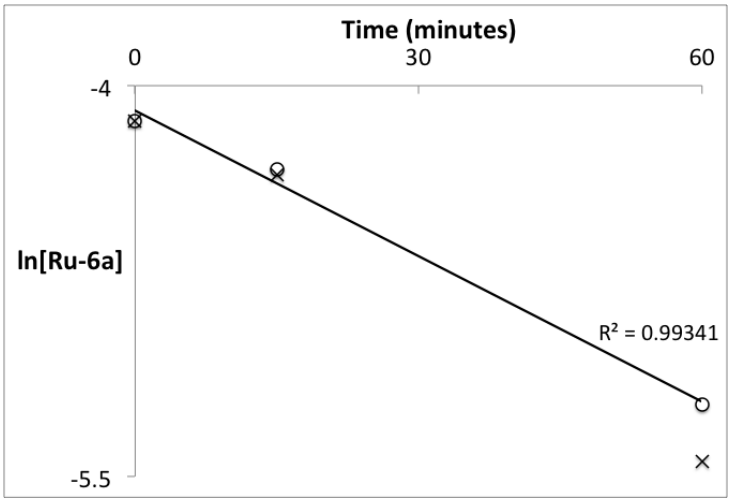


Figure 4.6 Plot of ln[**Ru-6a**] vs. time curves for the decomposition of methylidene **Ru-6a** at 25 °C. **O** = in presence of **10**; **X** = control experiment.

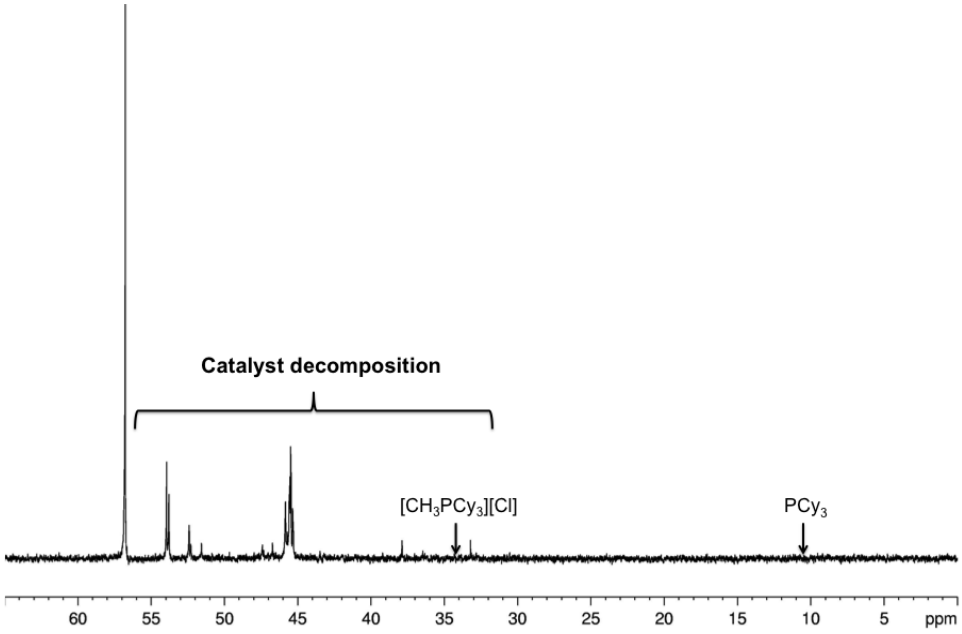
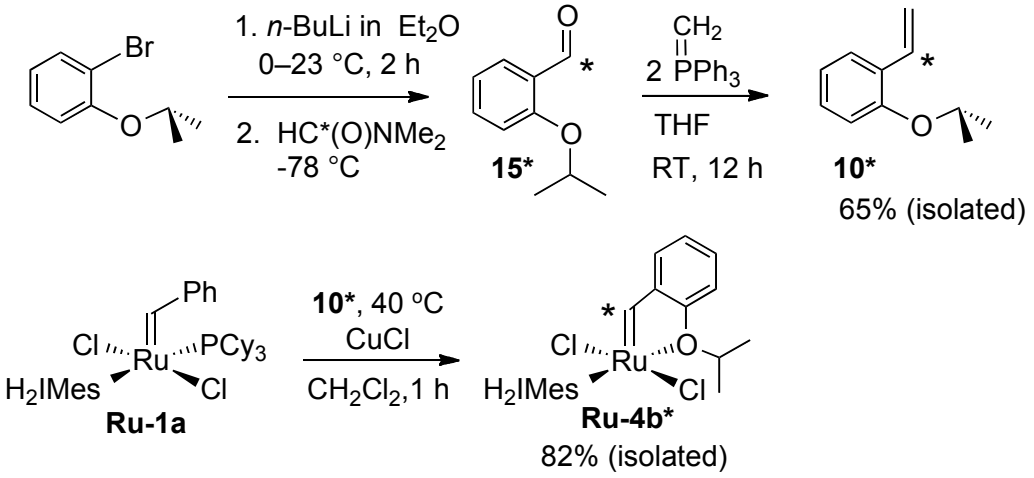


