THE DEVELOPMENT OF WATER-SOLUBLE OLEFIN METATHESIS CATALYSTS CONTAINING AN *N*-HETEROCYCLIC CARBENE LIGAND

Thesis by

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To Mom, Dad, Uncle Matt, and Aunt Jill.

You have really made a difference in my life.

“Of all tyrannies a tyranny sincerely exercised for the good of its victims may be the most oppressive. It may be better to live under robber barons than under omnipotent moral busybodies, The robber baron's cruelty may sometimes sleep, his cupidity may at some point be satiated; but those who torment us for our own good will torment us without end, for they do so with the approval of their own conscience.”

–C.S. Lewis

“Liberty is the very last idea that seems to occur to anybody, in considering any political or social proposal. It is only necessary for anybody for any reason to allege any evidence of any evil in any human practice, for people instantly to suggest that the practice should be suppressed by the police.”

“The free man owns himself. He can damage himself with either eating or drinking; he can ruin himself with gambling. If he does he is certainly a damn fool, and he might possibly be a damned soul; but if he may not, he is not a free man any more than a dog.”

–G. K. Chesterton

“The preservation of freedom is the protective reason for limiting and decentralizing governmental power. But there is also a constructive reason. The great advances of civilization, whether in architecture or painting, in science or in literature, in industry or agriculture, have never come from centralized government."

–Milton Friedman

"The American Republic will endure, until politicians realize they can bribe the people with their own money."

–Alexis d'Tocqueville

“I do not agree with what you have to say, but I'll defend to the death your right to say it.”

–Voltaire

ACKNOWLEDGEMENTS

Finally! We come to a section where the first person can be used with reckless abandon. Anyway, nobody is an island, and many people have contributed to my six years as a graduate student at Caltech. First, Professor Grubbs has been tremendously supportive through the years. I am grateful for both his patience and sound advice. One particularly poignant memory is when we conversed about my future beyond graduate school. Bob sensed my burgeoning desire to leave the field of chemistry, was very supportive and discussed with me possible careers that I might better enjoy, a topic that I was struggling with at the time. When I finally found that job, the one that "just felt right," Bob nicely assisted my application by both writing a recommendation letter and giving pointers on my job talk. While I am grateful for everything, for this in particular, Bob, I say thank you.

I have also been blessed with an excellent committee. Professors Tirrell and Goddard have been with me since candidacy, and both handled my often-rambling mannerisms with aplomb. I am grateful for the time and effort both of you have spent on my behalf, and your letters of recommendation are very much appreciated. Professors Jonas Peters and John Bercaw also served on my committee. I am thankful to Jonas for making time to participate in my proposal defense in the middle of his move to MIT. Of course this move to MIT required that I find a replacement committee member. I am indebted to John for his willingness to serve in this capacity.

As a rule, the Grubbs Group is always packed with talented chemists who are also fun to be around. In the interest of space I will not name everyone, but please know that I very much enjoyed the time that I spent with this fine group of people. However, I would like to highlight the contributions of a few of these individuals to my life.

First, I would like to acknowledge those graduate students and postdocs that had the greatest impact on my chemistry. I began my time in the group wanting to perform polymer synthesis. As a polymer chemist, Oren Scherman was the first to welcome me to the group and taught this micro-pipet-using bioorganic chemist how to perform chemistry that is sensitive to both air and moisture. It was Justin Gallivan who recruited me into aqueous metathesis. He was largely responsible for much of the research elaborated in chapter 2, and for this I am grateful. Brian Connell, Greg Beutner, Chris Douglas, Sebastian Smidt and J. P. Morgan were a valuable resource for answers to questions regarding general chemistry and lab technique. Brian Connell was a veritable well of chemical knowledge, which I drew from continuously. To this day, I am surprised that he never cringed at my sometimes-constant barrage of questions.

Professor Louis Kuo spent his sabbatical with the group in the summer of 2006. He came brimming with ideas for aqueous metathesis and the willingness to bring them to fruition. During his time at Caltech, he examined the ability of "my" catalysts to perform cross metathesis on ruthenium dyes and became the first to join two different cross-partners by aqueous cross metathesis. He also was an excellent resource for basic information regarding protein research. I am grateful for his ideas, efforts, and assistance.

Far and away the most important collaboration of my graduate career was with Soon Hong. Soon and I became a team while examining the effect of water on the stability of metathesis catalysts containing an *N*-heterocyclic carbene ligand. During this time, Soon became more interested in aqueous metathesis and decided to add his expertise to the development of water-soluble catalysts. His presence gave the aqueous-metathesis project a shot in the arm by producing the first catalyst capable of mediating the ring-closing

metathesis of α,ω-dienes in water. Soon is a good chemist and an even better person whose contributions to my graduate career I greatly appreciate.

Graduate school was more than just research, and many members of the Grubbs Group particularly enriched my everyday life. I was the second student to join the group of a class of four: Andrew Hejl, Jacob Berlin, Tim Funk, and I. While I never joined "Funk 'n Hejl" for their weekly game of golf, our viewings of the Fox TV show, *24*, became an enjoyable staple of my winter evenings. Jacob organized the Grubbs Group basketball team for most of my time here and did not yell at me too much as I "ran" up and down the court bricking layups and allowing our opponents to score.

John "Beef" Matson took over coaching basketball once Jacob left, and ensured that I got a good workout at least once a week. I swear I that I lost at least 10 pounds while playing under Coach Beef. John also was one of the organizers for the quarterly Grubbs Group Tribute to Inebriation, also called a pub crawl. While my memory of those events is suspect, I always enjoyed them. Finally, anyone who knows my dietary preferences understands that John's nickname is sufficient for me to hold him in high esteem.

I have had some fun bay mates over the years: Tim Funk, Kevin Kuhn, Paul Clark, and, most recently, Matthew Whited. Tim was a great man to work beside, and our shared love of Christmas music made the holiday season that much more enjoyable.

Kevin Kuhn joined me in Church 217 when Tim left to become a member of the merry band of "130C." Kevin loves movies and awoke my dormant enjoyment of that entertainment medium. We constantly discussed films, and, Kevin, if you are reading this, I still insist that *Lost in Translation* was incredibly overrated. Also thanks to Kevin, I find myself saying "that makes sense" far more often.

My last partner in crime in Church 217 was Paul Clark. It seemed that every time I turned around Paul was running a 100 g column. For Paul these large columns became so routine that he supplemented his chromatographic experience by doing crunches, as large columns were, evidently, not painful enough in themselves. Even so, Paul always had a smile on his face and never hesitated to offer a helping hand when he saw the need. He was a great guy to work beside.

My last bay mate was Matt Whited. Along with the rest of my bay mates, Matt was a very friendly and fun guy to be around. Also, he was willing to participate in long discussions on virtually any topic. Finally, a small demonstration of this man's character: when making change after our lunch at Matsuri's, Matt Whited gave me the *good* ten-dollar bill.

Two of my best friends in the group were Dan Sanders and Ron Walker. Like me, Dan comes from the fine state of Minnesota. More than that, we actually spent much of our lives within a few miles of each other, though we did not meet until our time here in the group. Being from Minnesota, Dan shared my state of complete football enlightenment, as he is also a Vikings fan. I am especially thankful to Dan for his willingness to meet with the "men in the dark suits" as a character reference for my national security clearance.

Ron Walker was a SURF in the group during the summer of 2002 before joining the group as a graduate student in 2003. Ron has an identical twin brother, which I discovered the hard way. (I came into lab one morning to find Ron sitting at his desk working. I next walked into the computer room to again see "Ron," this time at a computer. Classic double take ensued.) Ron and I shared a few hobbies, which we often discussed. Also, I attended Ron's wedding and left loaded for bear with Ron stories from his bachelor

party. Last, Ron had two excellent practical skill sets, cars and barbecue. Ron was always a great resource when my minivan had issues, and, trust me, ***NEVER*** miss an opportunity to partake of Ron's barbacue ribs. No sacrifice is too great. Ron is a good man and a good friend, and he also volunteered to meet the suits as a character reference for my security clearance. Ron, thank you.

My group of friends at Caltech extended beyond the Grubbs Group. In no particular order these are Uttam Tambar, Gretchen Keller, Jason "Texas Teacup" Keith, Dave Weinberg, Jonathon Owen, Ted Corcovilos, Steve Baldwin, Greg Drummand, Alex "Foos" Papendrew, Theo Agapie, Jeff Byers, Brian Leigh, Christine Thomas, and Yenn Nguyen. There are others, but I spent the most time with these individuals at different points in my graduate career. I would like to give a particular shout-out to my poker buddies: Dave, Gretchen, Steve, and Ted. Dave in particular is acknowledged for arranging these events. Also, Jason Keith gave me the nickname "Beaker" (after the Muppet scientist), which stuck. I know that there were/are people who do not know my actual name. I am thankful to all of these individuals for making my time at Caltech that much more enjoyable.

This brings me to my family. I have been blessed to have an aunt and uncle who live in Southern California. Matt and Jill are both fantastic people, and they have a terrific family of four sons. Their oldest, Shane, was one of the first people I saw upon moving to California. When I first saw Shane, he was still just dating Jen. I then shared a beer with Shane at their engagement party, attended their wedding, watched them buy their first house, and was at the hospital for the birth of their first-born son, my aunt and uncle's first grandchild, Lucas. Taylor Jordan is also a great guy, though a referee should always be present when he and I compete at a game of Catch Phrase. With a "legendary" fashion

sense and a laid-back attitude, Grant was always nice to hang with. As he lives in Alexandria, I have not seen as much of Justin. Even so, he is a good guy with whom to share a cigar on a lazy evening, and I look forward to spending more time with him when I move to Virginia.

Uncle Matt is a bit like The Godfather of the California Jordans. If you ever need anything, he is always the guy to call, and his generosity, particularly with his family, will not be found wanting. He gave me the minivan that I have driven these past four years and has treated me to more steaks than I can count. He also introduced me to the joy of spending time with friends and family while drinking fine wine and smoking a good cigar. He is very supportive, and his advice is always sound. Lastly, his ***many*** puns and his pantomimes during games of charades are always amusing and are the source of fond memories.

Aunt Jill is a fun person to know. She effortlessly mixes the desire to party with responsible behavior. Being an excellent cook, her ribs are a culinary masterpiece. She also spoils me mercilessly with Dutch Babies (pastry) on the mornings of most of my visits. She always made feel welcome and happily provided me with a home away from home.

That all said, Uncle Matt, Aunt Jill, Shane, Justin, Taylor, and Grant, the "Fifth Beatle" says thank you. You make me feel like a member of your family. I greatly enjoy my time with all of you, and I will remember my many days with you with fondness.

Uncle Dick and Aunt Michelle also contributed to my time on the West Coast. I often spent Thanksgiving with them in Nevada. You would be hard pressed to find a nicer guy than Dick, and Michelle was a lot of fun. They both were very supportive, and their daughter, Chandler, has also been a friend.

The greatest blessing in my life has always been my mother and father. It is impossible to exaggerate the amount of loving support these two people have given me over the years. I can only hope to emulate their example should I ever have a child of my own.

My father, Jim, is a man of very high character. He is always ready and willing to help when he sees a need and is a source of a great deal of encouragement. He also gives sound advice, which I have come to respect more as I get older. He always puts the needs of his family first and is unstinting in his aid. In other words, my father is a man of quality and has demonstrated by example how to live a good life.

My mom, Dee, is the most giving and selfless person that I know, and my life is pleasantly riddled with her many selfless actions. She always cares about what I think and how I feel and is very generous with her love. She is willing and even eager to provide a listening ear. My mom also embodies the definition of hard work. However, even after a long day of intense effort, she can find it in herself to smile and offer her assistance when the need presents itself.

Mom, Dad, I do not think that I will ever be able to fully express the depths of my gratitude. Whatever success I have experienced can be directly traced back to the foundation of support and love that you have provided. Thank you.

Finally, I would like to thank God. Things have turned out very well for me in this life, and I often see the hand of a higher power at work. My experience through these last six years took me down paths that I never expected to traverse, and I would be negligent to ignore the influence of divinity over this time in my life.

ABSTRACT

This research describes the development of new olefin metathesis catalysts that are stable and active in water. Earlier water-soluble metathesis catalysts rely on phosphine ligands functionalized with ionic groups. In contrast to these bis(phosphine) complexes, the catalysts reported in this research harness the increased stability and activity provided by *N*-heterocyclic carbene (NHC) ligands. As a result, these catalysts display an activity and stability that are unprecedented in aqueous olefin metathesis.

Initial efforts to produce the desired water-soluble metathesis catalysts employed poly(ethylene glycol) (PEG) to generate a complex that was soluble in water (Chapter 2). This catalyst was capable of the ring-opening metathesis polymerization (ROMP) of a challenging *endo*-norbornene monomer, which an earlier bis(phosphine) complex catalyzed poorly. While demonstrating the potential of NHC ligands to improve the activity of water-soluble metathesis catalysts, this catalyst was not sufficiently stable to mediate metathesis transformations involving acyclic olefins in water.

A careful examination of the described PEG catalyst inspired a few strategies to produce olefin metathesis catalysts with improved activities in water (Chapter 3). This strategic vision was honed by studies examining the effect of water on the decomposition of catalysts that contain an NHC ligand (Chapter 4). These studies indicated that phosphine ligands play an active role in the aqueous decomposition of ruthenium methylidene complexes, which are vital complexes for metathesis reactions involving terminal olefins. With these results in hand, incorporating NHC ligands into phosphine-free ruthenium complexes was pursued as a promising approach to producing active metathesis catalysts that are stable in water.

Catalysts supported by both isopropoxybenzylidene and NHC ligands were modified to include ammonium salts (Chapter 5). The water-soluble catalysts produced were stable in water and competently initiated aqueous ROMP. More importantly, these catalysts readily catalyzed the ring-closing metathesis of α,ω-dienes in water. The described catalysts were also able to homodimerize allyl alcohol and homoallyl alcohol in water, which are among the few known examples of cross metathesis in neat water.

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CHAPTER 1

The Olefin Metathesis Reaction and Its Function in Protic Environments: an Overview

The Olefin Metathesis Transformation

With the exception of radical and pericyclic processes, most classical organic reactions can be readily understood as interactions between nucleophiles and electrophiles. The challenge for organic chemists is to engineer reacting partners such that the chosen nucleophile reacts with the targeted electrophile in a selective manner. While this archetype of nucleophiles and electrophiles provides a rich field of chemical reactivity, it is limited by the reality that most complex molecules contain many electrophilic and nucleophilic centers, which can lead to undesired side reactions. The advent of transition-metal-catalyzed reactions has greatly expanded the ability of chemists to synthesize molecules by offering new modes of reactivity not available within the paradigm of nucleophiles and electrophiles.

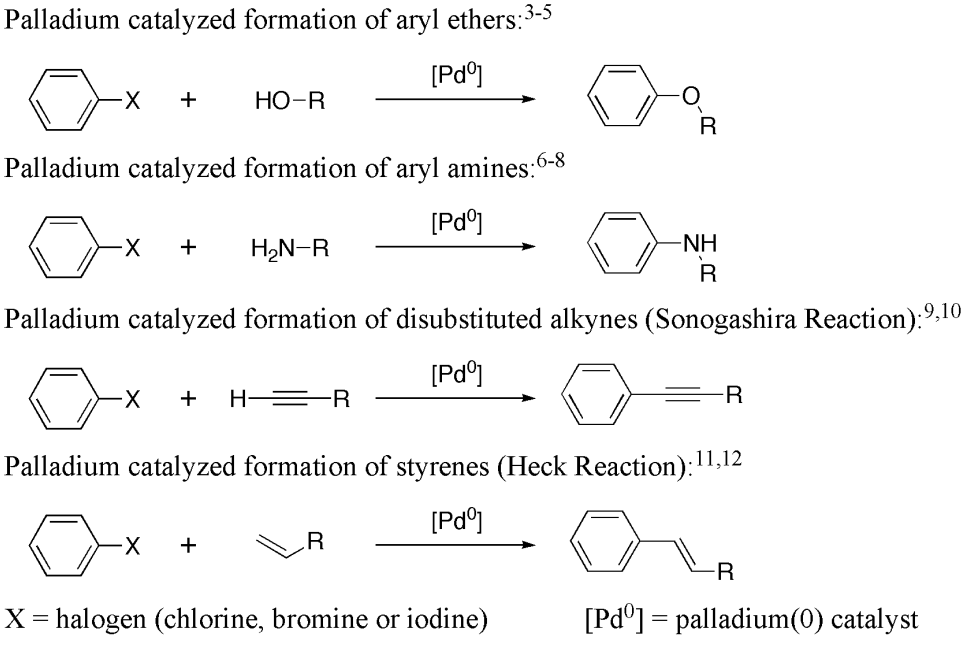


Figure 1.1. Palladium catalyzes the coupling of aryl halides with a variety of different partners. Just a few examples of the many palladium-mediated coupling reactions are shown.

The ability of transition metals to accommodate such processes as oxidative addition, reductive elimination, β-elimination, bond insertion and transmetallation allows for their use in a multitude of catalytic cycles.[1,2] For example, palladium-catalyzed coupling reactions can mediate the generation of new bonds between aryl halides and alcohols,[3-5] amines,[6-8] alkynes,[9,10] and olefins (Figure 1.1).[11,12] Moreover, the ability to readily modify a transition metal's ligands has inspired the development of a plethora of enantioselective metal-catalyzed processes.[13-17] Therefore, it is not surprising that transition-metal-mediated reactions are the topic of a vast amount of contemporary chemical research.

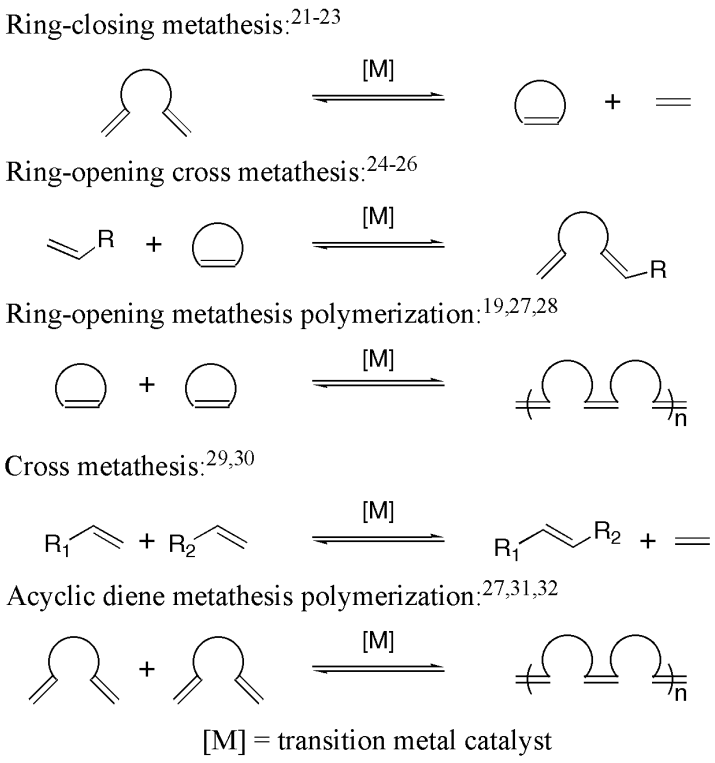
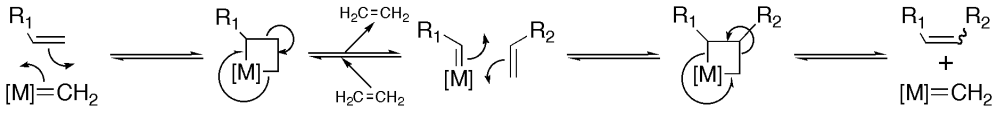


Figure 1.2. In olefin metathesis, a transition metal mediates the exchange of two olefins' substituents. This process enables the shown reactions.

One particularly powerful transition-metal-catalyzed transformation is the olefin metathesis reaction.[18,19] First discovered in 1959,[20] olefin metathesis is a process where two carbon-carbon double bonds exchange their substituents to form two new double bonds as illustrated in Figure 1.2. When the two olefins are components of an α,ω-diene, intramolecular olefin metathesis produces a new cycle in a reaction termed ring-closing metathesis (RCM).[21-23] In direct contrast, the metathesis reaction of a cyclic olefin and a terminal olefin can produce the linear product of ring-opening cross metathesis,[24-26] and the repeated intermolecular metathesis of cyclic olefins yields polymers through ring-opening metathesis polymerization (ROMP).[19,27,28] The olefin metathesis reaction of two linear olefins provides the linear products of cross metathesis.[29,30] Finally, repeated cross-metathesis reactions of α,ω-dienes produces polymeric products in a process referred to as acyclic diene metathesis polymerization (ADMET).[27,31,32]

Scheme 1.1.



[M] = transition metal complex

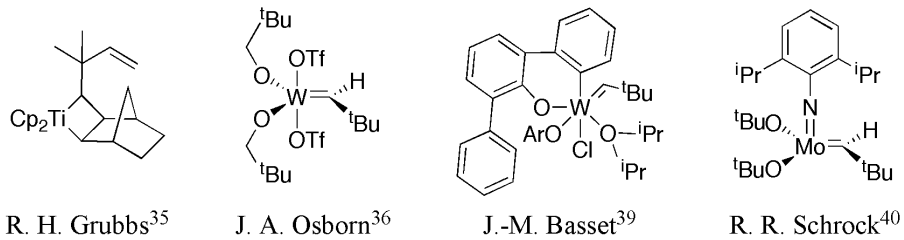
Chauvin first introduced the accepted mechanism for olefin metathesis in 1971, which is shown in Scheme 1.1.[33] Olefin metathesis involves the reaction of transition-metal alkylidenes with olefins to form a metallocyclobutane ring. Productive fragmentation of this metallocyclobutane yields a new metal alkylidene and the olefenic product. A fundamental property of this mechanism is that every step is fully reversible. Therefore, all metathesis reactions are equilibrium processes and require a

thermodynamic driving force. In the case of ROMP and ring-opening cross metathesis, this driving force is the release of ring strain. The driving force of RCM and cross metathesis is the loss of a volatile small molecule, most commonly ethylene.

The Transition-Metal Catalysts of Olefin Metathesis

The first olefin metathesis catalysts were ill-defined mixtures of an early transition metal and a main-group inorganic cocatalyst.[34] The most common transition metals used in these systems were molybdenum and tungsten, though systems employing other transition metals were also known.[34] A variety of cocatalysts were also utilized, though most cocatalysts contained aluminum. Whether catalysis with a given system was homogenous or heterogeneous was not always clear,[34] and examples of both types of catalysis were known.

Continued research in this area produced a variety of well-defined, early-metal metathesis catalysts (Figure 1.3). For example, application of the Tebbe reagent to norbornene yields a titanium complex capable of polymerizing norbornene in a living fashion.[35] Also, many tungsten and molybdenum alkylidenes can mediate olefin metathesis.[36-41] The best known and most widely employed of the early metal catalysts are the molybdenum family of catalysts developed in the lab of Richard R. Schrock.[40,42]

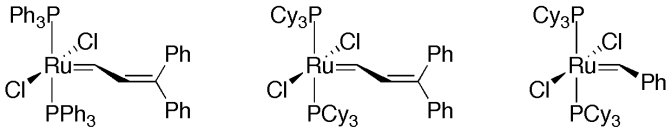


R. H. Grubbs[35] J. A. Osborn[36] J.-M. Basset[39] R. R. Schrock[40]

Figure 1.3. Initial olefin metathesis catalysts were based on early transition metals.

While the early metal systems are efficient mediators of the metathesis transformation, they are very sensitive to both air and moisture.[18,43] Moreover, being hard, electrophilic metals, these catalysts display a poor tolerance for many functional groups commonly found in organic molecules. For example, these early-metal alkylidenes often react with carbonyl groups, in a manner analogous to the phoshpine ylide of the Wittig reaction, to produce a new olefin and a metal oxo complex.[40,44] Therefore, a more stable and functional-group-tolerant catalyst is necessary for the metathesis reaction to be broadly applicable in organic synthesis.

Early research demonstrated that ruthenium(II) alkylidenes are highly tolerant of polar functional groups.[45-48] This inspired Grubbs and co-workers to examine ruthenium(II) alkylidenes as potential catalysts for olefin metathesis. Initial results produced well-defined ruthenium vinylidene **1**,[49] which is capable of the living ROMP of norbornene.[50] Exchanging the triphenylphosphine ligands of **1** for tricyclohexylphosphine yields catalyst **2**,[51] which shows increased ROMP activity and is capable of mediating the metathesis of acyclic substrates.[51,52] Finally, replacing the vinylidene ligand of **2** with a benzylidene ligand provides catalyst **3**, which is commonly identified as the Grubbs first-generation metathesis catalyst.[53,54]



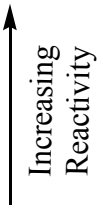
1 **2** **3**

Table 1.1 illustrates the functional-group tolerance of a metathesis catalyst as a function of the identity of the catalyst's transition-metal center.[43] As reflected in this table, ruthenium catalyst **3** tolerates a greater range of organic functionality than its early-

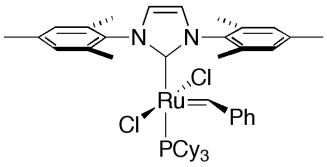
metal counterparts. This tolerance along with its improved stability towards air and moisture allows for the application of catalyst **3** to the synthesis of a wide range of polymer and small-molecule targets.[18,55] However, while **3** is both more stable and more functional-group tolerant than the early-metal systems, it is less active than these systems.[43,56]

Table 1.1. The relative reactivities of common functional groups with catalysts based on the indicated metal

Titanium	**Tungsten**	**Molybdenum**	**Ruthenium**
Acids	Acids	Acids	*Olefins*
Alcohols, Water	Alcohols, Water	Alcohols, Water	Acids
Aldehydes	Aldehydes	Aldehydes	Alcohols, Water
Ketones	Ketones	*Olefins*	Aldehydes
Esters, Amides	*Olefins*	Ketones	Ketones
Olefins	Esters, Amides	Esters, Amides	Esters, Amides



Replacing the triphenylphosphine ligands of catalyst **1** with the more sigma-donating tricyclohexylphosphine ligands yields catalyst **2**, which displays a greater metathesis activity than **1**.[51,57] Therefore, incorporating ligands with a greater sigma-donating ability than tricyclohexylphoshine may further increase the activity of ruthenium-based metathesis catalysts. One such class of strongly sigma-donating ligands are *N*-heterocyclic carbenes.[58-62] Replacing one of the tricyclohexylphoshpine ligands of **3** with an *N*-heterocyclic carbene (NHC) ligand produces catalysts **4** and **5**.[63,64] While maintaining the high tolerance for air, moisture and organic functionality of catalyst **3**, these catalysts demonstrate increased metathesis activity relative to **3**. Indeed, the activity of catalyst **5**, also known as the Grubbs second-generation metathesis catalyst, rivals that of the highly active molybdenum catalysts.[56]



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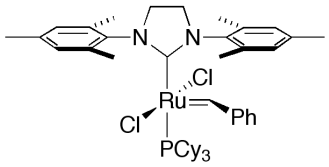

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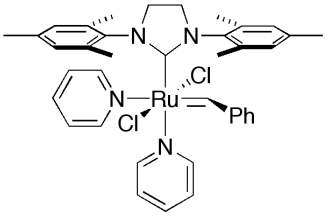

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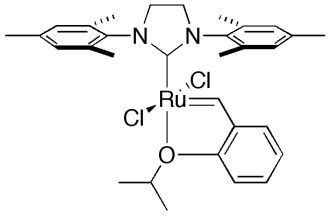


7

Due to its success, the effects of altering the ligand sphere of catalyst **5** have been widely researched.[65-86] A variety of NHC ligands have been examined.[64-76] These ligands include enantiopure, chiral NHC ligands for the production of stereoselective ruthenium metathesis catalysts.[65-68] Moreoever, the chlorides of catalyst **5** have been replaced with a variety of ligands such as alkoxides,[66,67,77,78] carboxylates,[79-81] sulfonates,[80] and other halides.[82] Also, the reaction of catalyst **5** with various pyridines yields bis(pyridine) catalysts, such as catalyst **6**,[83] which are fantastic ROMP initiators.[84,85] Finally, incorporating an isopropoxybenzylidene ligand provides a family of catalysts of type **7**, which show increased stability relative to catalysts **4**–**6**.[86]

Biologically Relevant Applications of Olefin Metathesis

Because of their stability and functional-group tolerance, ruthenium metathesis catalysts can be applied to a myriad of synthetic targets, including many molecules of biological interest.[18,87-109] One biological application is their use in the synthesis of bioactive molecules in pharmaceutical research.[18,87] Another application involves the

synthesis of polymers displaying short peptide chains[88-92] or saccharides[93-100] for the study of the interaction of theses molecules with proteins (Figure 1.4).[91-99]

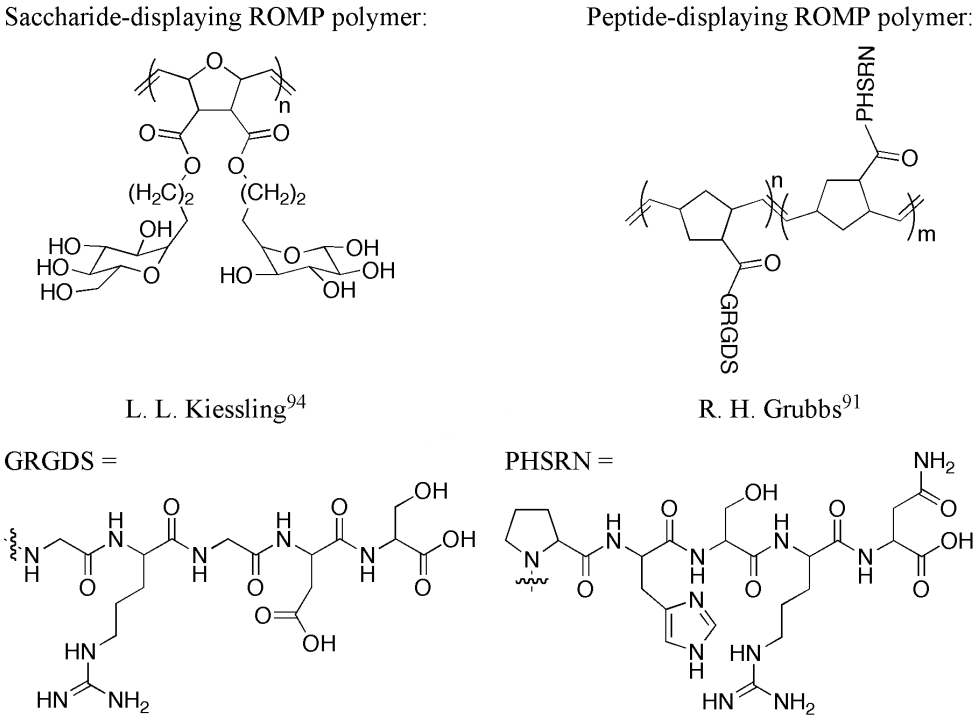
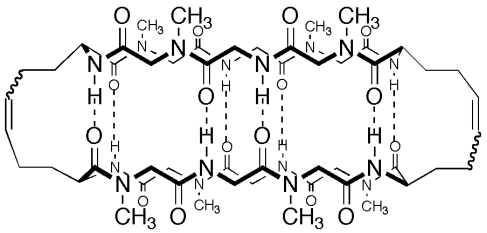


Figure 1.4. ROMP can be used to make polymers with bioactive pendent groups.

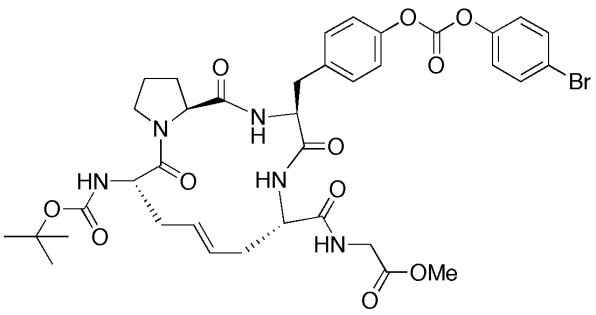
Olefin metathesis is also utilized to stabilize peptide secondary structure (Figure 1.5).[101-109] Ghadiri and coworkers used metathesis to stabilize the dimerization of two cyclic peptides while others have employed metathesis to reinforce a *β*-turn.[101-104] Also, short peptide helices were stabilized by the RCM of olefin side chains incorporated at positions *i* and *i* + 4.[105-107] Finally, replacing a C=O--H-N hydrogen bond that forms between the *i* and *i* + 4 residues at the N-terminus of an *α*-helix with a carbon-carbon bond produced by olefin metathesis encouraged short oligopeptides to form stable *α*-helical structures.[108,109]

Stabilized cyclic peptide dimer:



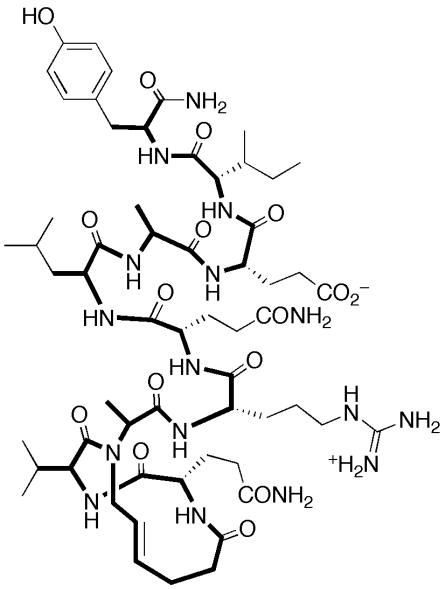
R. Ghadiri[101]

Stabilized peptide β-turn:



R. H. Grubbs[102]

Stabilized peptide α-helix:



P. S. Arora[109]

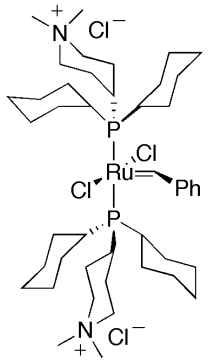
Figure 1.5. Metathesis can be used to stabilize the secondary structure of short peptides.

The utility for metathesis to augment protein structure is amplified by the fact that olefins are orthogonal to the functional groups displayed by the natural amino acids, which allows for the regioselective modification of polypeptides. Furthermore, techniques exist for the site-specific incorporation of unnatural amino acids displaying double bonds.[110-113] Therefore, olefin metathesis has the potential to provide a unique and useful method for both increasing the stability of protein secondary structure and tagging proteins with various probe molecules. However, polypeptides of biological interest are often only soluble in water, a solvent that does not dissolve commonly used and

moisture-tolerant catalysts **3**–**7**. Therefore, a catalyst that is soluble and stable in water is required to realize this potentially powerful application of olefin metathesis.

Olefin Metathesis in Polar Protic Solvents

Interestingly, ruthenium-based metathesis was first reported as a reaction in a polar protic solvent when Michelotti and Keaveney discovered that $RuCl_3$ catalyzed the ROMP of norbornene monomers in ethanol.[45] This result inspired Novak and Grubbs to closely examine the metathesis activity of ruthenium salts.[46] They found that while both ruthenium(II) and ruthenium(III) salts could ROMP norbornene monomers, ruthenium(III) must first disproportionate to form ruthenium(II) prior to productive metathesis.[46] This discovery led to the development of $Ru(H_2O)_6Tos_2$ (Tos = tosylate) as an active ROMP initiator in protic solvents, particularly water.[47,48] While these early ruthenium systems were incapable of catalyzing metathesis with acyclic olefins, they paved the way for the generation of well-defined bis(phosphine) catalyst **3**.



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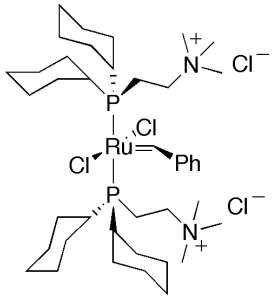


9

Desiring a water-soluble analog of catalyst **3**, Lynn, Mohr, and Grubbs synthesized electron-rich phosphine ligands displaying water-soluble ammonium functional groups.[114] Phosphine exchange with $(PPh_3)_2Cl_2Ru{=}CHPh$ provides water-

soluble catalysts **8** and **9**. Although these catalysts significantly decompose after two days in water, they are stable in methanol for a period of three weeks.[114,115] Also, catalysts **8** and **9** are very air sensitive in solution and decompose slowly when stored under air as a solid. Therefore, these catalysts must be stored and manipulated under an inert atmosphere with degassed solvents.[115,116]

Complexes **8** and **9** are active metathesis catalysts capable of polymerizing water-soluble norbornene and oxanorbornene derivatives **10** and **11** (Figure 1.6).[116] In neutral water, these polymerizations do not proceed to complete conversion and yield polymers with a broad polydispersity index (PDI).[117] However, the addition of hydrochloric acid dramatically increases the rate of polymerization, allowing for quantitative conversion of these monomers to polymers with narrow PDIs.[117] Notably, under acidic conditions, ROMP with these catalysts is a living process and can be readily used to generate block copolymers.[117]

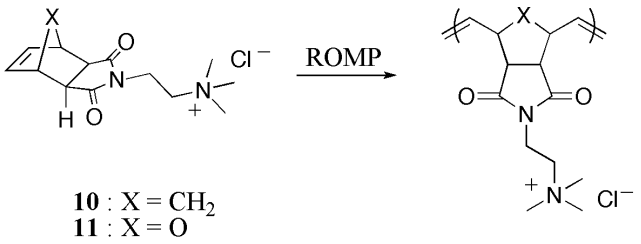
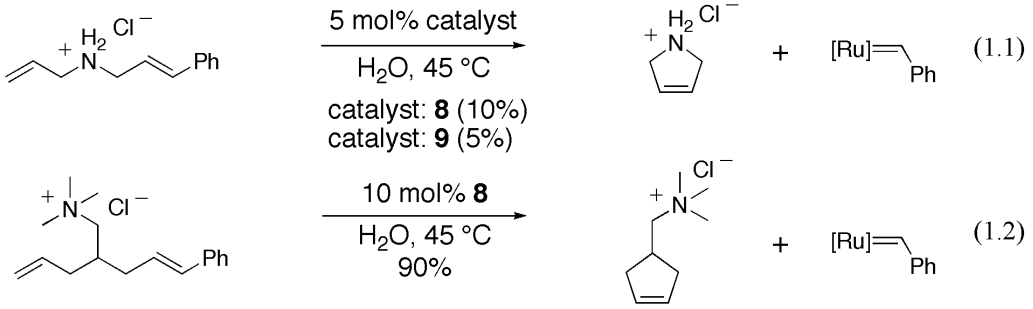


Figure 1.6. Catalysts **8** and **9** can mediate the ROMP of monomers **10** and **11** in a living manner.

The effect of acid on catalysts **8** and **9** is consistent with data on earlier ill-defined aqueous ruthenium metathesis catalysts. These early systems exhibit faster initiation at lower pH and decompose rapidly in an alkaline environment.[46] Catalysts **8** and **9** show the same instability toward base, and the addition of sodium hydroxide results in rapid

catalyst decomposition.[115] The acid possibly stabilizes the propagating species of **8** and **9** by eliminating any hydroxide produced by the autoprotolysis or phosphine deprotonation of water. Indeed, under acidic conditions, the propagating species of **8** and **9** generated during aqueous ROMP can be observed for a period of three months when in the presence of monomer.[117]

Catalysts **8** and **9** can also mediate the metathesis of acyclic substrates. Particularly, they are capable of RCM with a variety of substrates in polar protic media.[116] However, the methylidene derivatives of these complexes, [Ru]=CH_2, are highly unstable in methanol and water.[115,118] Therefore, successful ring closing with these catalysts requires substrates that avoid producing the methylidene intermediate, which is the propagating species for reactions involving two terminal olefins.[119,120] This is accomplished by employing ring-closing substrates that include one terminal and one substituted olefin (eqs 1.1 and 1.2). Metathesis with the terminal olefin is kinetically favored.[121,122] Hence, these catalysts first react with the terminal olefin prior to ring closing with the substituted olefin to generate the cyclic product and a ruthenium alkylidene. The ring-closed product of these substrates is identical to that of a substrate containing two terminal olefins.



(1.1)

(1.2)

Special emphasis should be placed on the RCM reactions shown in eqs 1.1 and 1.2. These are the first examples of successful RCM in water with any metathesis catalyst. However, higher catalyst loadings are required for aqueous RCM due to poor catalyst stability in water.[118]

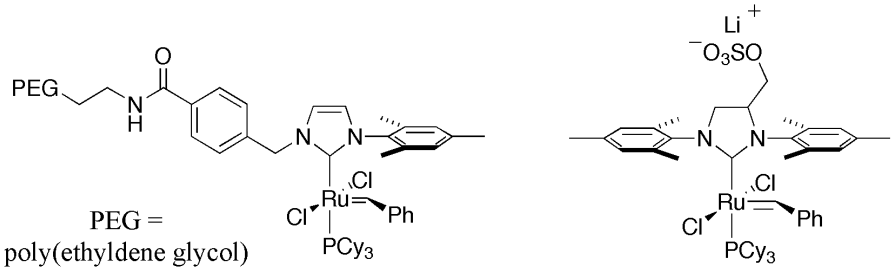
Analysis of catalysts **8** and **9** in deuterium oxide and methanol-d_4 reveal a novel reactivity of the alkylidene protons of the two catalysts in polar protic solvents.[123] When dissolved in deuterated methanol and water, the alkylidene protons of **8** and **9** participate in nondestructive exchange with the present deuterium. Furthermore, solutions of **3** in dichloromethane-d_2/methanol-d_4 solvent mixtures also display deuterium exchange at the alkylidene position. This indicates that this exchange behavior may be general to an entire family of ruthenium alkylidenes, though previously unobserved.

Thesis Research

Catalysts **8** and **9** were the first well-defined catalysts for aqueous olefin metathesis. However, they are not sufficiently stable and active to catalyze the full range of metathesis reactions in water. This thesis describes efforts to develop catalysts with improved stability and activity in water.

The increased stability and activity of NHC-containing olefin metathesis catalysts over their bis(phosphine) analogs inspires the production of water-soluble catalysts like **12** (Chapter 2).[56,124,125] The hypothesis is that the benefits that NHC ligands provide ruthenium-based olefin metathesis catalysts used in aprotic solvents will also be observed in their water-soluble analogs. Consistent with this hypothesis, catalyst **12** does show increased ROMP activity in water over water-soluble bis(phosphine) catalyst **7**.[126]

However, as described in Chapter 2, complex **12** is unable to mediate the metathesis of acyclic substrates in water and is less active than parent catalyst **4** in aprotic solvents.



12 **13**

A consideration of the structure and activity of catalyst **12** prompts various strategies to generate water-soluble metathesis catalysts with improved stabilities and activities (Figure 1.7). Chapter 3 describes early attempts to synthesize complexes resembling those shown in Figure 1.7. These efforts include the production of ruthenium complex **13**, which displays the sulfate group from the backbone of its NHC ligand.