Figure 4.7 $^{31}P\{^{1}H\}$ NMR spectrum (C_6D_6) of the crude residue mixture from reaction of methylidene **Ru-6a** with styrenyl ether **10** in the presence of Amberlyst-15 after heating at 40 ˚C for 35 min (27% yield of **Ru-4a** vs. TMB). No signals are seen for free PCy_3 (11 ppm) or $[CH_3PCy_3]Cl$ (34 ppm).

4.4 Synthesis of ^{13}C-labelled Ru-4a

A recent study by Marciniec described solid-state NMR studies of the second-generation catalyst **Ru-4b*** (Scheme 4.4) tethered to a silica support.[29] Of considerable interest to us was his associated synthesis of the ^{13}C-labelled styrenyl ether **10***, via lithium-halogen exchange of *o*-bromoisopropoxybenzene, followed by treatment with labelled dimethylformamide, and with Wittig reaction $Ph_3P{=}CH_2$. Synthesis of Hoveyda-class catalysts in which the benzylidene carbon bears a ^{13}C label provides a potentially very powerful way to probe the boomerang mechanism with minimal structural perturbation, and without the scrambling problems inherent in deuterium labelling. Specifically, we considered that the reaction between **Ru-4a** and the ^{13}C-labelled styrenyl ether should enable quantification of the rate and extent of background exchange between **Ru-4a** and the styrenyl ether, by integration of the alkylidene signals for **Ru-4a** (17.36 ppm; d, $^3J_{HP}$ = 4.7 Hz) vs. the straddling signal for **Ru-4a *** (17.36 ppm; dd, $^1J_{HC}$ = 162.7 Hz, $^3J_{HP}$ = 4.7 Hz).

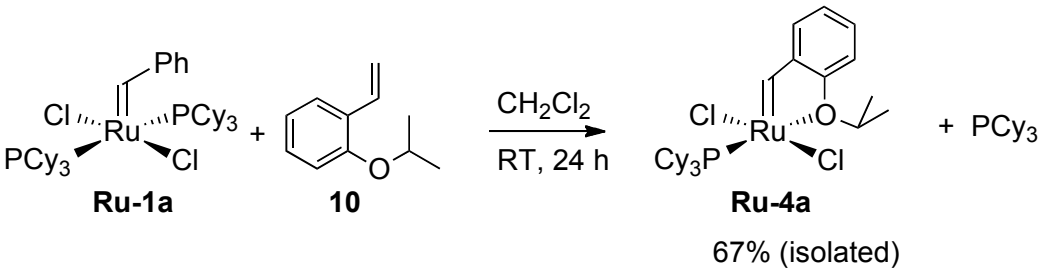


Scheme 4.4 Marciniec route to **Ru-4b*.**[29]

In our hands, distillation of 2-isopropoxybenzaldehyde **15*** as reported by Marciniec