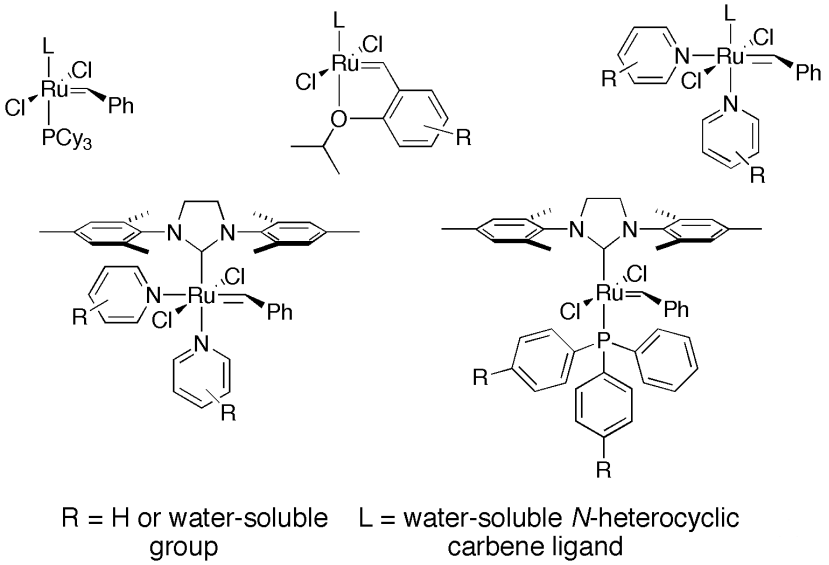
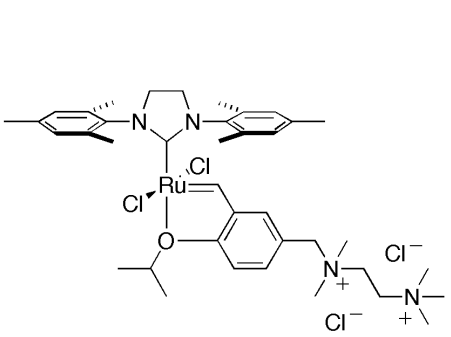


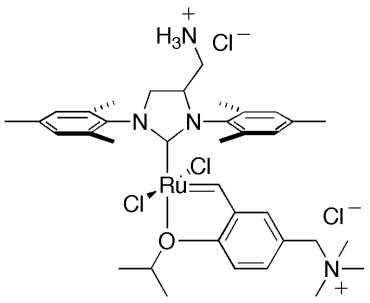
Figure 1.7. A variety of ligands can be employed to produce water-soluble, NHC-containing olefin metathesis catalysts.

Though **13** is more soluble in methanol than parent catalyst **5**, it is not soluble in water. Furthermore, attempts to incorporate other water-soluble ligands onto complex **13** fail to produce a water-soluble catalyst. While catalyst **13** was eventually abandoned, research centered on its development provided compounds that later played a vital role in the production of catalysts with improved stabilities and activities in water.

Examining the decomposition of the methylidene derived from catalyst **5** in the presence of water reveals that the tricylcohexylphosphine ligand plays an active role in catalyst decomposition (Chapter 4).[127] This prompts the pursuit of water-soluble analogs of phosphine-free catalyst **7**. Indeed, catalysts **14** and **15**, which are water-soluble analogs of complex **7**, are far more stable and active in water than earlier catalysts **8**, **9**, and **12**.[128,129]



14



15

The synthesis and activity of catalysts **14** and **15** is discussed in Chapter 5.[128,129] These catalysts both show increased ROMP activity over water-soluble catalysts **9** and **12**. More importantly, catalysts **14** and **15** both competently mediate RCM reactions in water and are among the only catalysts that can cyclize α,ω-dienes in neat water. Gratifyingly, though the substrate scope is limited, **14** and **15** can also catalyze cross-metathesis reactions in water. Indeed, catalyst **14** enables cross-metathesis reactions

between an olefin-displaying ruthenium dye and a few different cross partners.[129] While the conversions for these reactions are moderate at best, they are the first examples of cross metathesis between two different olefins in neat water.

Summary

Transition metal catalysis has greatly expanded the number of reactions available to synthetic chemists.[2-12] One particularly useful metal-catalyzed reaction is olefin metathesis, which mediates the exchange of two olefins' substituents.[18,19] Ruthenium-centered catalysts have proven particularly useful for this transformation.[43,47,57] Moreover, the excellent tolerance of ruthenium catalysts for moisture allows for the production of metathesis catalysts that are soluble and active in water.[46-48,114-117] This thesis describes the development of new, water-soluble, phosphine-free olefin metathesis catalysts.[128,129] These catalysts are more active than their predecessors and enable a greater range of metathesis transformations in water.

Finally, this author would be negligent to ignore the work of others in the area of aqueous olefin metathesis.[130-142] The facile catalysis of metathesis in water is a highly desirable goal and has been pursued by many scientists. Much of this work occurred concurrently with the research presented in this thesis and will be described in later chapters in more detail.

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CHAPTER 2

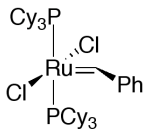
A PEG-Displaying Water-Soluble Olefin Metathesis Catalyst Containing an *N*-Heterocyclic Carbene Ligand

Abstract

The synthesis of an olefin metathesis catalyst displaying a poly(ethylene glycol) (PEG) chain from its *N*-heterocyclic carbene ligand is described. The PEG chain facilitates the dissolution of this catalyst in both aprotic and protic solvents, including water. While it appears to form aggregates resembling micelles in water, this catalyst is active in water and readily catalyzes the aqueous ring-opening metathesis polymerization of norbornene derivatives. The catalyst can mediate ring-closing metathesis reactions in both aprotic and protic organic solvents but is unable to perform metathesis on acyclic substrates in water. Also, the catalyst demonstrates the potential to use PEG's solubility properties to remove ruthenium from metathesis product mixtures.

Introduction

As outlined in Chapter 1, ruthenium complexes **1**–**4** are stable and active olefin metathesis catalysts that enable a variety of reactions useful in small-molecule,[1-3] macromolecular,[1,4,5] and supramolecular synthesis.[6-8] Also, since their first discovery, ruthenium-based metathesis catalysts have shown a tremendous resilience to polar protic solvents including water.[9-11] This stability toward moisture allowed for the development of water-soluble bis(phosphine) catalysts **5** and **6**.[12-15] These catalysts were capable of performing ROMP in water in a living manner and were the first catalysts to mediate ring-closing metathesis in polar protic solvents.[16] However, the inadequate stability of their alkylidene and methylidene derivatives limited the ability of catalysts **5** and **6** to perform metathesis on acyclic substrates in water.[15]



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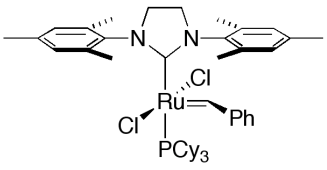

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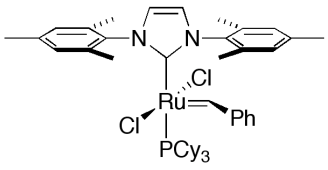

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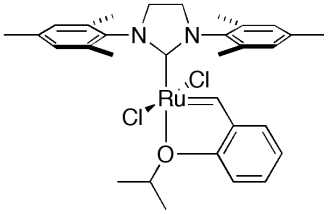

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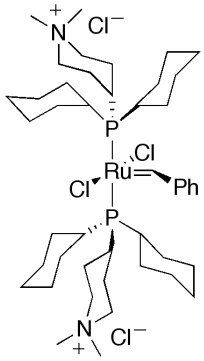

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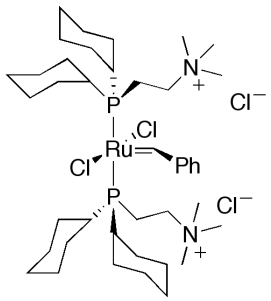


6

Ruthenium complexes **2** and **3**, which contain an *N*-heterocyclic carbene (NHC) ligand, are both more stable and more active than their bis(phosphine) counterparts.[17-19] Moreover, tethering the isopropoxybenzylidene ligand of catalyst **4** to a polyethylene glycol (PEG)-displaying resin produces a catalytic system capable of performing ring-closing metathesis in both methanol and water.[20] However, this catalytic resin is incapable of performing metathesis on hydrophilic substrates in water and is, therefore, believed to perform metathesis within the pores of the resin instead of the surrounding water.[20] This chapter describes the synthesis of a homogenous, water-soluble catalyst that harnesses the increased activity provided by an NHC ligand.

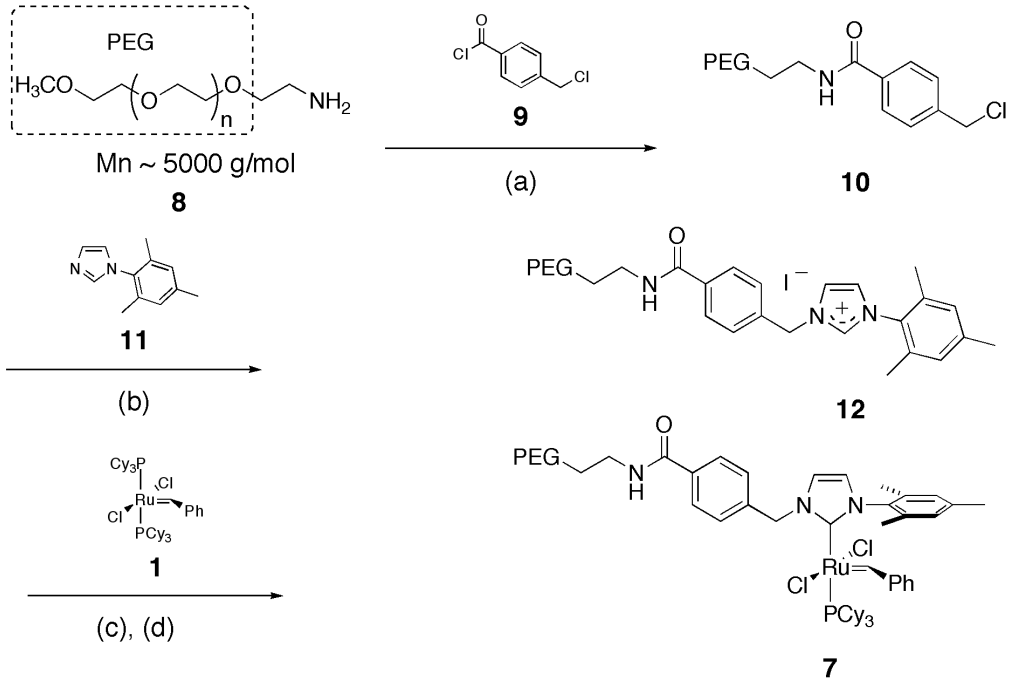
Results and Discussion

Catalyst synthesis and characterization. PEG was chosen to facilitate the targeted catalyst's solubility in water. PEG was anticipated to render this catalyst soluble in both water and also some common organic solvents but insoluble in diethyl ether. This solubility profile may allow for the facile removal of the PEG catalyst from organic products. For example, the catalyst could be removed from organics simply by the precipitation of the product mixture into diethyl ether. With these goals in mind, catalyst **7**, which incorporates PEG onto one of the nitrogen substituents of its NHC ligand, was synthesized (Scheme 2.1).

The synthesis of catalyst **7** is straightforward and is accomplished in three steps. Mixing PEG amine **8** (MW ≈ 5000 g/mol) with acid chloride **9** in the presence of proton-scavenging pyridine and dimethylamino pyridine (DMAP) catalyst yields benzyl chloride **10**. The sodium-iodide-catalyzed reaction of **10** with mesityl imidazole (**11**) then produces imidazolium salt **12**. Finally, the deprotonation of **12** with potassium *tert*-

butoxide followed by ligand exchange with ruthenium bis(phosphine) complex **1** gives catalyst **7** in moderate yield.

Scheme 2.1.

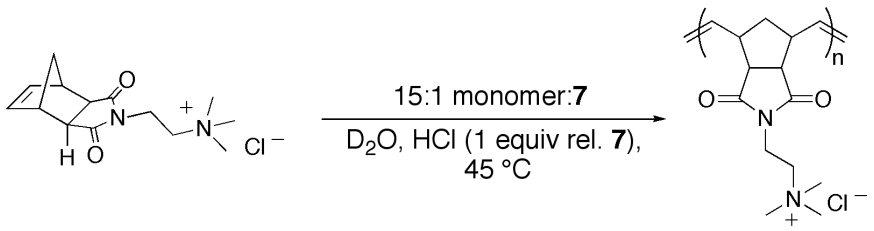


Reagents and conditions: (a) DMAP, pyridine, CH_2Cl_2, 25 °C, 4 h (87%), (b) NaI, acetone, 60 °C, 14 h (98%), (c) KO^tBu, toluene, 25 °C, 15 min, (d) **1**, toluene, 25 °C, 20 min (58 %).

The characterization of catalyst **7** is complicated by the presence of the large, polydisperse PEG chain. Even so, the catalyst can be characterized by NMR spectroscopy in deuterated benzene. The benzylidene proton resonance at 19.7 ppm in the ^{1}H NMR spectrum is consistent with a catalyst containing an NHC ligand.[21,22]

The PEG chain does facilitate the solubility of catalyst **7** in organic solvents such as dichloromethane and toluene, though it is insoluble in diethyl ether. Furthermore, catalyst **7** readily forms homogenous solutions in both methanol and water. However, in water, catalyst **7**'s ^{1}H NMR spectrum is very different from the spectrum obtained in

benzene and cannot be readily assigned. Initially, this result was interpreted to arise from rapid catalyst decomposition in water. However, later research on a different PEG-containing ruthenium metathesis catalyst revealed that, in water, it formed micelle-like aggregates.[23] The ^{1}H NMR spectrum of this catalyst in water closely resembled the spectrum of catalyst **7** in water. Therefore, it is now believed that catalyst **7** also forms micelle-like aggregates in water.



13 **14**

Catalyst activity. The ring-opening metathesis polymerization (ROMP) of *exo*-norbonene monomer **13** was used to investigate the reactivity of catalyst **7** in water. In deuterium oxide at 45 °C, catalyst **7** initiated the ROMP of **13** to give polynorbornene **14** in 73% conversion after 24 hours, as measured by ^{1}H NMR spectroscopy. Further conversion was not observed even after an additional 12 hours at 45 °C. However, the addition of one equivalent of hydrochloric acid allowed catalyst **7** to polymerize monomer **13** to 95% conversion within 15 minutes. This observation is consistent with mechanistic studies by Grubbs and co-workers, which showed that phosphine dissociation from catalysts **1**–**3** is required for entry into the catalytic cycle.[24] It is believed that dissociation of phosphine from catalyst **7** might be disfavored in water due to the energetic cost of solvating two neutral molecules. Thus, protonation of phosphine by hydrochloric acid scavenges free phosphine, which in turn promotes phosphine

dissociation, thereby increasing catalyst activity. Additionally, studies of water-soluble bis(phosphine) catalysts **5** and **6** showed that the addition of 0.3 to 1.0 equivalents of hydrochloric acid increased catalyst activity with the concomitant observation of protonated phosphine.[13-15]

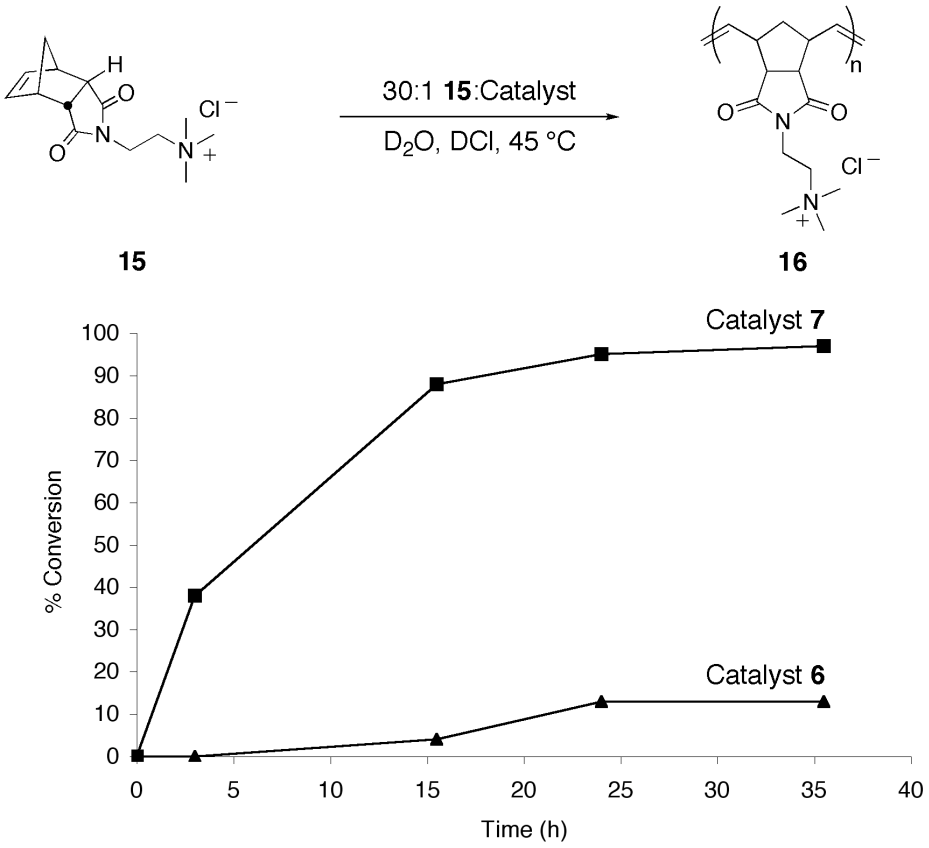
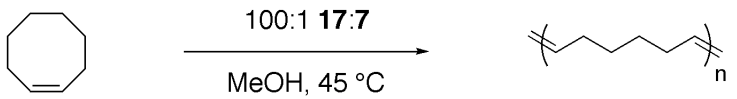


Figure 2.1. The relative activities of catalysts **6** and **7** were examined using the ROMP of challenging *endo*-norbornene monomer **15**.

Earlier work demonstrated that *endo*-norbornene monomers are challenging ROMP substrates.[25,26] For this reason, the ROMP of *endo*-norbornene **15** was used to compare the activities of catalyst **7** and the bis(phosphine) catalyst **6** (Figure 2.1). Gratifyingly, catalyst **7** was able to effect the ROMP of hindered norbornene **15**, and the polymerization proceeded to 95% conversion within 24 hours as judged by ^{1}H NMR

spectroscopy. The ROMP of **15** with catalyst **6** was slower and proceeded to only 13% conversion after 24 hours (Figure 2.1). These results suggest that, in aqueous media, the NHC-containing catalyst, **7**, is significantly more active for the polymerization of hindered norbornenes than the previous generation of bis(phosphine) catalysts.

Although an active catalyst species was not detected spectroscopically, the relatively long reaction times required to completely polymerize **15** suggested that some potentially active species must be present in solution beyond 24 hours. To further investigate the lifetime of **7** in solution, upon completion of the reaction detailed in Figure 2.1, the catalyst **7** reaction mixture was incubated at room temperature for 56 hours prior to the addition of ~8 equivalents of *exo*-monomer **13**. After 24 hours at 45 °C, ^{1}H NMR spectroscopy showed that 87% of the newly added monomer had been converted to polymer. In contrast, the addition of monomer **13** to a solution of **7** in acidic deuterium oxide that had undergone the same schedule of heating and standing gave only 4% polymer after 24 hours at 45 °C. This implies that some metathesis-active species is generated during ROMP with **7** that is more stable in acidic water than the parent benzylidene.

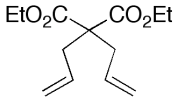
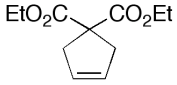
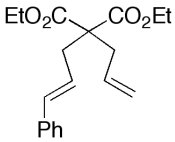
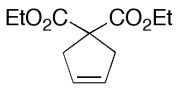
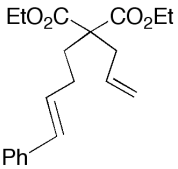
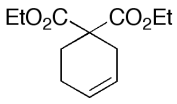


17 **18**

In methanol, polymerization of cyclooctene by catalyst **7** goes to 86% conversion within 14 hours at 45 °C, which demonstrates this catalyst's activity in protic organic solvents. To further examine the activity of **7**, several ring-closing metathesis reactions were attempted in methanol (Table 2.1). As an initial test, the ring closing of diethyl

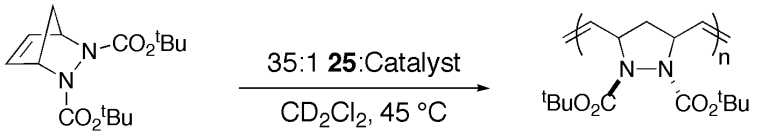
diallylmalonate (**19**) was attempted. Although the conversion for this transformation was low (40%), it represented a significant improvement over previous results with methanol-soluble bis(phosphine) catalysts (less than 5% product).[16] The low yields for the bis(phosphine) catalysts were attributed to the instability of the ruthenium methylidene intermediate produced after a single turnover.[16] Consistent with this hypothesis, ring-closing reactions using the phenyl-substituted substrates **21** and **23**, which avoid the methylidene intermediate, gave higher yields of cyclized product with bis(phosphine) catalysts **5** and **6**.[16] Similarly, catalyst **7** also generated higher cyclized yields with substrate **21** and **23** than with **19**, which suggests that the methylidene derivative of **7** is also unstable or less active in methanol**.** Accordingly, the cross metathesis of terminal olefins, which must proceed through a methylidene intermediate,[27] has currently been unsuccessful in protic media.

Table 2.1. Ring-closing metathesis reactions in methanol with catalysts **5**, **6**, and **7**

Substrate	Product	% Conversion with Catalyst		
		7[a]	**5**[b]	**6**[b]
 **19**	 **20**	40	<5	0
 **21**	 **22**	62	80	95
 **23**	 **24**	82	45	55

[a]Reactions were performed at 45 °C with 5 mol% catalyst and an initial substrate concentration of 0.2 M in methanol-d_4. Conversions were measured by ^{1}H NMR spectroscopy. [b]Data from reference 16.

Catalyst **7** also showed activity in aprotic organic solvents. For example, **7** mediates the ring-closing metathesis of substrate **19** in dichloromethane in 96% conversion, as measured by ^{1}H NMR spectroscopy. To further examine the activity of **7** in aprotic solvents, challenging monomer **25** was used to compare the activity of **7** to parent catalyst **3** in dichloromethane. This monomer has previously been polymerized by a molybdenum catalyst.[28] However, the polymerization of 35 equivalents of monomer **25** with catalyst **1** at 45 °C in dichloromethane proceeds in only 8% conversion after 24 hours.[29] Consistent with the increased activity of catalysts containing an NHC ligand, under the same conditions, catalyst **3** mediates the ROMP of monomer **25** to polymer **26** in 88% conversion after 24 hours.[29] In contrast, PEG catalyst **7** is unable to polymerize monomer **25** even after extended reaction times. This loss of activity is not fully understood but is likely the result of poor catalyst stability and/or the long PEG chain limiting access to catalyst **7**'s ruthenium center.



25 **26**

Catalyst **7** is insoluble in diethyl ether. Therefore, precipitation of a reaction mixture followed by filtration is expected to provide a simple way to remove **7** from organic products. This is an attractive feature as ruthenium by-products are often difficult to remove from metathesis reactions.[30,31] Gratifyingly, precipitation of the reaction mixture from the ring-closing of **23** with catalyst **7** (Table 2.1) from diethyl ether followed by filtration reduces the mixture's PEG content by nearly 97%.[29] While the diminution of the mixture's PEG content does not guarantee a reduction of its ruthenium

content, this is a promising result for the proposed strategy of ruthenium extraction. Indeed, later research demonstrates that PEG's solubility properties can be used to remove ruthenium form olefin metathesis product mixtures.[18,32]

Summary

This chapter described the synthesis and activity of PEG-displaying catalyst **7**, which was the first homogenous olefin metathesis catalyst containing an NHC ligand that was soluble and active in water. While **7** appeared to form aggregates resembling micelles in water, it was active in water and readily mediated the aqueous ROMP of monomer **13**. Catalyst **7** showed increased activity over catalyst **6** for the ROMP of challenging *endo*-norbornene monomer **15** in water, and, though **7** was unable to perform ring-closing metathesis or cross metathesis in water, it was able to cyclize dienes **19**, **21**, and **23** in methanol. In addition, **7** performed metathesis in aprotic organic solvents, although it showed a lower activity than parent catalyst **3**. Finally, catalyst **7** was used to demonstrate the potential for utilizing the solubility properties of PEG to remove ruthenium from olefin metathesis product mixtures.

Acknowledgements

First and foremost, the author wishes to acknowledge the extensive contributions of Professor Justin P. Gallivan to this work. The PEG catalyst was his idea, and he performed many of the experiments described in this chapter. Drs. J. P. Morgan, Jen Love, Tina Trnka, Steve Goldberg, and Brian Connell are also acknowledged for helpful discussions.

Experimental

General considerations. All glove-box manipulations were performed in a N_2-filled Vacuum Atmospheres glove box (O_2 < 2.5 ppm). Otherwise reactions run under inert conditions were performed using standard Schlenk techniques under an atmosphere of dry argon employing flame or oven-dried glassware. All NMR spectra were recorded on a Varian Mercury 300 (299.817 MHz for ^{1}H, 75.4 MHz for ^{13}C, and 121 MHz for ^{31}P) and reported in parts per millon (ppm) downfield from trimethylsilane as referenced to residual protio solvent peaks. Multiplicity abbreviations used when reporting ^{1}H NMR spectra are: s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet, br = broad. All thin-layer chromatography (TLC) of organic compounds was accomplished on silica-gel 60 F254 percoated plates with a fluorescent indicator and visualized by UV light and/or by standard potassium permanganate stains. All flash chromatography of organic compounds was performed with silica-gel 60 (230–400 mesh).

Materials. All deuterated solvents and deuterium chloride were purchased from Cambridge Isotope Laboratories. Deuterated dichloromethane was dried over 4 Å molecular sieves, and deuterated methanol was dried over calcium sulfate. Both deuterated methanol and deuterated dichloromethane were degassed by three freeze, pump, and thaw cycles while deuterium oxide was degassed by a generous argon sparge. All other solvents were purchased from Fischer Scientific. Solvents were dried by passage through purification columns packed with alumina and degassed by a generous argon sparge. All commericial materials were used as obtained, and ruthenium complex **1**

was a gift from Materia. 4-(chloromethyl)Benzoyl chloride (**9**), *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride, *N,N*-dimethyl-ethylenediamine, anhydrous pyridine, potassium *tert*-butoxide, 4-dimethylaminopyridine, and Amberlite IRA-400(Cl) ion-exchange resin were purchased from Aldrich. Molecular weight 5000 methoxy poly(ethylene glycol) amine (**8**) was purchased from Shearwater, and sodium iodide was purchased from Mallinckrodt. Sodium sulfate was purchased from EMS, and iodomethane was purchased from Alfa Aesar. 1-Mesitylimidazole (**11**),[33] monomer **13**,[14] substrate **21**,[34] substrate **23**,[16] monomer **25**,[28] and catalysts **3**[21] and **6**[12] were prepared following literature procedures.

Synthesis of 4-chloromethyl-*N*-{methoxy-poly(ethylene glycol)}-benzamide (10). A flame-dried round-bottom flask, equipped with a stir bar, was charged with compound **8** (3.5 g, 0.67 mmol) and compound **9** (298 mg, 1.6 mmol, 2.4 equiv). The solids were dissolved in dry, degassed dichloromethane (15 mL) followed by the addition of 4-dimethylaminopyridine (56 mg, 0.46 mmol, 0.70 equiv) and anhydrous pyridine (200 μL, 0.025 mmol, 0.037 equiv). The reaction was allowed to continue for 2.5 hours at ambient temperature under a positive argon pressure. The product was isolated by precipitation of the reaction mixture into diethyl ether (200 mL) followed by vacuum filtration. The filtered solid was rinsed generously with diethyl ether and purified by column chromatography (6% methanol in chloroform) to obtain 2.8 g (77%) of a white, crystalline product. ^{1}H NMR ($CDCl_3$, ppm): δ 7.79 (d, J = 8.1 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 6.96 (s, 1H), 4.58 (s, 2H), 3.81–3.40 (broad m), 3.35 (s, 3H). ^{13}C NMR ($CDCl_3$,

ppm): δ 166.62, 140.40, 134.372, 128.40, 127.47, 73.57, 71.76, 70.40 (br, polymeric), 58.89, 45.35, 39.69.

Synthesis of 1-(4-{methoxy poly(ethylene glycol) carbamoyl}-benzyl)-3-(2,4,6-trimethyl-phenyl)-3*H*-imidazol-1-ium; idodide (12). A flask, equipped with stir bar, was charged with compound **10** (2.5 g, 0.46 mmol), compound **11** (107 mg, 0.58 mmol, 1.3 equiv), sodium iodide (150 mg, 1.0 mmol, 2.2 equiv), and acetone (25-30 mL). The reaction flask was attached to a condenser and brought to reflux (~60 ˚C). After refluxing overnight (14 h), the product was isolated by precipitation of the reaction mixture into diethyl ether (200 mL) followed by vacuum filtration. The product was rinsed with diethyl ether, dissolved in dichloromethane, and dried over sodium sulfate. The volatiles were removed by rotary evaporation before lyophilization from benzene yielded 2.2 g (83%) of a pale yellow powder. ^{1}H NMR ($CDCl_3$, ppm): δ 9.96 (s, 1H), 7.82 (s, 1H), 7.75 (d, J = 8.1 Hz, 2H), 7.54 (d, J = 8.1 Hz, 2H), 7.18 (s, 2H), 6.86 (s, 2H), 5.87 (s, 2H), 3.64–3.41 (broad m), 3.23 (s, 3H), 2.20 (s, 3H), 1.93 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 166.37, 140.98, 136.87, 136.45, 135.21, 133.89, 130.34, 129.56, 128.65, 128.00, 123.40, 123.34, 73.57, 71.67, 70.31 (br, polymeric), 58.81, 52.39, 39.56, 20.97, 17.66.

Synthesis of PEG-conjugated catalyst (7). In a N_2-filled glove box, compound **12** (527.7 mg, 0.092 mmol), ruthenium complex **1** (117 mg, 0.14 mmol, 1.5 equiv), and potassium *tert*-butoxide (10.6 mg, 0.094 mmol, 1.0 equiv) were weighed into separate vials. The potassium *tert*-butoxide was transferred into the vial containing compound **12** using dry, degassed toluene (10–11 mL). The reaction mixture, consisting of undissolved

PEG-ligand and potassium *tert*-butoxide in a clear, yellow solution, was mixed vigorously and allowed to react for 20 minutes prior to the addition of ruthenium complex **1.** The dark maroon solution was mixed vigorously and removed from the glove box. The product mixture was filtered through celite, and the product was isolated by precipitation into diethyl ether (150 mL) followed by vacuum filtration while minimizing exposure to air. The product was lyophilized from benzene to obtain 258.6 mg (46%) of a light brown powder. ^{1}H NMR (C_6D_6, ppm): δ 19.7 (benzylidene proton resonance), ^{31}P NMR (C_6D_6, ppm): δ 37.5. (Note: This reaction gave inconsistent yields and did not always provide product. Optimization of the reaction conditions would likely solve this problem, but its poor activity precipitated the abandonment of this catalyst prior to such an optimization.)

Synthesis of *endo*-*N*-(*N*',*N*'-dimethylammonio)ethyl-bicyclo[2.2.1]hept-5-ene-2,3-dicarboximide. A flame-dried round-bottom flask, equipped with a stir bar, was charged with c*is*-5-norbornene-*endo*-2,3-dicarboxylic anhydride (1.03 g, 6.3 mmol), *N,N*-dimethyl-ethylenediamaine (0.67 mL, 6.1 mmol, 0.97 equiv), and dry, degassed benzene (50 mL). This flask was equipped with a Dean-Stark trap and a reflux condenser, and the reaction mixture was heated to 110 ˚C and stirred for 18 hours at this temperature. Upon cooling to room temperature, the volatiles were removed by rotary evaporation to yield a dark maroon, highly viscous liquid. Distilled water (30 mL) was added and the solution was made acidic with concentrated hydrochloric acid. The water layer was rinsed with diethyl ether (5×), neutralized with sodium bicarbonate, and extracted with diethyl ether (5×). The combined diethyl ether extracts were dried over sodium sulfate, and the

volatiles were removed by rotary evaporation to obtain a flaky, white solid, which was dried under high vacuum to give 630 mg (44%) of product. ^{1}H NMR ($CDCl_3$, ppm): δ 6.03 (dd, J = 1.8Hz, 2H), 3.39 (t, J = 7.0 Hz, 2H), 3.34–3.31 (m, 2H), 3.22 (d, J = 1.5 Hz, 1H), 3.21 (d, J = 1.5 Hz, 1H), 2.27 (t, J = 7.0 Hz, 2H), 2.17 (broad s, 6H), 1.67 (dt, J_D = 8.6Hz, J_T = 1.8Hz , 1H), 1.49 (doublet of broad singlets, J = 8.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, ppm): δ 177.62, 134.36, 56.36, 52.20, 45.88, 45.51, 44.97, 36.33.

Synthesis of *endo*-*N*-(*N*',*N*',*N*'-trimethylammonio)ethyl-bicyclo[2.2.1]hept-5-ene-2,3-dicarboximide; chloride (15). A round-bottom flask, equipped with a stir bar, was charged with *endo*-*N*-(*N*',*N*'-dimethylammonio)ethyl-bicyclo[2.2.1]hept-5-ene-2,3-dicarboximide (433 mg, 1.9 mmol), iodomethane (0.57 mL, 9.2 mmol, 4.8 equiv), and THF (9 mL). The reaction mixture was stirred at room temperature for 10 minutes. The product precipitated during the course of the reaction and was isolated by vacuum filtration and rinsed liberally with diethyl ether. The product was dissolved in a minimal amount of distilled water and passed through a column packed with Amberlite IRA-400(Cl) ion-exchange resin to generate the chloride salt. Water was removed by lyophilization to obtain 447 mg (85%) of a white, solid product. ^{1}H NMR (D_2O, ppm): δ 6.13 (dd, J = 1.8 Hz, 2H), 3.84 (t, J = 7.5 Hz, 2H), 3.51 (d, J = 1.7 Hz, 1H), 3.50 (d, J = 1.7 Hz, 1H), 3.39–3.34 (m, 4H), 3.16 (s, 9H), 1.72 (dt, J_D = 9.0 Hz, J_T = 1.7 Hz, 1H), 1.61 (doublet of broad singlets, J = 9.0 Hz, 1H). ^{13}C NMR (D_2O, ppm): δ 180.71, 134.69, 61.66, 53.34, 52.25, 46.12, 44.99, 32.10.

General procedures for experiments comparing the ring opening metathesis polymerization of monomer 15 with catalysts 6 and 7. In a N_2-filled glove box, compound **15** (25 mg, 0.095 mmol, 30 equiv) and catalyst (0.0032 mmol) were weighed directly into a screw-cap NMR tube. Outside of the glove box, a solution of 0.0032 M deuterium chloride and 0.031 M 3-(trimethylsilyl)-1-propane sulfonic acid, sodium salt in degassed deuterium oxide (1 mL) was added to each sample using an air-tight syringe. The samples were heated to 45 ˚C, and the reaction conversions were followed using ^{1}H NMR spectroscopy (reported times reflect the time spent on heat). For subsequent monomer additions, in a N_2-filled glove box, monomer (7.6 mg, 0.027 mmol, 8.3 equiv) was weighed into a round-bottom flask. This flask was equipped with a stir bar, sealed with a septum and removed from the glove box. Employing standard Schlenk techniques, the monomer was dissolved in degassed deuterium oxide and transferred to the NMR tube containing catalyst **7**.

General procedures for ring-closing metathesis experiments. In a N_2-filled glove box, catalyst **7** (15 mg, 0.0024 mmol) and substrate (0.048 mmol, 20 equiv) were weighed into a screw-cap NMR tube. Methanol-d_4 (0.6 mL) was added, and the tube was sealed with a septa-cap. Outside of the box, the reaction mixture was heated to 45 °C, and the conversion was followed by ^{1}H NMR spectroscopy. For substrate **19**, 0.01 mmol of catalyst and 0.2 mmol of substrate were mixed in 1 mL of deuterated methanol.

General procedures for comparing the ring opening metathesis polymerization of monomer 25 with catalysts 1, 2, and 7. In a N_2-filled glove box, catalyst (0.0033 mmol)

was weighed into a screw-cap NMR tube. The tube was sealed with a septa-cap and removed from the glove box. A 0.11 M solution of monomer **25** in dry, degassed deuterated dichloromethane (1.0 mL, 33 equiv) was added to this NMR tube using an air-tight syringe. The sample was heated to 45 °C, and its conversion was followed using ^{1}H NMR spectroscopy.

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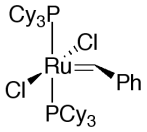
CHAPTER 3

Initial Efforts to Develop a Small-Molecule Water-Soluble Olefin Metathesis Catalyst Containing an *N*-Heterocyclic Carbene Ligand

Abstract

Early research pursuing a discrete, water-soluble olefin metathesis catalyst containing an *N*-heterocyclic carbene (NHC) ligand is reported. Two general strategies for generating the desired catalyst are outlined. The first strategy incorporates water-soluble groups into the NHC ligand. The second strategy incorporates water-soluble groups onto phosphine, pyridine, and isopropoxybenzylidene ligands, which are ligands that dissociate during metathesis reactions. The syntheses of ligands and ruthenium complexes inspired by these two strategies are described.

Introduction



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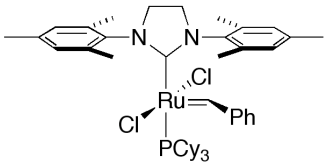

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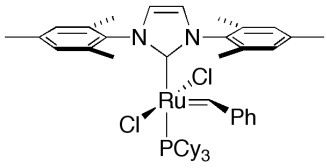

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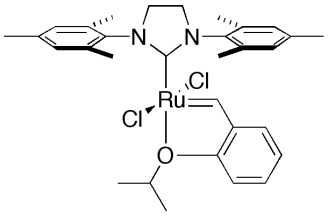

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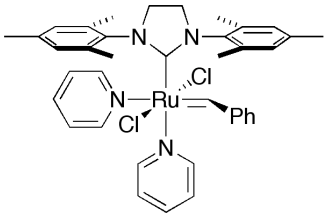

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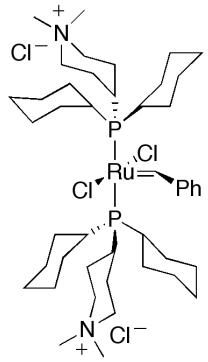

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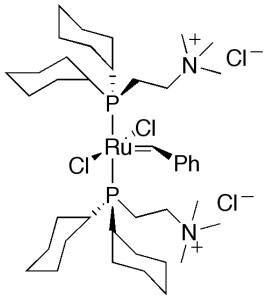

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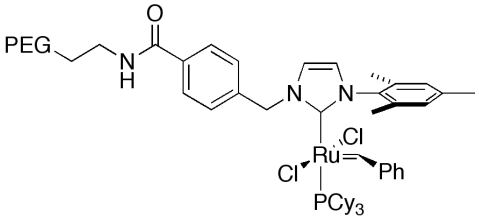

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Earlier chapters describe the development and utility of catalysts **1**–**8** and their impact on olefin metathesis.[1-14] Of particular interest to this chapter are catalysts **6**–**8**, which are soluble and operate in polar protic solvents, including water.[9-14] The first homogenous, well-defined water-soluble catalysts, complexes **6** and **7**, are capable of performing ring-opening metathesis polymerization (ROMP) in water and show limited ring-closing metathesis activity in polar protic solvents.[9-13] The development of catalyst **8**

is described in Chapter 2. This catalyst also shows metathesis activity in polar protic solvents.[14]

The increased stability and activity of *N*-heterocyclic carbene (NHC)-containing olefin metathesis catalysts over their bis(phosphine) analogs inspires the production of water-soluble catalysts like **8**.[15-17] The hypothesis is that the benefits that NHC ligands impart on ruthenium-based olefin metathesis catalysts used in aprotic solvents will also be observed in their water-soluble analogs. Consistent with this hypothesis, catalyst **8** does show increased ROMP activity in water over the water-soluble bis(phosphine) catalyst **7**.[14] However, as described in Chapter 2, complex **8** is unable to mediate the metathesis of acyclic substrates in water and is less active than parent catalyst **3** in aprotic solvents.

Three augmentations of catalyst **8** may yield a water-soluble catalyst with improved stability and activity. First, one of the nitrogen substituents of the NHC ligand of complex **8** positions two benzyl protons close to the ruthenium center. One of the decomposition pathways of metathesis catalysts is ruthenium insertion into a carbon-hydrogen bond presented by a nitrogen substituent of the NHC ligand.[18] Therefore, avoiding the amino-benzyl protons of catalyst **8** should produce a catalyst with greater stability. Second, the NHC ligand of catalyst **8** has an unsaturated backbone. As NHC ligands with saturated backbones yield metathesis catalysts with higher activities,[1,19] trading the unsaturated NHC ligand of catalyst **8** with a saturated analog should increase the catalyst's metathesis activity. Finally, the long, polydisperse poly(ethylene oxide) (PEG) chain of catalyst **8** complicates its characterization and possibly inhibits the approach of substrate molecules to the catalyst's ruthenium center. Thus, catalysts that

replace PEG with water-soluble ionic groups, such as quaternary amines, can be better characterized and may show improved activity over catalysts displaying PEG.

Figure 3.1 illustrates various strategies to generate water-soluble olefin metathesis catalysts, which contain saturated NHC ligands and avoid the amino-benzyl protons of catalyst **8**. As shown in Figure 3.1, water-soluble groups can be incorporated onto the NHC ligand or onto pyridine, phosphine or isopropoxybenzylidene ligands to produce water-soluble analogs of catalysts **3**–**5**. This chapter describes early efforts to synthesize such NHC-containing, water-soluble olefin metathesis catalysts. Although these efforts did not produce a water-soluble catalyst, they did lay the groundwork for future success in aqueous metathesis as described in Chapter 5.

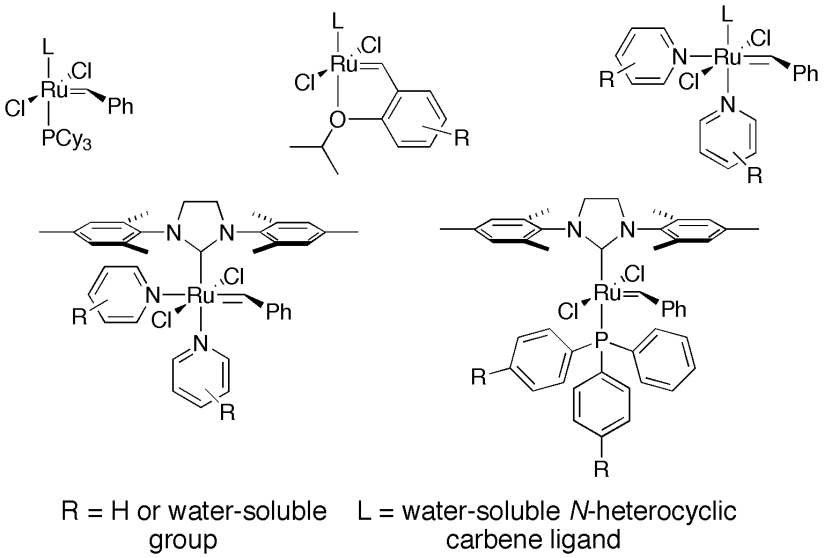


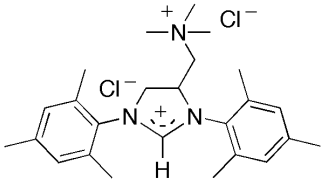
Figure 3.1. Water-soluble groups can be incorporated onto NHC ligands or ligands that dissociate during metathesis reactions to produce NHC-containing olefin metathesis catalysts that are soluble in water.