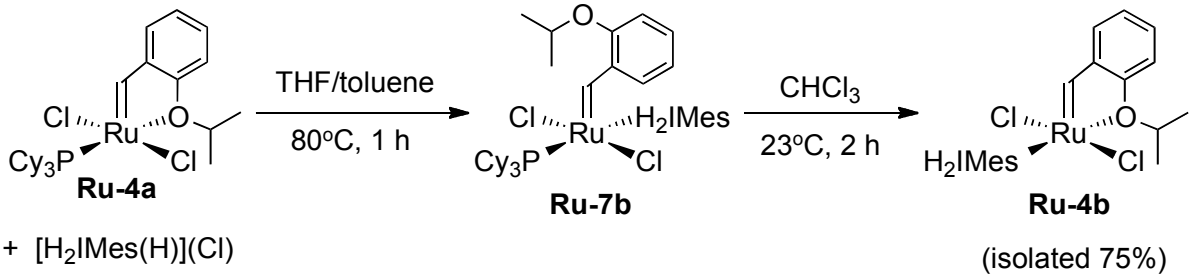
was problematic on small scale, and the crude aldehyde was found to be highly sensitive to decomposition. Better results were obtained via a one-pot procedure in which the Wittig reaction was carried out without intermediate workup, enabling more convenient access to **10*** in a 61% overall yield

Various routes have been developed to the first-generation Hoveyda catalyst **Ru-4a**. Most relevant to installation of the labelled styrenyl ether **10*** is the reaction of **Ru-1a** with 2-isopropoxystyrene **10** (Scheme 4.5).[2,8]



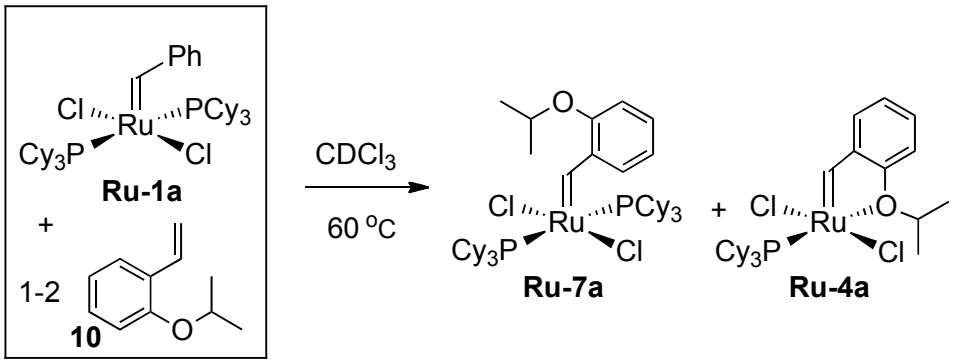
Scheme 4.5 Routes to first-generation Hoveyda catalyst **Ru-4a** by ligand exchange with **Ru-1a**.

In our hands, the Hoveyda route[2] yielded only 40% **Ru-4a** at 24h, significant **Ru-1a** remaining unreacted (52%). Even at 50 °C, full conversion was not achieved. After 5 days at 50 °C, the proportion of **Ru-4a** was only 57%, with 20% unreacted **Ru-1a**. Also observed were small proportions of a complex tentatively identified as phosphine adduct **Ru-7a** (6%), the NMR values for which agree closely with those reported by Blechert for the corresponding H_2IMes chemistry.[3] (Blechert effected transformation of **Ru-7b** into the desired **Ru-4b** by treatment with $CHCl_3$ for 2 h at 23 °C, presumably by degrading the chloroform-sensitive alkylphosphine into its phosphonium chloride).(Scheme 4.6).[3]



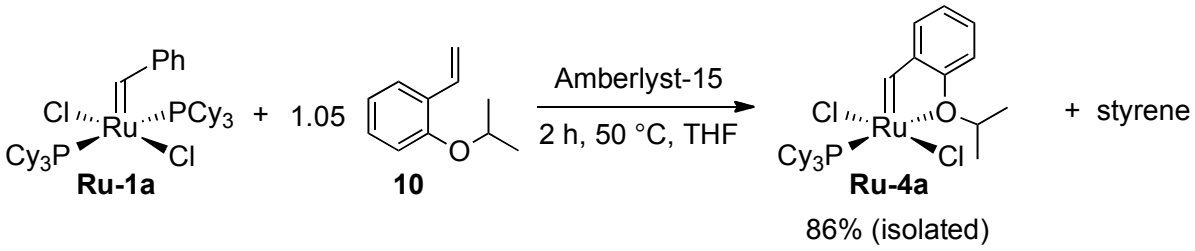
Scheme 4.6 Synthesis of **Ru-4b** as reported by Blechert.[3]