Results and Discussion

Strategies involving water-soluble NHC ligands. Early efforts to synthesize catalysts with improved stability and activity in water focused on incorporating water-soluble groups onto NHC ligands. The driving force for this direction of research is the persistent coordination of the NHC ligand to the ruthenium center. In contrast, as part of the mechanism of olefin metathesis, water-soluble phosphine, pyridine or isopropoxybenzylidene ligands will dissociate from the metal center to yield a fourteen-electron complex.[20-22] The solubility of the fourteen-electron complex in water is unknown though there is evidence that it prefers a nonpolar environment.[23] Therefore, the solubility of catalysts containing water-soluble groups only on their dissociating ligands may change during a metathesis reaction with possible deleterious effects.[24] In contrast, catalysts that incorporate water-soluble groups onto their NHC ligands should remain dissolved in water throughout the catalytic cycle of olefin metathesis.

NHC ligands containing ammonium salts. Imidazolium salts **9** and **10** were the NHC ligand precursors initially targeted. These salts contain tetraalkylamines as the water-soluble functional group. Ammonium salts were chosen because they are noncoordinating, readily made, and were the functional group employed by catalysts **6** and **7** to achieve solubility in water.[9,11,12] However, care must be taken with the choice of counter-ion for these NHC ligands as anions such as iodide, bromide, carboxylates, and sulfonates are known to replace the chloride ligands of metathesis catalysts to yield ruthenium complexes with lower activities.[20,25-27] The chloride anion was chosen because of its successful use in water-soluble catalysts **6** and **7**. While ruthenium complexes

incorporating **9** and **10** were not produced, precursors **9** and **10** are representative of this strategy of incorporating water-soluble groups onto NHC ligands.



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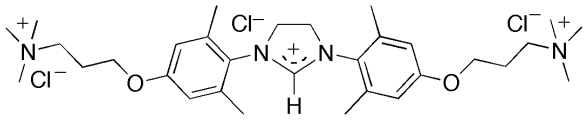

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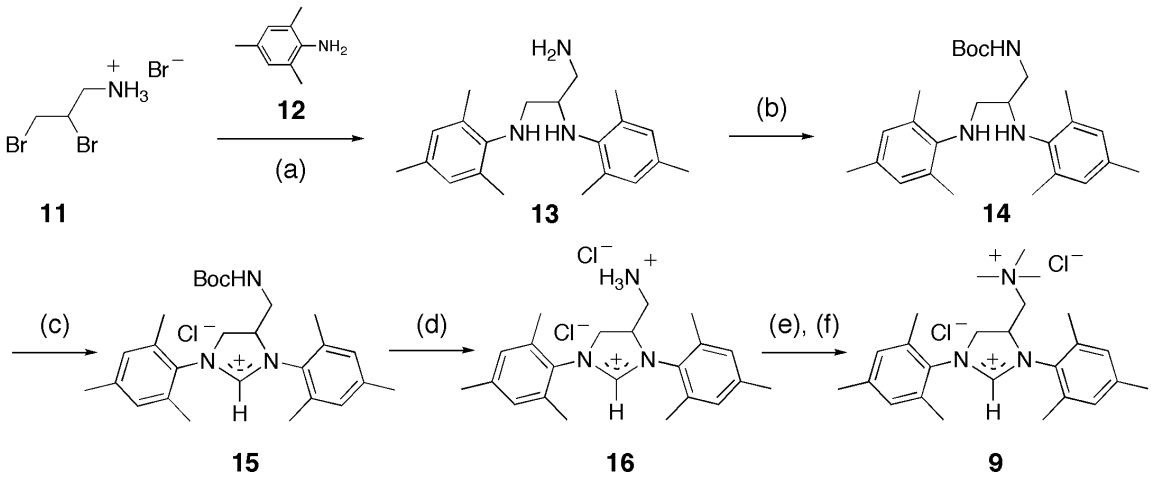
The synthesis of NHC precursor **9** is presented in Scheme 3.1. The nucleophilic displacement of the bromides of readily-made 2,3-dibromopropane-1-amine hydrobromide (**11**)[28] by 2,4,6-trimethylaniline (**12**) provides triamine **13**. The selective protection of the primary amine of **13** with a *tert*-butyloxycarbonyl (Boc) group provides diamine **14**, which can be readily cyclized with triethylorthoformate to produce Boc-protected imidazolium salt **15**. The Boc deprotection of **15** with hydrochloric acid followed by methylation with iodomethane then yields **9** after anion exchange and desalination.

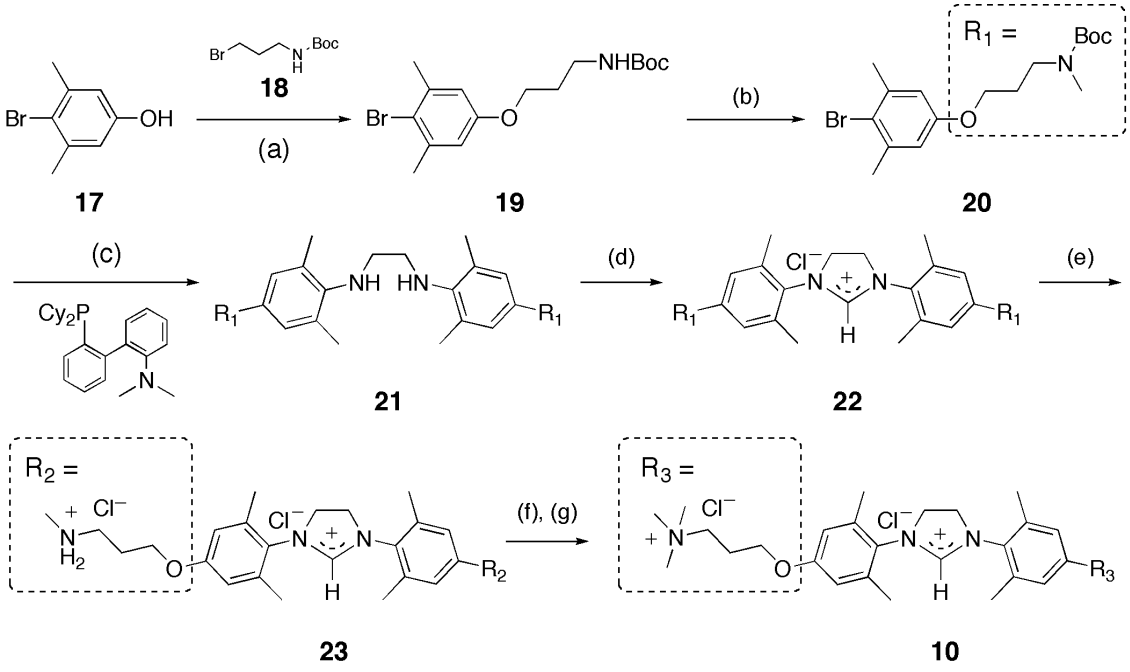
Scheme 3.1.



Reagents and conditions: (a) 120 °C, 19 h (39%), (b) Boc_2O, CH_2Cl_2, rt, 13 h (86%), (c) $HC(OEt)_3$, 120 °C, 16 h (90%), (d) HCl (aq), MeOH, rt, 30 min (88%), (e) MeI, K_2CO_3, MeOH, 70 °C, 32 h, (f) HCl (aq), MeOH, rt, 2 h (64%, 2 steps).

The synthesis of NHC precursor **10** is more involved than the synthesis of **9** (Scheme 3.2). The alkylation of commercially available 4-bromo-3,5-dimethylphenol (**17**) with readily made *tert*-butyl 3-bromopropylcarbamate (**18**)[29] provides aryl ether **19**. As palladium will couple aryl bromides to carbamate nitrogens,[30-32] **19**'s carbamate nitrogen must be methylated with iodomethane prior to the challenging palladium-mediated coupling reaction with ethylene diamine to yield product diamine **21**.[33] Cyclization with triethylorthoformate followed by Boc deprotection with hydrochloric acid provides imidazolium salt **23**, which can be methylated with iodomethane to produce **10** after ion exchange and desalination.

Scheme 3.2.



Reagents and conditions: (a) K_2CO_3, MeCN, 90 °C, 72 h (56%), (b) MeI, NaH, THF, reflux, 6 h (79%), (c) ethylene diamine, $Pd_2(dba)_3$, NaO^{t}Bu, toluene, 100 °C, 24 h (31%), (d) $HC(OEt)_3$, NH_4Cl, 120 °C, 16 h (68%), (e) HCl (aq), MeOH 25 °C, 14 h (94%), (f) MeI, K_2CO_3, MeOH, 70 °C, 32 h, (g) HCl (aq), MeOH, rt, 3 h (72%, 2 steps).

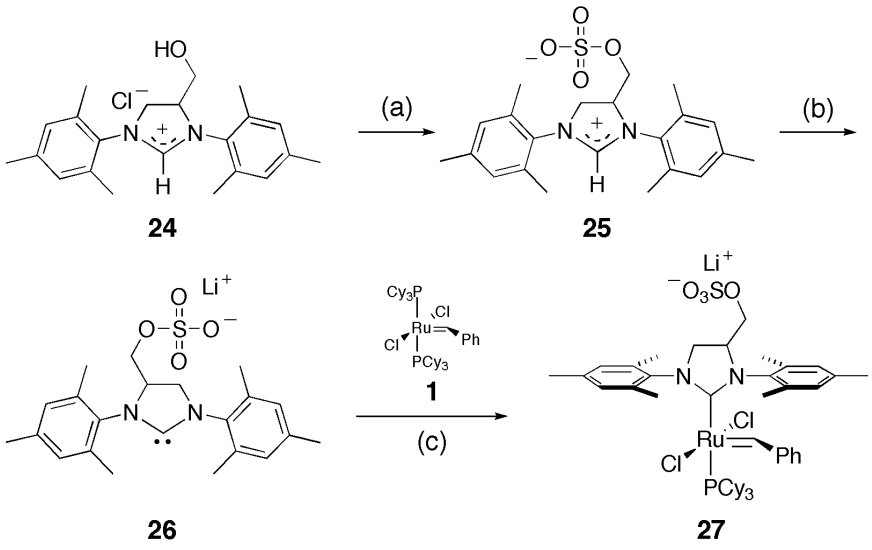
As previously mentioned, neither compound **9** nor **10** were ever used to generate a water-soluble olefin metathesis catalyst. The formation of the free carbene from precursor **9** failed due to the decomposition of **9** upon treatment with base, and the low-yielding, expensive multi-step synthesis of **10** limited its production. A new synthetic route to **10** was required for it to provide useful amounts of an NHC ligand. However, this was abandoned in favor of other projects and more promising leads. While neither **9** nor **10** led to water-soluble metathesis catalysts, Boc-protected imidazolium salt **15**, which was produced during the synthesis of **9**, was utilized in future research and was ultimately used to produce a new water-soluble metathesis catalyst (Chapter 5).[34,35]

NHC ligand and metathesis catalyst containing a sulfate group. Imidazolium salt **24**, which presents an alcohol from its backbone, can be readily made following literature procedures.[36] This alcohol provides a synthetic handle for the incorporation of water-soluble functional groups. However, reactions with this alcohol and various acid chlorides, including PEG-acid chloride, met with limited success**.** Pleasingly, the alcohol of **24** reacts smoothly with the sulfur trioxide pyridine complex to provide the zwitterionic NHC precursor **25** (Scheme 3.3), which displays the water-soluble sulfate group.[37]

Complex **25** is a very crystalline solid with a limited solubility in most solvents. Even so, it is readily deprotonated by potassium hexamethyldisilazane in THF to form the soluble carbene. However, the free carbene, **26**, readily accepts a proton from undetermined sources to reform compound **25**, which precipitates from solution. This complicates the synthesis and isolation of ruthenium complex **27**. Fortunately, the use of

the irreversible base, *tert*-butyl lithium and a mild excess of ruthenium complex **1** allow for the isolation of catalyst **27** in a reasonable yield and good purity (Scheme 3.3).

Scheme 3.3.

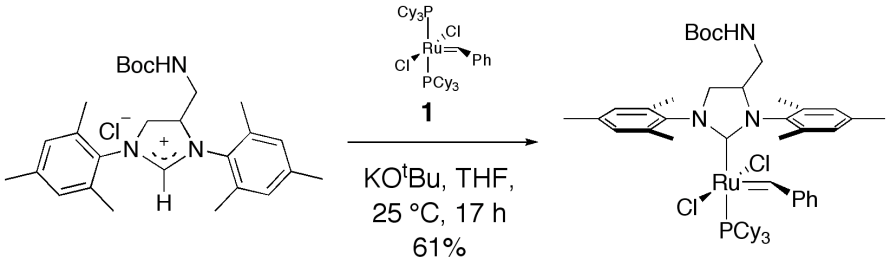


Reagents and conditions: (a) SO_3•Pyr, $CHCl_3$, 25 °C, 6 h (75%), (b) ^{t}BuLi, THF, –78 °C, 25 min, (c) 0 °C – rt, 16 h (69%, 2 steps).

Observation of rotational isomers by NMR spectroscopy. NMR spectroscopy reveals some interesting structural behavior of catalyst **27**. At room temperature, the ^{1}H NMR spectrum of catalyst **27** contains one broad benzylidene proton resonance. This resonance corresponds to two broad phosphorus resonances in the ^{31}P NMR spectrum. The benzylidene proton and phosphorus resonances both separate and sharpen into two distinct peaks when the NMR sample of **27** is heated to 75 °C. Furthermore, three benzylidene resonances are visible in the ^{1}H NMR spectrum of compound **27** when the sample is cooled to –72 °C. Finally, the original NMR spectra are again observed when a heated or cooled sample is returned to room temperature.

This NMR behavior is believed to be a property of ruthenium complexes containing an NHC ligand with an unsymmetrical backbone. To further examine this

hypothesis, imidazolium salt **15** was deprotonated with potassium *tert*-butoxide followed by ligand exchange with ruthenium complex **1** to form complex **28**, which also contains an NHC ligand with an unsymmetrical backbone. As anticipated, the NMR behavior of ruthenium complex **28** is similar to that of complex **27**. This NMR behavior is illustrated in Figure 3.2. For clarity, only the variable temperature spectra of complex **28** are shown.



The NMR behavior of complexes **27** and **28** can be understood by considering the rotation around two different ruthenium-carbon bonds, the NHC carbon-ruthenium bond and the benzylidene carbon-ruthenium bond. If rotation around the NHC carbon-ruthenium bond is slower than the chemical-shift NMR time scale, the ruthenium complex will appear as a mixture of two different rotational isomers by NMR spectroscopy (**A** and **B**, Figure 3.3). In the same way, restricted rotation around the benzylidene carbon-ruthenium bond can also yield a mixture of two different rotational isomers (**A** and **C**, Figure 3.3). Cumulatively, restricted rotation around both bonds produces four different rotational isomers (**A**–**D**, Figure 3.3). At room temperature, rotation around the NHC carbon-ruthenium bond of ruthenium complexes **27** and **28** is slow, which allows isomers **A** and **B** to be observed by NMR spectroscopy. Furthermore, rotation around the benzylidene carbon-ruthenium bond is sufficiently retarded at room temperature to broaden the observed phosphorus and benzylidene proton resonances.

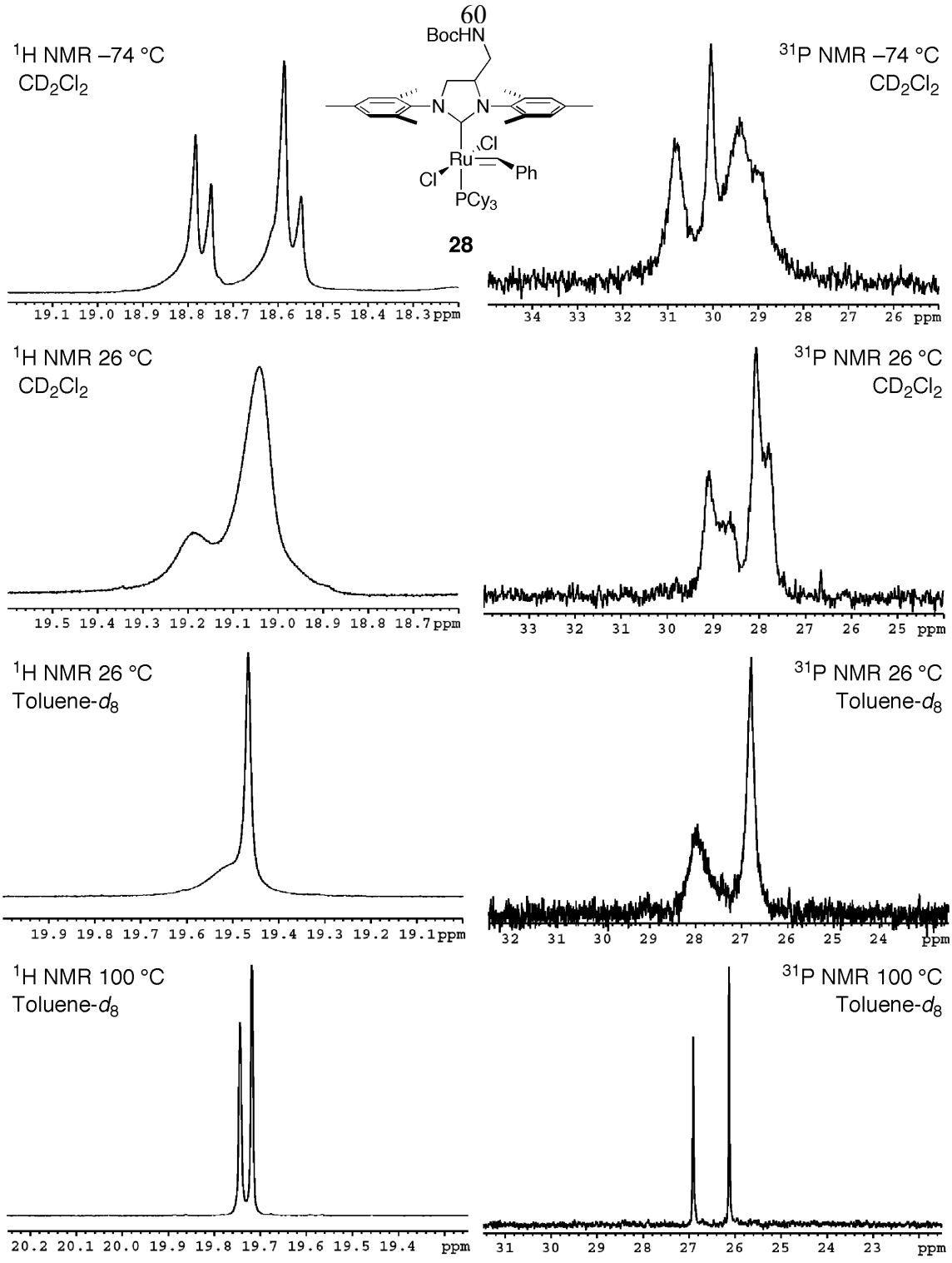


Figure 3.2. The NMR spectra of ruthenium complex **28** show fully reversible, temperature-dependent behavior. For clarity, only the benzylidene proton resonances of the ^{1}H NMR spectra are shown.

Heating the samples allows for free rotation around the benzylidene carbon-ruthenium bond, which causes the benzylidene proton and phosphorus resonances to sharpen. Finally, at low temperatures, rotation around the NHC carbon-ruthenium and benzylidene carbon-ruthenium bonds is sufficiently slow to allow all four rotational isomers of complex **28** to be observed, though only three isomers are observed for complex **27**. Interestingly, free rotation around the NHC carbon-ruthenium bond is not observed even at temperatures as high as 100 °C. This is consistent with earlier results, which show that the half-life for rotation around the NHC carbon-ruthenium bond of parent catalyst **2** is approximately 1.2 seconds at 85 °C.[38]

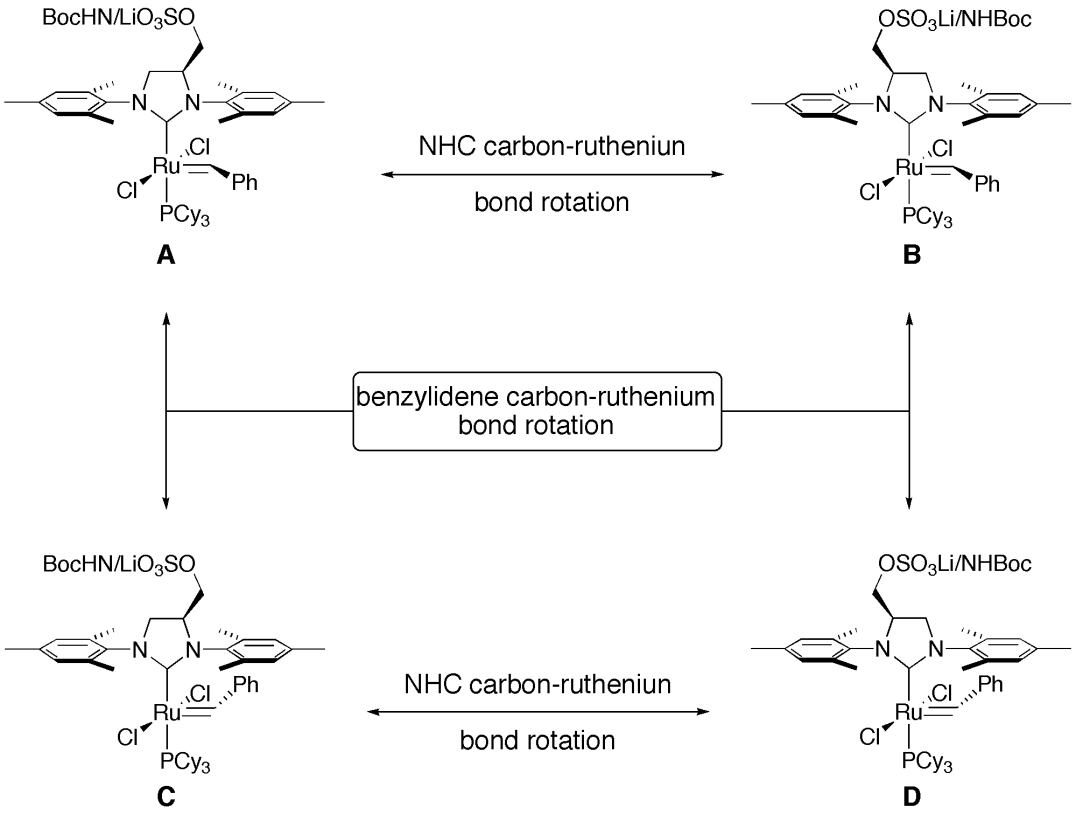


Figure 3.3. Because of the unsymmetrical backbone of their NHC ligands, ruthenium complexes **27** and **28** can exist as four different rotational isomers **A**–**D**.

Solubility and activity of catalyst 27. Catalyst **27** is soluble in such common organic solvents as dichloromethane and THF. While soluble in benzene and toluene, **27** forms aggregates in aromatic solvents as revealed by its ^{1}H NMR spectrum in toluene.[39] While not soluble in water, compound **27** is soluble in the polar protic solvent methanol. This is an improvement over parent catalyst **2**, which is insoluble in polar protic solvents.

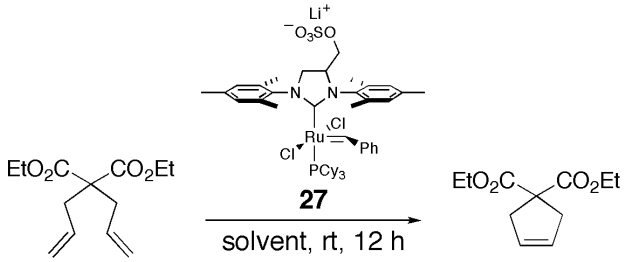


Table 3.1. Ring-closing metathesis of DEDAM in various solvents with catalyst **27**[a]

Solvent[b]	**Conversion (%)**[c]
Dichloromethane	92
Benzene	100
Toluene	94
Methanol	31

[a]Reactions were performed with 5 mol% of **27** and an initial DEDAM concentration of 0.2 M. All conversions represent the average of two trials. [b]All solvents were deuterated, anhydrous and degassed. [c]Conversions were determined by ^{1}H NMR spectroscopy.

The ring-closing metathesis of diethyl diallylmalonate (DEDAM) was used to examine the metathesis activity of catalyst **27** (Table 3.1). Catalyst **27** readily mediates the cyclization of DEDAM in organic solvents to high conversion. Unfortunately, these conversions are typically lower than with parent catalyst **2**.[40,41] Furthermore, the 31% conversion observed for the ring-closing of DEDAM in methanol is mildly less than the 40% conversion observed with catalyst **8** for the same reaction.[14] Interestingly, while initially a heterogenous reaction due to poor catalyst solubility, five mol% of parent catalyst **2** quantitatively ring-closes DEDAM in methanol at 50 °C in 4 hours.

Attempts were made to produce a water-soluble catalyst using complex **27**. Complexes **29**–**31** were all targeted as potentially providing a water-soluble catalyst (Figure 3.4). Unfortunately, complexes **29**–**31** were not produced cleanly. For example, attempts to produce complex **29** gave a mixture of three new benzylidenes complexes, of which none were soluble in water. Also, endeavors to synthesize compounds **30** and **31** yielded product mixtures that were both difficult to purify and insoluble in water.

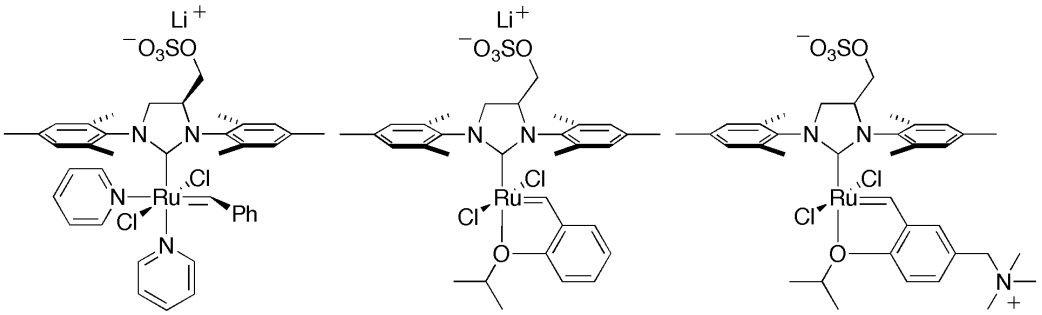
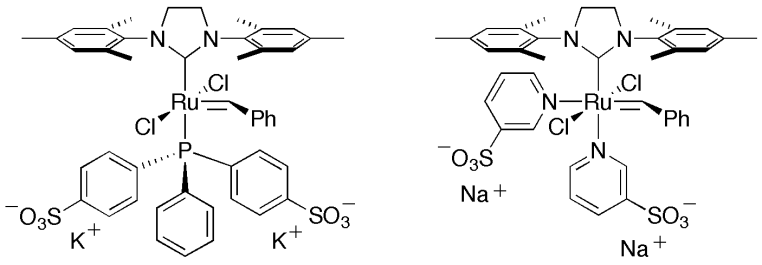


Figure 3.4. Ruthenium complexes **29**–**31** were targeted as potential water-soluble derivatives of catalyst **27**. None of these complexes were ever fully isolated, and the products of their attempted syntheses were not soluble in water.

Strategies involving sulfate-displaying NHC ligand **26** were eventually abandoned. The reasons include the relatively poor metathesis activity of sulfate catalyst **27** and the difficulty in forming water-soluble catalysts from **27**. However, 1-(4-isopropoxy-3-vinylphenyl)-*N*,*N*,*N*-trimethanaminium chloride (**32**), which was originally synthesized for the production complex **31**, was eventually used to produce an active, water-soluble metathesis catalyst (Chapter 5).[34,35]

Strategies involving water-soluble dissociating ligands. Water-soluble functional groups can also be incorporated onto ligands that dissociate during the catalytic cycle of olefin metathesis. Such ligands include phosphine, pyridine, and isopropoxystyrene

ligands. The initial complexes targeted as part of this strategy were compounds **33** and **34**, which contain a water-soluble phosphine and pyridine ligands respectively (Figure 3.5).



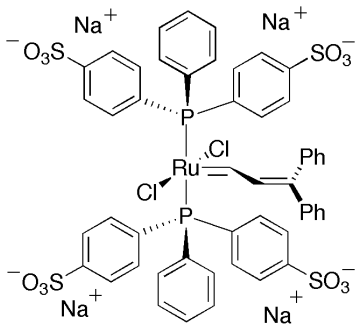
33 **34**

Figure 3.5. Though never isolated, ruthenium complexes **33** and **34** were initial targets for the strategy to incorporate water-soluble groups onto dissociating ligands.

In 1995, Grubbs and co-workers report the synthesis of complex **35** whose triaryl-phosphine ligands display sulfonate groups on the phenyl rings *para* to the phosphorus atom.[42] While complex **35** is not metathesis active, it is soluble in water and prompts the generation of complex **33**. Unfortunately, mixing bis(pyridine) catalyst **5** with commercially available phosphine **36** produces a diverse mixture of products.

Employing water-soluble pyridine ligands to generate an analog of catalyst **5** is a potentially simple manner to produce a water-soluble metathesis catalyst. Bis(pyridine) catalysts are usually readily synthesized by simply mixing catalyst **2** with a heavy excess of the pyridine ligand.[21] Indeed, mixing **2** with an excess of commercially available sodium pyridine-3-sulfonate (**37**) does produce a new benzylidene. However, isolating the product benzylidene from residual pyridine **37** is difficult. This, in combination with the generally lower stability of bis(pyridine) catalysts[21] and the known instability of

catalysts containing an NHC ligand to the presence of protic solvents and base,[43] led to the pursuit of other strategies to produce a water-soluble metathesis catalyst.



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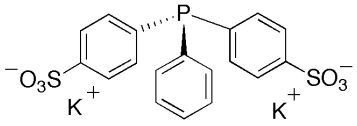

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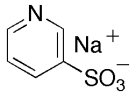
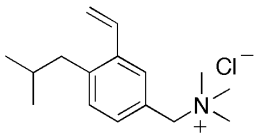


37

The final strategy for incorporating water-soluble groups onto dissociating ligands utilizes isopropoxybenzylidene ligands. Isopropoxystyrene **32**, which contains a single tetraalkyl ammonium chloride salt, is mentioned earlier during the pursuit of complex **31**. Styrene **38**, which displays two tetraalkyl ammonium chloride salts, is the second compound examined as part of this strategy. Pleasingly, both isopropoxystyrenes **32** and **38** can be used to produce water-soluble metathesis catalysts containing an NHC ligand.[34,35] The synthesis of these styrenes and the water-soluble catalysts that they produce are described in Chapter 5.



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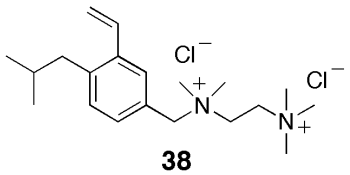

38

Summary

This chapter described initial efforts to synthesize a discrete, water-soluble metathesis catalyst that contains an NHC ligand and displays improved activity over catalyst **8**. Two general strategies pursued to achieve this goal were outlined.

Initial efforts focused on the strategy of including water-soluble functional groups onto the NHC ligand. Research in this area produced NHC precursors **9**, **10**, and **25**, which contain one tetraalkyl ammonium chloride, two tetraalkyl ammonium chloride and a single sulfate group(s) respectively. Though neither compound **9** nor **10** led to a water-soluble catalyst, compound **15** produced during the synthesis of **9** was used in ruthenium complex **28** and in water-soluble catalysts (Chapter 5).[34,35] Ruthenium catalyst **27** was synthesized using NHC precursor **25**. While this catalyst, along with complex **28**, produces interesting NMR spectra, **27** is not soluble in water and shows a lower catalytic activity relative to catalysts **2** and **8** in organic solvents and methanol.

The second strategy to produce the desired metathesis catalyst involved displaying water-soluble groups from phosphine, pyridine and isopropoxystyrene ligands, which are ligands that dissociate during a metathesis reaction. Unfortunately, water-soluble metathesis catalysts incorporating phosphine **36** or pyridine **37**, which display sulfonate salts, were not isolated. However, research into isopropoxystyrenes containing ammonium chloride salts produced isopropoxystyrenes **32** and **38**, which were later used to synthesize active, water-soluble olefin metathesis catalysts (Chapter 5).[34,35]

The work described in this chapter amply demonstrates a common phenomenon in chemical research. Research that fails to deliver the desired result (Chapter 3) can often provide the components for future success (Chapter 5).

Acknowledgements

The author would like to thank Professor Brian Connell for his extensive help and advice during the course of this research. Drs. Dan Sanders, Sebastian Smidt, Jacob Berlin, and Andrew Hejl are also acknowledged for helpful discussions. The author is also grateful to Dr. Scott Ross for his aid with variable temperature NMR spectroscopy and Dr. Mona Shahgholi for mass spectroscopic analysis. The National Institutes of Health (5R01GM068647) is acknowledged for funding.

Experimental

General considerations. All glove-box manipulations were performed in a N_2-filled Vacuum Atmospheres glove box (O_2 < 2.5 ppm). Otherwise reactions run under dry, degassed conditions were performed using standard Schlenk techniques under an atmosphere of dry argon using flame or oven-dried glassware. The variable temperature NMR spectroscopy of compounds **27** and **28** were performed on a Varian Inova 500 (499.85 MHz for ^{1}H; 202.34 MHz for ^{31}P; 125.69 MHz for ^{13}C). All other NMR spectra were recorded on a Varian Mercury 300 (299.817 MHz for ^{1}H, 75.4 MHz for ^{13}C, and 121 MHz for ^{31}P) and reported in parts per millon (ppm) downfield from trimethylsilane as referenced to residual protio solvent peaks. Multiplicity abbreviations used when reporting ^{1}H NMR spectra are: s = singlet, d = doublet, ψt = pseudo-triplet, dd = doublet of doublets, dt = doublet of triplets, q = quartet, p = pentad, m = multiplet, br = broad. All thin-layer chromatography (TLC) of organic compounds was accomplished on silica-gel 60 F254 percoated plates with a fluorescent indicator and visualized by UV light and/or by standard potassium permanganate stains. All flash chromatography of organic compounds was performed with silica-gel 60 (230-400 mesh). Neutral Brockman grade

III alumina was generated by mixing 6% water (by mass) with neutral Brockman grade I alumina (~150 mesh). For anaerobic chromatography, columns are first purged with argon, and all eluant is degassed with a generous argon sparge (at least 30 minutes). Product is then eluted under argon and collected in a round-bottom flask already purged with argon and equipped with a magnetic stir bar while under a stream of argon. Eluant is then removed *in vacuo* (not by rotary evaporation). Desalination was performed on Waters' Sep-Pak Vac 35cc (10g) C18 cartridges.

Materials. All deuterated solvents were purchased from Cambridge Isotope Laboratories. Deuterated dichloromethane, deuterated THF and deuterated DMF were dried over 4 Å molecular sieves, and deuterated methanol was dried over calcium sulfate. Deuterated methanol, deuterated methylene chloride and deuterated THF were degassed by three freeze, pump and thaw cycles while deuterium oxide and deuterated DMF were degassed by a generous argon sparge. Anhydrous methanol was purchased from Aldrich and degassed with a generous argon sparge. All other solvents were purchased from Fischer Scientific. Solvents were dried by passage through purification columns packed with alumina and degassed by a generous argon sparge. All commericial materials were used as obtained. Ruthenium complexes **1** and **2** were gifts from Materia. 2,4,6-trimethylaniline (**12**), di-*tert*-butyl dicarbonate, 4-dimethylamino pyridine (DMAP), triethylorthoformate, 4-bromo-3,5-dimethylphenol (**17**), iodomethane, 60% sodium hydride (suspended in mineral oil), sodium *tert*-butoxide, ethylene diamine, diethyl diallylmalonate, and potassium hexamethyldisilazane were purchased from Aldrich. Tris(dibenzylideneacetone)dipalladium(0), 2-(dicyclohexylphosphino)-2'-(*N*,*N*-

dimethylamino)biphenyl, and bis(*p*-sulfonatophenyl)phenylphosphine dihydrate dipotassium salt were purchased from Strem. Potassium *tert*-butoxide and 1.7 M *tert*-butyl lithium in *n*-pentane were purchased from Alfa Aesar. Potassium carbonate was purchased from JT Baker. Sodium pyridine-3-sulfonate (**37**) was purchased from TCI Americal. Sodium hydroxide, ammonium chloride, concentrated hydrochloric acid, sodium bicarbonate, and sodium chloride were purchased from Malinkrodt, and sodium and magnesium sulfate were purchased from EMS. Compounds **5**,[21] **11**,[28] **18**,[29] 2,3-bis(mesitylamino)propan-1-ol,[36] and $Cl_2Ru(=CH\text{-}o\text{-}O\text{-}i\text{-}PrC_6H_4)PPh_3$[44] were made following literature procedures. The synthesis of isopropoxystyrenes **32** and **38** are described in Chapter 5.[34]

N,N'-Dimesitylpropane-1,2,3-triamine (13). A round-bottom flask, equipped with a stir bar, was charged with 2,3-dibromopropane-1-amminium bromide (**11**) (5.00 g, 17 mmol) and 2,4,6-trimethylaniline (**12**) (30.5 mL, 217 mmol, 12.9 equiv) and equipped with a condenser. After purging with argon, the flask was heated to 120 °C. The reaction was allowed to continue for 19 hours at 120 °C under a positive argon pressure. Upon reaction completion, this mixture was cooled to room temperature, fully dissolved with diethyl ether and 15% aqueous sodium hydroxide and transferred to a separatory funnel. The organic and aqueous layers were separated, and the organic layer was rinsed with water (1×) and with brine (1×) prior to drying over sodium sulfate. Diethyl ether was removed by rotary evaporation to obtain a brown oil. Short-path distillation for 1.5 hours at 100 °C and 0.1 mmHg was used to remove much of the excess 2,4,6-trimethylaniline. The material was further purified chromatographically on silica-gel 60 (10% methanol in

dichloromethane) to obtain 2.15 g (39%) of product as a brown oil. (Note: Unpurified material is a ~1:1 mixture of product and a fully symmetrical side-product resulting from aziridination followed by ring-opening with 2,4,6-trimethylaniline at the less-hindered carbon.) ^{1}H NMR ($CDCl_3$, ppm): δ 6.81 (s, 4H), 3.45 (p, J = 5.7 Hz, 1H), 3.16 (dd, J = 12 Hz, 5.4 Hz, 1H), 2.92 (dd, J = 4.5 Hz, 1.2 Hz, 2H), 2.88 (dd, J = 12 Hz, 5.7 Hz, 1H), 2.82–2.46 (br, 4H), 2.30 (s, 6H), 2.23 (s, 6H), 2.21 (s, 6H). ^{13}C NMR ($CDCl_3$, ppm): δ 143.8, 142.0, 131.5, 130.9, 130.0, 129.9, 129.6, 129.0, 58.7, 51.6, 45.0, 20.7, 20.7, 19.4, 18.5. HRMS (EI+) *m*/*z* calc for $C_{21}H_{32}N_3$: 326.2596, found 326.2595.

***tert*-Butyl 2,3-bis(mesitylamino)propylcarbamate (14).** A round-bottom flask, equipped with a stir bar and purged with argon, was charged with **13** (4.93 g, 15 mmol), di-*tert*-butyl dicarbonate (3.31 g, 15 mmol, 1 equiv) and degassed (argon sparge), reagent grade dichloromethane (30 mL). The flask was cooled to 0 °C prior to the addition of DMAP (185 mg, 1.5 mmol, 0.1 equiv). The reaction was allowed to continue at 0 °C for 30 minutes prior to warming to room temperature and stirring for an additional 2 hours, all while under a positive argon pressure. The product mixture was transferred to a separatory funnel and rinsed with water (2×) and with brine (2×). The organic layer was dried over sodium sulfate, and the dichloromethane was removed by rotary evaporation. Purification by chromatography on silica-gel 60 (15% ethyl acetate in hexanes) yields 5.57 g (86%) of product as a white powder. ^{1}H NMR ($CDCl_3$, ppm): δ 6.85 (s, 2H), 6.83 (s, 2H), 5.04 (s, 1H), 3.53–3.23 (br m, 5H), 3.14 (dd, J = 12 Hz, 5.7 Hz, 1H), 2.90 (dd, J = 12 Hz, 4.5 Hz, 1H), 2.29 (s, 6H), 2.26 (s, 3H), 2.25 (s, 3H), 2.24 (s, 6H), 1.49 (s, 9H). ^{13}C NMR ($CDCl_3$, ppm): δ 156.6, 143.7, 141.5, 131.5, 131.2, 130.1, 130.0, 129.6, 129.0,

79.6, 57.2, 50.9, 43.4, 28.6, 20.7, 20.7, 19.2, 18.5. HRMS (FAB+) *m*/*z* calc for $C_{26}H_{40}N_3O_2$: 426.3121, found 426.3107.

5-((*tert*-Butoxycarbonylamino)methyl)-1,3-dimesityl-4,5-dihydro-1*H*-imidazol-3-ium chloride (15). A flame-dried round-bottom flask, equipped with a stir bar, was charged with **14** (5.57g, 13 mmol), ammonium chloride (739 mg, 14 mmol, 1.0 equiv), and triethylorthoformate (33 mL, 199 mmol, 15 equiv). The flask was equipped with a condenser and purged with argon prior to heating to 120 °C. The reaction was allowed to continue at 120 °C for 16 hours under a positive argon pressure. After 16 hours, the reaction mixture was cooled to room temperature, and the product precipitated from diethyl ether. The white solid precipitate was isolated by vacuum filtration and rinsed generously with diethyl ether to yield 5.59 g (90%) of product as a white powder. ^{1}H NMR ($CDCl_3$, ppm) : δ 9.34 (s, 1H), 6.82 (s, 4H), 5.29–5.14 (m, 1H), 4.51 (dd, *J* = 12 Hz, 8.3 Hz, 1H), 4.23 (ψt, *J* = 12 Hz, 1H), 3.59–3.44 (m, 1H), 3.17–3.06 (m, 1H), 2.35 (s, 3H), 2.30 (s, 3H), 2.26 (s, 3H), 2.19 (s, 9H), 1.29 (s, 9H). ^{13}C NMR ($CDCl_3$, ppm): δ 159.6, 156.6, 140.3, 140.0, 135.1, 135.0, 130.5, 130.2, 130.1, 129.8, 129.0, 79.3, 62.5, 55.3, 41.4, 28.4, 21.1, 21.0, 18.9, 18.5, 18.2, 17.8. HRMS (FAB+) *m*/*z* calc for $C_{27}H_{38}N_3O_2$: 436.2964, found 436.2977.

5-(ammoniomethyl)-1,3-dimesityl-4,5-dihydro-1*H*-imidazol-3-ium chloride (16). A solution of compound **15** (440 mg, 0.93 mmole) in methanol (3.6 mL) was cooled to 0 °C. To this solution was added concentrated hydrochloric acid (1.2 mL). The reaction was stirred at 0 °C for 10 minutes prior to warming to warm to room temperature. The

reaction was allowed to continue an additional 20 minutes at room temperature before removing the volatiles by rotary evaporation. The product was dried extensively under high vacuum to obtain 336 mg (88%) of an off-white solid. ^{1}H NMR (DMSO-d_6, ppm): δ 9.29 (s, 1H), 9.00 (s, 3H), 7.13 (s, 2H), 7.10 (s, 2H), 5.51–5.37 (m, 1H), 4.90–4.83 (m, 1H), 4.69 (ψt, J = 12 Hz, 1H), 3.58–3.51 (m, 1H), (ψd, J = 10 Hz, 1H), 2.43–2.22 (m, 18H). ^{13}C NMR (DMSO-d_6, ppm): δ 160.6, 139.9, 136.0, 135.7, 135.4, 130.5, 130.2, 129.7, 129.6, 128.6, 60.0, 55.0, 20.6, 20.6, 18.1, 17.9, 17.6, 17.2. HRMS (FAB+): m/z calc for $C_{22}H_{30}N_3$: 336.2440, found 336.2452.