We found that $CDCl_3$ was inefficient as a phosphine scavenger. Incomplete conversion to **Ru-4a** was observed at various temperatures (23 °C, 40 °C, 50 °C and 60°C). At 60 °C, full conversion to **Ru-4a** was still incomplete even after 6 h reaction with a twofold excess of styrenyl ether **10** (20 mM **Ru-1a**). After 6 h, a mixture of desired **Ru-4a** (67%), intermediate **Ru-7a** (8%) and unreacted **Ru-1a** (10%) remained in refluxing $CHCl_3$. Under these conditions, **Ru-1a** decomposes at a rate of approximately 3% per hour, based on integration of the alkylidene singlet against TMB (cf. 19% decomposition after 5 days at 50 °C in C_6D_6).



Scheme 4.7 Reaction of **Ru-1a** with 2-isopropoxystyrene **10** at 60 °C (n = 1, 1.5, 2). Even at 2 equiv, full conversion to **Ru-4a** cannot be achieved without a phosphine scavenger.

Amberlyst-15 resin offers an attractive, efficient alternative to the commonly employed CuCl as a phosphine scavenger, as demonstrated in Chapter 3.[30] Its efficacy in synthesis of **Ru-4a** was explored by stirring the Grubbs catalyst **Ru-1a** with 1.05 equiv of the non-labelled styrenyl ether **10** in the presence of Amberlyst-15 (4 equiv) and TMB as internal standard. Conversion to **Ru-4a** was complete after 2 h at 50 °C in THF. Workup involved filtering off the resin and extracting it with 3 x 2 mL THF, stripping the filtrate to dryness, and washing the precipitate with -35 °C pentane to extract styrene. Brown **Ru-4a** was then obtained in 86% yield. ^{13}C-labelled **Ru-4a*** was likewise obtained in 85% yield. ^{1}H NMR analysis showed the expected alkylidene doublet for **Ru-4a** at 17.36 ppm ($^{3}J_{HP}$ = 4.7 Hz, C_6D_6), while $^{31}P\{^{1}H\}$ NMR analysis showed a single phosphorous peak at 58 ppm, indicating no residual PCy_3).



Scheme 4.8 Route to **Ru-4a** (and **Ru-4a***) using Amberlyst-15 resin as a phosphine scavenger**.**

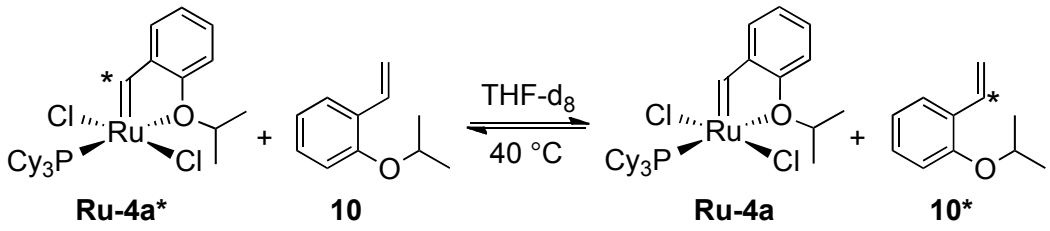
4.5 Ligand Exchange of Ru-4a with 2-isopropoxystyrene.

Ligand exchange of **Ru-4a** with unlabelled and labelled styrenyl ethers in THF-d_8 was undertaken to measure rates of re-uptake of styrenyl ether **10** by active methylidene species **Ru-5a** during metathesis, and to gauge the extent of initiation of **Ru-1a** in the absence of substrate. THF was employed as solvent, rather than the common metathesis solvent CD_2Cl_2,

because Ru metathesis catalysts decompose in chlorinated solvents over extended periods.[23]

A 1:1 mixture of **Ru-4a*** and styrenyl ether **10** in THF-d_8 at 40 ˚C resulted in 20% uptake of the unlabelled tag after 11 h, reaching a 43:57 ratio of **Ru-4a*** and **Ru-4a** after 4 days. No sign of decomposition evident from integration against internal standard (Figure 4.8). No further change was observed over the next 2 days. (The deviation from the expected 1:1 ratio is attributed to weighing errors due to the small scale of the reaction). The analogous experiment for **Ru-4a** and **10*** **(**Figure 4.8) showed a 44:56 ratio between **Ru-4a* and Ru-4a** after 3 days.

This is consistent with the slow exchange previously reported for deuterium-labelled **Ru-4b^{D}** by Blechert[23] and Grela.[20] These experiments took 48 h to reach equilibrium, albeit at RT under more dilute concentrations (5 mM and 20 mM, respectively). However, we were surprised to discover that CM between first-generation **Ru-4a** and **10*** is much slower to reach equilibrium than reported for second-generation **Ru-4b**. Thus, RT exchange between **Ru-4a*** and **10** in C_6D_6 (20 mM, as in the Blechert study) required 19 days to reach equilibrium (46:54 ratio). To our knowledge, this distinction in the rate of initiation between the first and second-generation Hoveyda complexes has not previously been noted. A better understanding of the origin of this effect could provide significant insight into means of regulating initiation efficiency in the Hoveyda-class catalysts, and perhaps more generally in Ru metathesis catalysts. Such control could help in designing (e.g.) sustained-release catalysts capable of functioning as a well-regulated reservoir for challenging metathesis reaction.



Scheme 4.9 Equilibration of **Ru-4a*** and 1 equivalent of **10** in THF-d_8 (40 mM). A 44:56 ratio is reached after 3 days (See Figure 4.8).

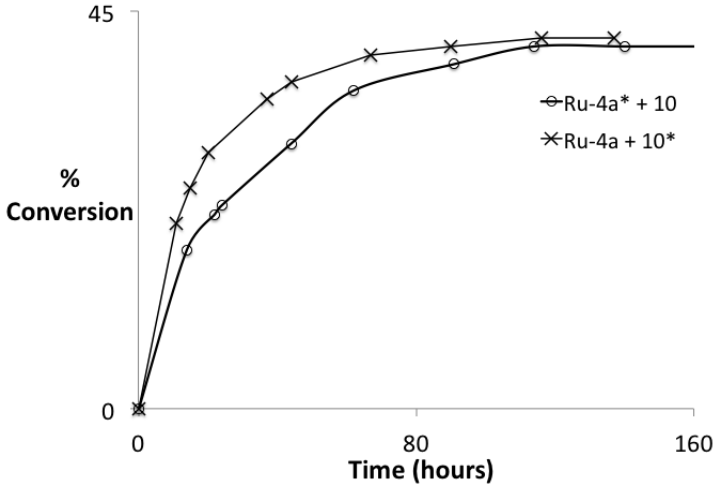


Figure 4.8 Equilibration curves for the addition of 1 equivalent of styrenyl ether **10** to labelled **Ru-4a*** and 1 equivalent of labelled styrenyl ether **10*** to **Ru-4a** in THF-d_8 at 40 °C (40 mM; TMB used as internal standard).

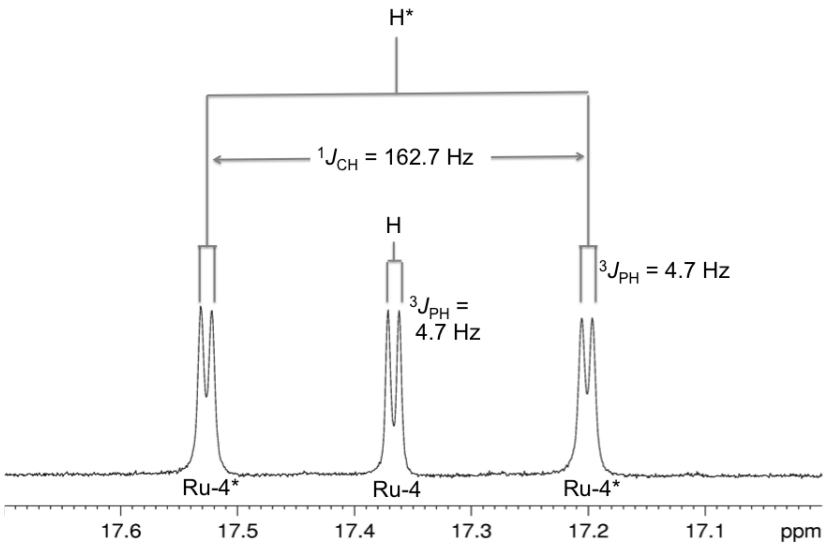


Figure 4.9 ^{1}H NMR spectrum of equilibration (t = 88 h) between **Ru-4a** and **10*** in C_6D_6 (20 mM) showing coupling constants for H and H*. Conversion of **Ru-4a** to **Ru-4a*** is measured via integration against TMB internal standard.