1,3-dimesityl-5-((trimethylammonio)methyl)-4,5-dihydro-1*H*-imidazol-3-ium chloride (9). A flame-dried round-bottom flask, purged with argon and equipped with a stir bar and a condenser, was charged with compound **16** (188 mg, 0.46 mmol), potassium carbonate (128 mg, 0.92 mmol, 2.0 equiv), iodomethane (0.16 mL, 2.6 mmol, 5.0 equiv), and of dry, degassed methanol (2.3 mL). The reaction was heated to 70 °C and allowed to continue under an atmosphere of argon. After 22 hours, additional potassium carbonate (129 mg, 0.93 mmol, 2.0 equiv) and iodomethane (0.16 mL, 2.6 mmol, 5.0 equiv) were added. The reaction was stirred for an additional 10 hours prior to cooling to room temperature and removing the volatiles by rotary evaporation. Methanol (23 mL) was added to the crude material, and the solution was cooled to 0 °C before adding concentrated hydrochloric acid (7.6 mL, 92 mmol, 200 equiv). The solution was stirred at 0 °C for 20 minutes then at room temperature for 1 hour. The product mixture was passed through a plug of celite, and the volatiles were removed by rotary evaporation. The product was again dissolved in methanol and passed through a plug of

celite. After removing the volatiles by rotary evaporation, the product was dissolved in minimal methanol and precipitated into dietyl ether (~200 mL), and the solid product was collected by vacuum filtration. Desalination was accomplished by loading the product onto a Waters' Sep-Pak Vac 35 cc (10g) C18 cartridge with water (using minimal methanol as required), repeatedly flushing the column with water (4×) and eluting the product with acetonitrile. Removing the volatiles by rotary evaporation yields 133 mg (64%) of a slightly yellow, solid product. ^{1}H NMR (DMSO-d_6, ppm): δ 9.15 (s, 1H), 7.16 (d, J = 3.0 Hz, 2H), 7.12 (s, 2H), 5.71 (q, J = 10 Hz, 1 H), 4.99 (ψt, J = 12 Hz, 1H), 4.75–4.53 (m, 3H), 3.17 (s, 9H), 2.41 (s, 8H), 2.34–2.26 (m, 10H). ^{13}C NMR (DMSO-d_6, ppm): δ 160.9, 140.2, 140.1, 136.6, 135.8, 135.7, 135.1, 130.2, 130,1, 129.5, 127.9, 63.4, 57.9, 56.7, 52.8, 20.7, 20.6, 18.3, 18.2, 17.7, 17.6. Compound decomposes (eliminates trimethylamine) during mass-spectral analysis.

***tert*-Butyl 3-(4-bromo-3,5-dimethylphenoxy)propylcarbamate (19).** A round-bottom flask, equipped with a stir bar and a condenser, was charged with compound **17** (754 mg, 3.8 mmol), compound **18** (1.07 g, 4.5 mmol, 1.2 equiv), potassium carbonate (543 mg, 3.9 mmol, 1.0 equiv), and acetonitrile (7.5 mL). The reaction was allowed to continue for 3 days at 95 °C. After cooling to room temperature, the product mixture was diluted with diethyl ether and rinsed with a saturated solution of sodium bicarbonate in water (1×), water (1×), and brine (1×). The diethyl ether layer was collected, dried over sodium sulfate, and concentrated to dryness by rotary evaporation. The crude material was eluted from a flash column with 20% ethyl acetate in hexanes, and the material was then dissolved in diethyl ether and rinsed with a 15% solution of sodium hydroxide in water

(5x). The diethyl ether layer was dried over magnesium sulfate and concentrated to dryness by rotary evaporation. Drying the material under high vacuum yields 742 mg (56%) of product as a white solid. ^{1}H NMR ($CDCl_3$ (w/TMS), ppm): δ 6.64 (s, 2H), 4.80 (br s, 1H), 3.97 (t, J = 6.0 Hz , 2H), 3.31 (q, J = 6.3 Hz, 2H), 2.38 (s, 6H), 1.96 (p, J = 6.3 Hz, 2H), 1.45 (s, 9H). ^{13}C NMR ($CDCl_3$ (w/TMS), ppm): δ 157.4, 156.2, 139.3, 118.5, 114.6, 79.4, 66.0, 38.1, 29.7, 28.6, 24.2. HRMS (FAB+): *m*/*z* calc for $C_{16}H_{24}NO_3Br$: 359.0919, found 359.0912.

***tert*-Butyl 3-(4-bromo-3,5-dimethylphenoxy)propylmethylcarbamate (20).** A flame-dried round-bottom flask, equipped with a stir bar and purged with argon, was charged with compound **19** (578 mg, 1.6 mmol), iodomethane (1 mL, 16 mmol, 10 equiv), and dry, degassed THF (8.1 mL) and cooled to 0 °C. Sodium hydride (60% in mineral oil, 202 mg, 5.0 mmol, 3.1 equiv) was added, and the reaction was allowed to continue at 0 °C for 40 minutes under a positive argon pressure. The flask was then equipped with a flame-dried condenser and refluxed (75 °C) 22 hours under a positive argon pressure. The reaction was then cooled to room temperature before quenching with excess water, transferred to a separatory funnel and extracted with dichloromethane (3×). The combined dichloromethane extracts were rinsed with brine (1×) and dried over sodium sulfate before removing the volatiles by rotary evaporation. Eluting the crude material from a flash column with 15% ethyl acetate in hexane yields 474 mg (79%) of pure product as a clear oil. ^{1}H NMR ($CDCl_3$, ppm): δ 6.63 (s, 2H), 3.92 (t, J = 6.0 Hz, 2H), 3.39 (t, J = 6.9 Hz, 2H), 2.87 (s, 3H), 2.37 (s, 6H), 2.04–1.92 (m, 2H), 1.44 (s, 9H). ^{13}C NMR ($CDCl_3$, ppm): δ 157.5, 156.0, 139.2, 118.3, 114.5, 79.5, 65.8 and 65.2 (Boc

rotamers), 46.0, 34.7, 28.6, 28.0 and 27.8 (Boc rotamers), 24.2. HRMS (FAB+): *m*/*z* calc for $C_{17}H_{27}NO_3Br$: 372.1174, found 372.1189.

***tert*-Butyl 3,3'-(4,4'-(ethane-1,2-diylbis(azanediyl))bis(3,5-dimethyl-4,1-phenylene))bis(oxy)bis(propane-3,1-diyl)bis(methylcarbamate) (21).** In a N_2-filled glove box, tris(dibenzylideneacetone)dipalladium(0) (14.1 mg, 0.015 mmol, 0.10 equiv), 2-(dicyclohexylphosphino)-2'-(*N*,*N*-dimethylamino)biphenyl (10.0 mg, 0.025 mmol, 0.17 equiv), and sodium *tert*-butoxide (42.0 mg, 0.44 mmol, 2.9 equiv) were weighed into a flame-dried Schlenk flask, which was equipped with a stir bar. The flask was sealed with a septum, removed from the box and brought under argon. Compound **20** (111 mg, 0.30 mmol, 2.0 equiv) was added as a solution in dry, degassed toluene (0.1 mL). To this mixture was added ethylene diamine (0.01 mL, 0.15 mmol) and dry, degassed toluene (0.5 mL). The septum was replaced by a ground glass stopper, and the flask was sealed and heated to 100 °C. The reaction was stirred at 100 °C for 24 hours. The dark green reaction mixture was cooled to room temperature, diluted with diethyl ether, and passed through a celite plug. Removal of the volatiles by rotary evaporation and purification by flash chromatography with 40% ethyl acetate in hexane yields 30.2 mg (31%) of product as an oil. ^{1}H NMR ($CDCl_3$ (w/TMS), ppm): δ 6.56 (s, 4H), 3.92 (t, J = 6.0 Hz, 4H), 3.39 (t, J = 6.9 Hz, 4H), 3.21–3.06 (br, 2H), 3.08 (s, 4H), 2.88 (s, 6H), 2.30 (s, 12H), 2.04–1.91 (m, 4H), 1.45 (s, 18H). ^{13}C NMR ($CDCl_3$ (w/TMS), ppm): δ 156.0, 154.2, 139.4, 132.0, 114.7, 79.5, 65.7 and 65.3 (Boc rotamers), 49.6, 46.1, 34.7, 28.6, 28.3 and 27.9 (Boc rotamers), 18.8. HRMS (FAB+): *m*/*z* calc for $C_{36}H_{58}N_4O_6$: 642.4356, found 642.4332.

1,3-Bis(4-(3-(*tert*-butoxycarbonyl(methyl)amino)propoxy)-2,6-dimethylphenyl)-4,5-dihydro-1*H*-imidazol-3-ium chloride (22). A flame-dried round-bottom flask, equipped with a stir bar and a condenser, was charged with compound **21** (1.23 g, 1.9 mmol), triethylorthoformate (4.8 mL, 29 mmol, 15 equiv), and ammonium chloride (109 mg, 2.0 mmol, 1.1 equiv). The reaction mixture was heated to 120 °C and allowed to continue at that temperature for 16 hours under a positive argon pressure. After cooling to room temperature, residual triethylorthoformate was removed *in vacuo*, and the crude material was purified by elution from a flash column with 11% methanol in dichloromethane to obtain 905 mg (68%) of product solid. ^{1}H NMR (DMSO-d_6, ppm): δ 9.00 (s, 1H), 6.83 (s, 4H), 4.41 (s, 4H), 3.96 (t, J = 6.0 Hz, 4H), 3.31 (t, J = 6.6 Hz, 4H), 2.78 (br s, 6H), 2.35 (s, 12H), 1.90 (p, J = 6.3 Hz, 4H), 1.36 (s, 18H). ^{13}C NMR (DMSO-d_6, ppm): δ 160.7, 159.0, 154.8, 137.2, 126.2, 114.4, 78.4, 65.5 and 65.2 (Boc rotamers), 51.0, 45.2, 34.1, 28.0, 27.2 and 27.0 (Boc rotamers), 17.5. HRMS (ESI+): m/z calc for $C_{37}H_{57}N_4O_6$: 653.4278, found 653.4281.

1,3-Bis(2,6-dimethyl-4-(3-(methylammonio)propoxy)phenyl)-4,5-dihydro-1*H*-imidazol-3-ium trichloride (23). A 1-dram vial, equipped with a stir bar, was charged with compound **22** (249 mg, 0.36 mmol) and a solution of concentrated hydrochloric acid in methanol (3 M HCl, 1.2 mL, 3.6 mmol, 10 equiv). The reaction was stirred at room temperature for 14 hours before removing the volatiles by rotary evaporation. Dissolving the crude material in minimal methanol and precipitation from acetone (~176 mL) yields an yellow-orange precipitate after incubation in the freezer (~14 hours). Isolation of the

precipitate yields 190 mg (94%) of a yellow-orange, solid product. ^{1}H NMR (DMSO-d_6, ppm): δ 9.46 (br s, 4H), 9.02 (s, 1H), 6.86 (s, 4H), 4.41 (s, 4H), 4.33 (br s, 4H), 4.11 (br s, 4H), 2.97 (br s, 6H), 2.35 (s, 12H), 2.10 (br s, 4H). ^{13}C NMR (DMSO-d_6, ppm): δ 160.7, 158.7, 137.3, 126.4, 114.5, 65.1, 51.0, 45.3, 32.3, 25.3, 17.6. HRMS (FAB+): *m*/*z* calc for $C_{27}H_{41}N_4O_2$: 453.3229, found 453.3241.

1,3-Bis(2,6-dimethyl-4-(3-(trimethylammonio)propoxy)phenyl)-4,5-dihydro-1*H*-imidazol-3-ium trichloride (10). A flame-dried round-bottom flask, equipped with a stir bar and a condenser and purged with argon, was charged with compound **23** (340 mg, 0.60 mmol), methanol (3 mL), iodomethane (0.38 mL, 6.0 mmol, 10 equiv), and potassium carbonate (337 mg, 2.44 mmol, 4.0 equiv). The reaction mixture was heated to 70 °C and stirred for 22 hours under an atmosphere of argon. Additional iodomethane (0.38 mL, 6.0 mmol, 10 equiv) and potassium carbonate (336 mg, 2.4 mmol, 4.0 equiv) were added, and the reaction was allowed to continue for an additional 10 hours at 70 °C under an atmosphere of argon. Upon cooling the reaction mixture to room temperature, the volatiles were removed by rotary evaporation. The product mixture was dissolved in methanol (46 mL) and cooled to 0 °C. Concentrated hydrochloric acid (15 mL) was added drop-wise, and the reaction was stirred at 0 °C for 10 minutes before heating to room temperature and stirring for an additional 3 hours. The product mixture was passed through a plug of celite, and the volatiles were removed by rotary evaporation. The material was dissolved in ethanol (15 mL) prior to the addition of acetone (~210 mL). The produced suspension was placed in the freezer for 1 hour before removing the precipitate by vacuum filtration through a fine frit. The filtrate was collected and

concentrated to dryness by rotary evaporation. Desalination was accomplished by loading the material onto a Waters' Sep-Pak Vac 35 cc (10g) C18 cartridge with methanol and repeatedly flushing the column with water (4×). Product was eluted with acetonitrile to obtain 255 mg (72%) of a yellow-orange solid. ^{1}H NMR (DMSO-d_6, ppm): δ 8.96 (s, 1H), 6.87 (s, 4H), 4.43 (s, 4H), 4.08 (t, J = 6.0 Hz, 4H), 3.53–3.44 (m, 4H), 3.12 (s, 18H), 2.36 (s, 12H), 2.24–2.12 (m, 4H). ^{13}C NMR (DMSO-d_6, ppm): δ 160.6, 158.6, 137.3, 126.5, 114.5, 65.1, 62.8, 52.3, 51.1, 22.5, 17.6.

5-(hydroxymethyl)-1,3-dimesityl-4,5-dihydro-1*H*-imidazol-3-ium chloride (24). Compound **24** was synthesized following a slight modification of literature procedures.[36] A flame-dried round-bottom flask, equipped with a stir bar and a condenser, was charged with 2,3-bis(mesitylamino)propan-1-ol (28.4 g, 71 mmol),[36] ammonium chloride (4.00 g, 75 mmol, 1.0 equiv) and triethylorthoformate (142 mL, 855 mmol, 12 equiv). The reaction was heated to 120 °C and allowed to continue for 10 hours at that temperature under a positive argon pressure. Upon cooling to room temperature, the precipitate was isolated by vacuum filtration and rinsed with excess hexanes and diethyl ether. The trimethylsilane-protected product was dissolved in methanol (~210 mL), and concentrated hydrochloric acid (18 mL, ~3 equiv) was added. The deprotection reaction was stirred for 30 minutes before removing the volatiles by rotary evaporation. The crude material was purified by flash chromatography with 10% methanol in dichloromethane to obtain 20.2 g (76%) of product as a white solid. ^{1}H NMR (DMSO-d_6, ppm): δ 9.14 (s, 1H), 7.07 (s, 4H), 6.16 (ψt, J = 5.1 Hz, 1H), 4.98–4.87 (m, 1H), 4.61–4.43 (m, 2H), 3.61–3.51 (m, 1H), 3.41–3.29 (m, 1H), 2.53–2.21 (m, 18H). ^{13}C NMR (DMSO-d_6, ppm): δ

160.1, 139.6, 139.2, 136.6, 135.8, 135.4, 135.3, 131.1, 129.7, 129.4, 129.3, 64.7, 58.0, 51.7, 20.6, 20.5, 17.9, 17.4, 17.2. HRMS (FAB+): *m*/*z* calc for $C_{22}H_{29}N_2O$: 337.2280, found 337.2270.

(1,3-dimesityl-4,5-dihydro-1*H*-imidazol-3-ium-5-yl)methyl sulfate (25).[37] A flame-dried round-bottom flask, equipped with a stir bar and purged with argon, was charged with compound **24** (3.00 g, 8.0 mmol), sulfur trioxide pyridine complex (6.41 g, 40 mmol, 5.0 equiv) and chloroform (161 mL). The reaction was allowed to continue for 6 hours at room temperature under a positive argon pressure. The volatiles were removed by rotary evaporation, and the material was dissolved in methanol (~161 mL) and stirred for ~14 hours at room temperature. Concentrating the mixture to dryness by rotary evaporation produces a yellow oil, which solidifies over time. The crude product was purified by flash chromatography with 4% methanol in dichloromethane to obtain 2.51 g (75%) of a white solid. ^{1}H NMR (DMF-d_7, 70 °C, referenced to DMF's aldehyde proton, ppm): δ 9.08 (s, 1H), 7.10 (s, 4H), 5.36–5.25 (m, 1H), 4.78 (ψt, J = 12 Hz, 1H), 4.70–4.61 (m, 1H), 4.11 (dd, J_{dd} = 12 Hz, J_d = 2.7 Hz, 1H), 3.83 (dd, J_{dd} = 12 Hz, J_d = 2.3 Hz, 1H), 2.60–2.25 (m, 18H). ^{13}C NMR (DMF-d_7, 70 °C, referenced to DMF's aldehyde carbon, ppm): δ 161.9, 141.2, 140.9, 138.2, 136.7, 132.4, 131.1, 131,0, 130.8, 130.6, 64.9, 63.9, 53.6, 21.3, 21.3, 18.6. HRMS (FAB+): *m*/*z* calc for $C_{22}H_{29}N_2O_4S$: 417.1848, found 417.1849.

Ruthenium complex 27. In a N_2-filled glove box, a 20 mL vial, equipped with a stir bar, was charged with compound **25** (140 mg, 0.34 mmol) and dry, degassed THF (9 mL).

Also in the glove box, ruthenium complex **1** (304 mg, 0.37 mmol, 1.1 equiv) was weighed into a flame-dried round-bottom flask equipped with a stir bar. The vial was sealed with a septa-cap and the flask with a septum, and both vessels were removed from the glove box. The seals of both vessels were reinforced with Teflon tape, and they were brought under a positive argon pressure. The *tert*-butyl lithium solution in *n*-pentane was prepared by passing 1.7 M *tert*-butyl lithium in *n*-pentane (2.5 mL) through an oven-dried micro-filter into a flame-dried 20 mL vial that was sealed with a septa-cap and purged with argon. The actual concentration of the *tert*-butyl lithium solution was determined by titrating the filtered solution against recrystalized 2,6-di-*tert*-butyl-4-methylphenol (BHT) (202 mg) in dry, degassed THF (2 mL) at –78 °C with fluorene as an indicator. (Note: *tert*-Butyl lithium in *n*-pentane is pyrophoric. Handle with care under inert conditions. Be careful to know how to quench any residual *tert*-butly lithium solution prior to running this reaction.) The filtered *tert*-butyl lithium solution (1.4 M, 0.25 mL, 0.35 mmol, 1.0 equiv) was added to the vial containing the solution of compound **25** in THF at –78°C. This mixture was stirred at –78 °C for 20 minutes under a positive argon pressure to form NHC ligand **26**. This solution was transferred to the flask containing complex **1,** precooled to 0 °C, using a cannula. The reaction mixture was stirred at 0 °C for 20 minutes before warming to room temperature. The reaction was allowed to continue at room temperature for 16 hours. Using standard Schlenk techniques, the crude material was passed through a flame-dried fine frit into a flame-dried round-bottom flask under a positive argon pressure. Dry, degassed THF rinses were used to ensure quantitative transfer, and the THF was removed *in vacuo*. Degassed *n*-pentane (270 mL), pre-cooled to 0 °C, was added to the product solid, and the suspension was stirred at 0 °C for 30

minutes. Isolating the precipitate by vacuum filtration and drying under high vacuum provides 225 mg (69%) of a maroon, solid product. As described above, NMR characterization of complex **27** is complicated by restricted rotation around the NHC carbon-ruthenium bond, which yields broad peaks. Therefore, only peak locations and multiplicities are provided. ^{1}H and $^{31}P\{^{1}H\}$ NMR spectra are provided in Appendix 1. ^{1}H NMR (CD_2Cl_2, ppm): δ 19.1 (s), 8.91 (s), 7.72–6.37 (m), 5.73 (s), 4.74–3.38 (m), 3.01–0.56 (m). $^{31}P\{^{1}H\}$ NMR (CD_2Cl_2, ppm): δ 29.6, 29.2.