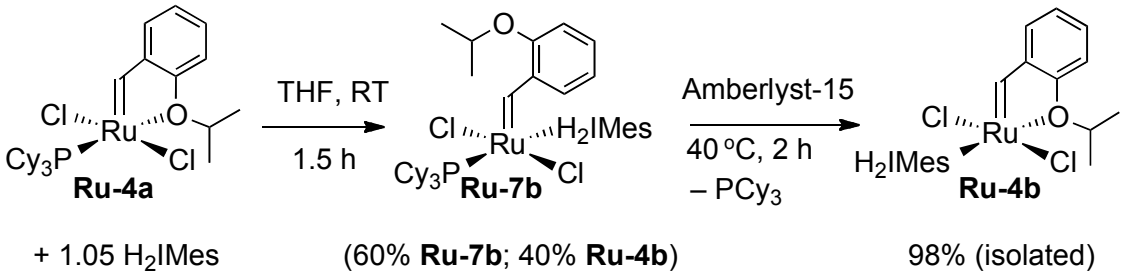
4.6 Free-carbene synthesis of Ru-4b

An obvious goal in this chemistry is extension of these experiments to the second-generation system **Ru-4b**. Parallel work was focused on developing such synthetic routes. These have now been successful, as described below, opening the door to study of the boomerang mechanism for **Ru-4b**.

The low lability of a phosphine ligand trans to an N-heterocyclic carbene makes synthesis of **Ru-4b** more challenging than that of **Ru-4a**. In particular, Blechert has reported that the cross-metathesis of **Ru-1c** with styrenyl ether **10** tends to halt at the intermediate stage (phosphine adduct **Ru-7b**), with a pendant, non-chelated ether ligand. The Blechert group has further noted that chloroform can function as a phosphine scavenger to promote

transformation of **Ru-7b** into the product **Ru-4b** within a few hours at RT.[3] As chloroform can trigger decomposition of these ruthenium complexes, we carry out the initial CM reaction in benzene. On then stripping off the solvent and redissolving in 1 mL $CDCl_3$, free PCy_3 is consumed almost immediately ($^{31}P\{^1H\}$ NMR analysis) but unreacted **Ru-7b** (60%) is present even after 2 h at RT. Heat appears necessary to completely convert **Ru-7b** to **Ru-4b**. At 40 °C, **Ru-7b** was completely converted into **Ru-4b** after 2 h, with no trace of free PCy_3 by $^{31}P\{^1H\}$ NMR.

More effective, however, was use of Amberlyst, as described above and in Chapter 3. Thus, stirring **Ru-4a** with H_2IMes in THF at RT for 1.5 h, adding the resin and stirring at 40 °C for a further two hours yielded second-generation **Ru-4b** in 98% yield on 8 g scale (Scheme 4.10).



Scheme 4.10 Transformation of first-generation **Ru-4a** to second-generation **Ru-4b** via intermediate **Ru-7b** and using Amberlyst-15 (4 equiv).

4.7 Conclusions

This chapter showcases improved, convenient routes to the important first- and second-generation Hoveyda catalysts **Ru-4a** and **Ru-4b** through use of a recyclable

phosphine scavenger. It also exploited a ^{13}C-labelled **Ru-4a*** and methylidene **Ru-6a** to provide novel mechanistic insight into the disputed Hoveyda boomerang mechanism, providing quantifiable evidence for the re-uptake of the styrenyl ether unit by active methylidene species **Ru-5a**.

Future work will include assessment of the background decomposition of Ru catalysts in various solvents and at temperatures relevant to the studies described above (i.e. **Ru-1a** in $CDCl_3$ at 60 °C; **Ru-4a** and **Ru-6a** in THF-d_8 at 25°C and 40 °C). Furthermore, the equilibration studies described for **Ru-4a** and **Ru-4a*** will be repeated in a more metathesis-compatible solvent (eg. toluene, CD_2Cl_2), as well as in the presence of an olefinic substrate. This may result in very different catalyst behaviour, which can be easily quantified via the integration of the alkylidene signals in **Ru-4a** and **Ru-4a*** against an internal NMR standard. Modification of the reaction set-up will, however, be necessary as generation of ethylene in a sealed vessel leads to unproductive metathesis and skewed results.

Experimental design of the studies using the methylidene catalyst, **Ru-6a**, will also be optimized. A rate curve for decomposition in the presence of resin at 25 °C can easily be carried out in an open vessel inside the glovebox. However, the corresponding rate curve at 40 °C may require more rigorous experimental design. The methylidene species is sensitive to oxygen and moisture, and heating in a sealed vial outside of the glovebox will trap ethylene in the reaction headspace as it is generated.

A set of parallel studies using the second-generation Hoveyda catalyst, **Ru-4b**, are currently underway, and will help to confirm or deny our postulation regarding faster initiation of **Ru-4a** as compared to **Ru-4b.**

4.8 References

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5 Conclusions and Future Work

Robust, high-yield routes to the dominant metathesis catalysts are becoming increasingly important as these catalysts approach industrial deployment. Clean, high-yield syntheses of these complexes are essential for process reproducibility and economics. Existing routes to the important second-generation Grubbs and Hoveyda catalysts, $RuCl_2(PCy_3)(H_2IMes)(=CHPh)$ and $RuCl_2(H_2IMes)[=CH(o\text{-}O^iPr)C_6H_4]$, respectively, are unsatisfactory. In situ methods are used to generate the H_2IMes ligand, owing to widespread perceptions of the instability of this species. Such methods undermine stoichiometric control, and result in contamination by ruthenium and alkali metal byproducts. This thesis work demonstrated that free H_2IMes is readily handled under water-free conditions, and developed clean, convenient, near-quantitative routes to these second-generation catalysts by ligand exchange of their first-generation counterparts with free H_2IMes. An important aspect of their workup was sequestration of the liberated phosphine using an ion-exchange resin. These methods are also relevant to the synthesis of NHC complexes of other metals, for purposes beyond olefin metathesis.

A second focus was examination of the much-debated "boomerang" hypothesis, in which the high productivity of the Hoveyda catalysts is proposed to reflect re-uptake of the styrenyl ether functionality released in the initial cycle of metathesis. Current evidence for and against this "boomerang" hypothesis is critically examined, and new approaches to examining its operation are described. Specifically, the rate of decomposition, vs. re-uptake, is examined for the active species $RuCl_2(PCy_3)(=CH_2)$, and background exchange of the parent catalyst with free styrenyl ether is measured by use of a ^{13}C-labelled styrenyl ether. These studies provide the most conclusive evidence to date for the relevance of the

boomerang mechanism for first-generation Hoveyda catalysts.

Development of a robust route to the corresponding H_2IMes catalyst, as noted above, enables extension of these studies to the important second-generation Hoveyda catalyst. A comparison between the first- and second-generation methylidene species would be highly useful, as these represent the active species for the majority of Ru metathesis catalysts currently in existence (L = PCy_3, H_2IMes). Parallel studies of the decomposition of the first- and second-generation methylidene catalysts should be undertaken under conditions of catalysis, with kinetic studies to determine the order of decomposition with respect to ruthenium and substrate. These studies may afford new insights into deactivation pathways for the important [Ru]=CH_2 species.

A previously overlooked difference in initiation rates for first- and second-generation Hoveyda complexes was also uncovered. Closer study of the origin of this behaviour could yield insight into the factors governing catalyst initiation in these systems, with potentially broader relevance.

Appendix A: List of Contributions

1) van Lierop, Bianca J., Reckling, Amy. M., Lummiss, Justin A. M., Fogg, D. E. "Clean, convenient, high-yield access to second-generation Ru metathesis catalysts from commercially available precursors." *ChemCatChem*, **2012**, *4*, 2020-2025.