Ruthenium complex 28. In an N_2-filled glove box, a 20 mL vial, equipped with a stir bar, was charged with compound **15** (693 mg, 1.45 mmol, 1.2 equiv), potassium *tert*-butoxide (95%, 172 mg, 1.46 mmol, 1.2 equiv), and dry, degassed THF (12 mL). The suspension was stirred for 10 minutes at room temperature over which time a yellow solution forms. This solution was transferred to a round-bottom flask and charged with ruthenium complex **1** (1.0g, 1.21 mmol). Additional THF (12 mL) was added to the reaction mixture; the flask was capped with a septum, and the reaction was stirred for 17 hours at room temperature. Upon reaction completion, the reaction flask was removed from the glove box, and the THF was removed *in vacuo*. The crude product was purified by anaerobic chromatography (as previously described in the General considerations section) on TSI silica gel-60 with 25% diethyl ether in *n*-pentane, though the product was loaded with degassed benzene. The product was lyophilized from degassed benzene and extensively dried under high vacuum (~24 hours) at 45 °C to obtain 721 mg (61%) of a fine, magenta powder. (Note: Product is air-sensitive in solution. Performing product collection and eluant removal under aerobic conditions yields product contaminated with

a small amount of tricyclohexylphosphine oxide.) As described above, NMR characterization of **28** is complicated by restricted rotation around the NHC carbon-ruthenium bond yielding broad peaks. Therefore, only peak locations and multiplicities are provided. ^{1}H and $^{31}P\{^{1}H\}$ NMR spectra are provided in Appendix 1. ^{1}H NMR (CD_2Cl_2, 40 °C, ppm): δ 19.23–19.11 (s with broad shoulder), 7.38 (ψt, J = 7.4 Hz), 7.11 (ψt, J = 7.6 Hz), 7.04 (s), 7.01 (s), 5.05–4.80 (br), 4.40–4.22 (br), 4.10 (ψt, J = 11 Hz), 3.97 (ψt, J = 11 Hz), 3.82–3.61 (m), 3.44–3.07 (m), 2.88–2.05 (m), 1.90 (s), 1.65–1.20 (m), 1.16–0.73 (m). $^{31}P\{^{1}H\}$ NMR (CD_2Cl_2, 40 °C, ppm): δ 29.4, 28.5. HRMS (FAB+) *m*/*z* calc for $C_{52}H_{76}N_3O_2Cl_2PRu$: 977.4096, found 977.4143.

General procedure for ring-closing metathesis reactions with catalyst 27. In a N_2-filled glove box, a 1-dram vial was charged with catalyst **27** (8.6 mg, 0.0086 mmol, 0.050 equiv) and deuterated solvent (0.5 mL). This vial and a screw-cap NMR tube were sealed with septa-caps and removed from the glove box. The seals of both the vial and the NMR tube were reinforced with Teflon tape, and both vessels were brought under a positive pressure of argon. DEDAM (42 μl, 0.17 mmol) was added to the vial containing **27**, and the reaction mixture was transferred to the screw-cap NMR tube by syringe. The reaction was allowed to continue for 12 hours at room temperature before determining its conversion by ^{1}H NMR spectroscopy. All reported conversions are the average of two trials.

Attempt to synthesize ruthenium complex 29. An oven-dried 20 mL vial, equipped with a stir bar and charged with ruthenium complex **27** (196 mg, 0.20 mmol), was

brought into an N_2-filled glove box. Dry, degassed dichloromethane (0.66 mL) and dry, degassed pyridine (0.66 mL, 8.2 mmol, 40 equiv) were added to the vial, and the reaction was stirred at ambient temperature for 15 minutes. The reaction mixture was transferred, drop-wise, to a flame-dried round-bottom flask, which contained ~50 mL of dry, degassed *n*-pentane and a stir bar. The flask was capped with a septum, removed from the glove box and brought under a positive argon pressure. The suspension of green, precipitated product in *n*-pentane was stirred at room temperature for 30 minutes prior to isolating the product by vacuum filtration. This material was dried under vacuum to obtain 166 mg of a green, solid product as a mixture of compounds. ^{1}H NMR (CD_2Cl_2, benzylidene proton resonances, ppm): δ 19.0 (s, relative integration: 2.5), 17.9 (s, relative integration: 1.0), 17.5 (s, relative integration 3.2). The ^{31}P NMR spectrum indicated the absence of any phosphorus-containing compound.

Attempt to synthesize ruthenium complex 30. In an N_2-filled glove box, a 1-dram vial, equipped with a stir bar, was charged with $Cl_2Ru(=CH\text{-}o\text{-}O\text{-}i\text{-}PrC_6H_4)PPh_3$[44] (19.2 mg, 0.033 mmol), complex **25** (21.0 mg, 0.050 mmol, 1.5 equiv), potassium hexamethyldisilazane (95%, 10.7 mg, 0.051 mmol, 1.5 equiv), and dry, degassed THF (1 mL). The reaction was allowed to continue at room temperature for 6 hours before. Upon reaction completion, the product mixture was passed through a fine frit and precipitated into diethyl ether to obtain a green solid, which was further purified by flash chromatography on TCI silica gel 60 with 10% methanol in dichloromethane. An impure, green solid product was obtained in low yield. ^{1}H NMR (CD_3OD, benzylidene proton

resonance, ppm): δ 16.6 (s). The ^{31}P NMR spectrum indicated the absence of any phosphorus-containing compound.

Attempt to synthesize ruthenium complex 31. In an N_2-filled glove box, a 1-dram vial was charged with ruthenium complex **27** (20.5 mg, 0.021 mmol), compound **32** (5.6 mg, 0.021 mmol, 0.98 equiv), and copper(I)chloride (2.3 mg, 0.023 mmo, 1.1 equiv) and equipped with a stir bar. The vial was sealed with a septa-cap and removed from the glove box. Dry, degassed dichloromethane (0.5 mL) was added to the vial, and its seal was reinforced with Teflon tape. The reaction mixture was heated to 40 °C, and the reaction was allowed to continue at that temperature for 1 hour. After cooling to room temperature, the product mixture was passed through a plug of celite, and the volatiles were removed by rotary evaporation. The crude material was purified chromatographically on neutral, Brockman grade III alumina with 20% methanol in dichloromethane to obtain a somewhat impure green solid product in low yield. ^{1}H NMR (CD_3OD, benzylidene proton resonance, ppm): δ 16.7 (s). The ^{31}P NMR spectrum indicated the absence of any phosphorus-containing compound.

Attempt to synthesize ruthenium complex 33. A flame-dried round-bottom flask, equipped with a stir bar, was charged with ruthenium complex **4** (51.4 mg, 0.071 mmol, 1.0 equiv), bis(*p*-sulfonatophenyl)phenylphosphine dihydrate dipotassium salt (31.5 mg, 0.069 mmol) and dry, degassed DMF (6.9 mL). The reaction was stirred at room temperature for 20 minutes under a positive argon pressure. The DMF was then removed *in vacuo* at an elevated temperature (40–60 °C). The product was then dissolved in

methanol and precipitated into diethyl ether. The precipitate was isolated by vacuum filtration and rinsed with diethyl ether (2×) to obtain 59.5 mg of a light-pink material. Both ^{1}H and ^{31}P NMR spectroscopy of this material in deuterated methanol reveal the presence of multiple complexes.

Attempt to synthesize ruthenium complex 34. A flame-dried, two-necked round-bottom flask, equipped with a stir bar, was charged with ruthenium complex **5** (17.0 mg, 0.023 mmol), sodium pyridine-3-sulfonate (**37**) (8.5 mg, 0.047 mmol, 2.0 equiv), dry, degassed methanol (0.6 mL), and dry, degassed toluene (1.7 mL). The reaction mixture was stirred for 30 minutes at room temperature and the volatiles were removed *in vacuo*. Additional dry, degassed methanol (0.6 mL) and dry, degassed toluene (1.7 mL) were added, and the reaction mixture was stirred for 15 minutes before removing the volatiles *in vacuo*. This process of methanol and toluene addition followed by stirring and volatile removal was repeated two more times. Drying under high vacuum for 4 hours yields a green solid product of questionable purity and identity. ^{1}H NMR (CD_3OD, benzylidene proton resonances, ppm): δ 18.4 (s, relative integral: 2.45), 17.5 (s, relative integral: 1.00).

References and Notes

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CHAPTER 4

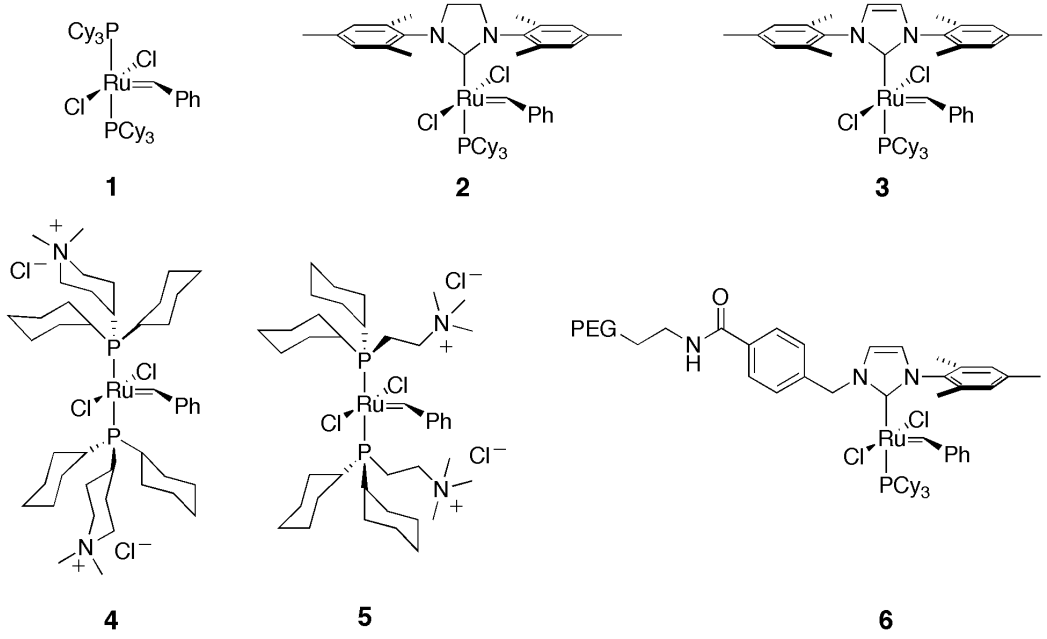
Effect of Water on the Stability and Initiation of Olefin Metathesis Catalysts Containing an *N*-Heterocyclic Carbene Ligand

Abstract

To aid the development of a water-soluble, ruthenium-based olefin metathesis catalyst containing an *N*-heterocyclic-carbene ligand, the decomposition of $(H_2IMes)(PCy_3)(Cl)_2Ru{=}CHPh$ (H_2IMes = 1,3-dimesityl-imidazolidine-2-ylidine, PCy_3 = tricyclohexylphosphine) and its methylidene and ethylidene analogs are examined in water/THF solvent mixtures. While the benzylidene is quite stable towards water, the ethylidene and methylidene analogs are much less stable. The methylidene analog decomposes the most rapidly of the three complexes examined, and this decomposition is only mildly affected by the presence of added chloride ion or PCy_3. The initiation of both the benzylidene and methylidene complexes is more rapid in water, which yields higher concentrations of the reactive fourteen-electron species and may contribute to the increased decomposition rates. Furthermore, methylidene analog decomposition occurs through multiple pathways, though most pathways involve the generation of tricyclohexyl(methyl)phosphonium chloride salt. The decomposition behavior of both the methylidene and ethylidene analogs in the presence of water indicate a direct interaction between water and the ruthenium complex. Finally, two interesting characteristics of ethylidene decomposition are observed.

Introduction

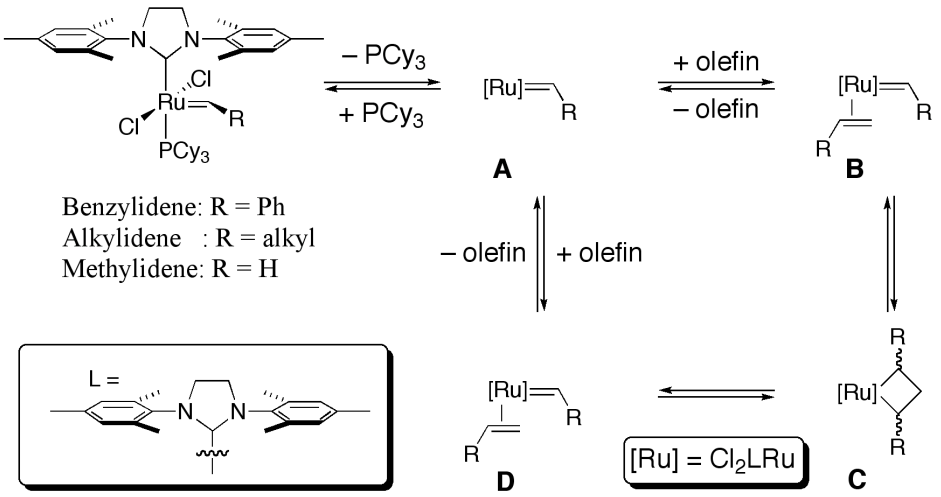
Up to this point, the focus of aqueous metathesis has been modifying the ligand scaffold of catalysts **1**–**3** to increase their solubility in water. The results of this research are water-soluble catalysts **4**–**6**.[1-6] While catalysts **4**–**6** all perform olefin metathesis in water, they are insufficiently stable to mediate the full range of metathesis processes. As described in Chapters 2 and 3, the goal of this thesis is the production of water-soluble catalysts containing an *N*-heterocyclic carbene (NHC) ligand. For reasons explained in Chapter 3, water-soluble analogs of catalyst **2** are of particular interest. To assist the design of such catalysts that are stable and soluble in water, the effect of water on the decomposition of parent catalyst **2** is of interest.



Scheme 4.1 illustrates the accepted mechanism of ruthenium-based olefin metathesis.[7] Every step of this mechanism is fully reversible. The catalytic cycle is initiated by the dissociation of the phosphine ligand to yield the fourteen-electron species

A. The interaction of **A** with a substrate molecule forms olefin-bound complex **B**, which further reacts to generate metalocyclobutane **C**. Fragmentation of the metalocyclobutane and dissociation of the product olefin from complex **D** completes the catalytic cycle. In olefin metathesis reactions, the initial ruthenium-benzylidene complex (R = Ph, benzyl carbene) reacts with substrate to form either an alkylidene (R = alkyl, alkyl carbene) or methylidene (R = H, methylidene carbene) complex. In productive metathesis, the alkylidene complex reacts with a second substrate molecule to generate product and a propagating ruthenium alkylidene or methylidene complex when the second substrate's olefin is internal or terminal respectively. Therefore, to fully understand catalyst stability, the relative stabilities of the ruthenium benzylidene and its alkylidene and methylidene analogs must be examined. This prompts the study of the decomposition of catalyst **2** and the alkylidene/ethylidene (**7**) and methylidene (**8**) analogs of **2** in the presence of water.

Scheme 4.1.



Earlier research reveals a few aspects regarding the decomposition of ruthenium-based olefin metathesis catalysts.[8-14] Ulman and Grubbs report that the bis(phosphine)

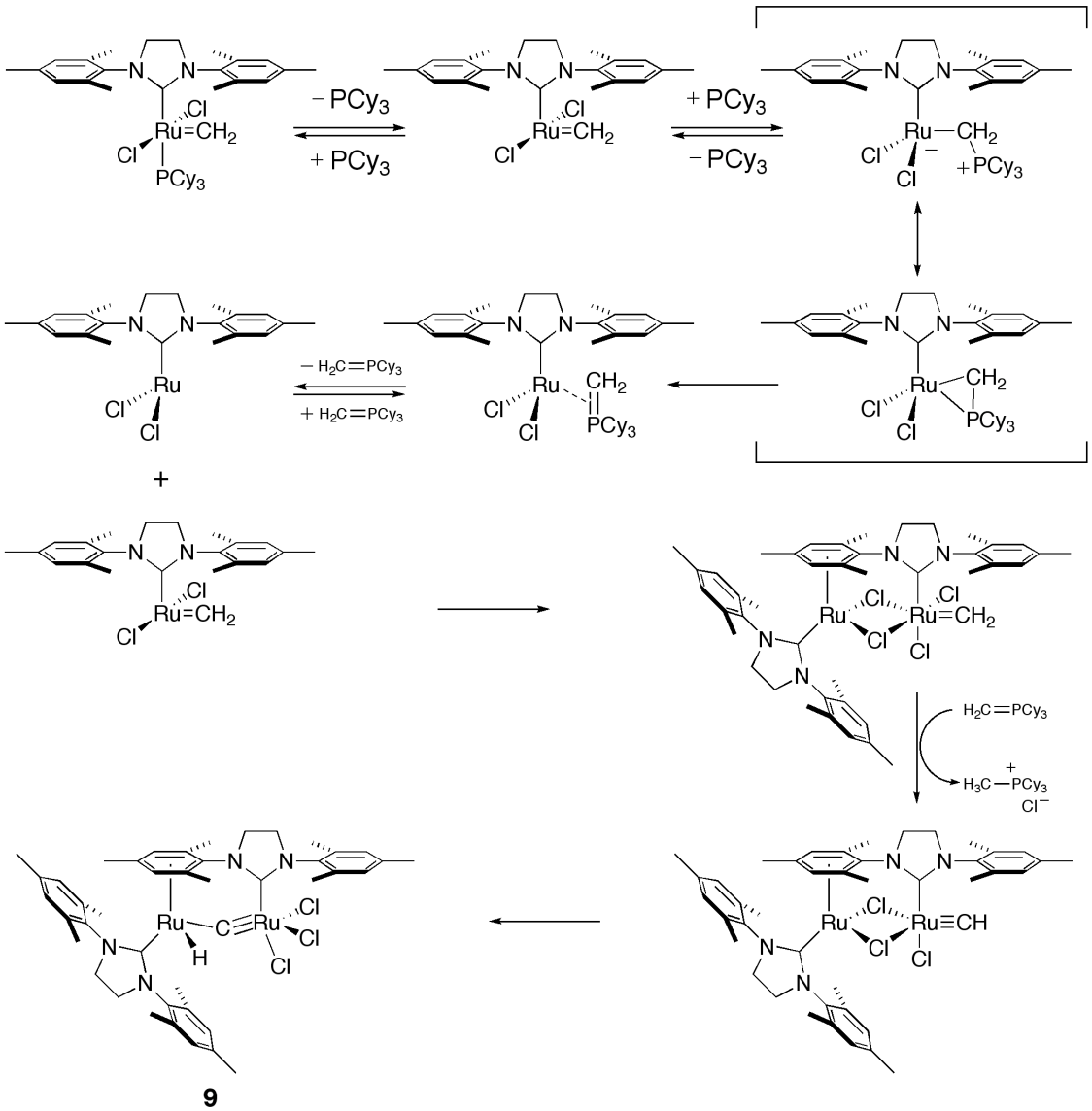
methylidene complex decomposes by a very different mechanism than alkylidene complexes.[8,9] The rate of bis(phosphine) methylidene decomposition is clearly first order in the methylidene complex. In contrast, alkylidene complexes decompose by bimetallic mechanisms as revealed by the formation of 3-hexene during the decomposition of the bis(phosphine) propylidene complex.[8] The results of this research indicate that the order of complex stability is benzylidene > alkylidene > methylidene.[9]

More recent studies examine the decomposition of ruthenium catalysts containing NHC ligands.[10-14] The available research suggests that, like the bis(phosphine) complexes, the order of complex stability for catalysts containing an NHC ligand is benzylidene > alkylidene > methylidene.[10] However, in general, the stabilities of catalysts containing an NHC ligand are one or two orders of magnitude higher than their bis(phosphine) analogs.[11,12] Furthermore, research by Hong and Grubbs illuminates the decomposition of ruthenium methylidene complex **8** in organic solvents.[13,14] They show that the free tricyclochexylphosphine (PCy_3) generated upon complex initiation can nucleophilically attack the carbon double-bonded to the ruthenium center, the methylidene carbon.[13,14] This is the first step along a decomposition pathway that produces the bimetallic ruthenium hydride complex, **9**, as shown in Scheme 4.2. The rate of this decomposition is independent of the concentration of free PCy_3.[13]

Methylidene complex, **8**, is a crucial intermediate formed during the metathesis of terminal olefins with catalyst **2**.[9-11,15] However, as described above, **8** is the least stable ruthenium complex produced during olefin metathesis.[10,13,14] Moreover, methylidene complexes are particularly unstable in aqueous environments.[5,6] Therefore, this research, which pursues the production of stable, water-soluble metathesis catalysts, will focus on

understanding the effect of water on the decomposition of methylidene complex **8**, though the decomposition of benzylidene **2** and alkylidene/ethylidene **7** will also be examined.

Scheme 4.2.



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Results and Discussion

Experimental approach. The decomposition rates were determined using ^{1}H NMR spectroscopy by following the diminution of the integral of the ruthenium complex's alkylidene-hydrogen resonance over time.[16] Water/THF solvent mixtures were the chosen media for these studies due to the high solubility of water in THF. This solubility allowed for the measurement of decomposition in solutions with water concentrations as high as 8 M. Poor catalyst solubility in THF solutions with water concentrations ≥10 M prevented the examination of decomposition in the presence of higher water concentrations.[17] Protio water was utilized in these experiments to avoid any proton/deuterium exchange of the alkylidene hydrogen, as has been previously observed for other ruthenium alkylidene complexes in this solvent environment.[18] Therefore, to attain adequate solute signal to noise, at water concentrations >4 M, solvent suppression was used to minimize the proton resonance due to water. All samples were freshly prepared prior to each experiment. Limited stability of the examined compounds in THF prohibited the use of stock solutions.

Decomposition of ruthenium benzylidene complex 2 in the presence of water. Previous research showed that ruthenium benzylidene complex **2** is quite stable in organic solvents, even in the presence of trace water.[7,11] Consistent with this data, following the decomposition of **2** at ambient temperature in 4 M water/THF yields a half-life of roughly 6 days. Moreover, **2** can be observed for hours at 50 °C in 8 M water/THF without noticeable decomposition. These data suggest that ruthenium benzylidene complexes that contain an NHC ligand are reasonably persistent in an aqueous

environment. Therefore, it is believed that their stability is likely sufficient for a water-soluble analog of catalyst **2**.

Decomposition of methylidene complex 8 in the presence of water. In contrast with complex **2**, ruthenium methylidene complex, **8**, fully decomposes in less than 10 minutes at 50 °C in the presence of just 20 equivalents (0.46 M) of water in THF. However, at 25 °C, its rate of decomposition is sufficiently slow to allow for its measurement at water concentrations as high as 8 M. Representative plots for the observed sample decomposition over time are provided in Figure 4.1. Additionally, the measured decomposition rate constants for complex **8** at 25 °C and multiple water concentrations are listed in Table 4.1.

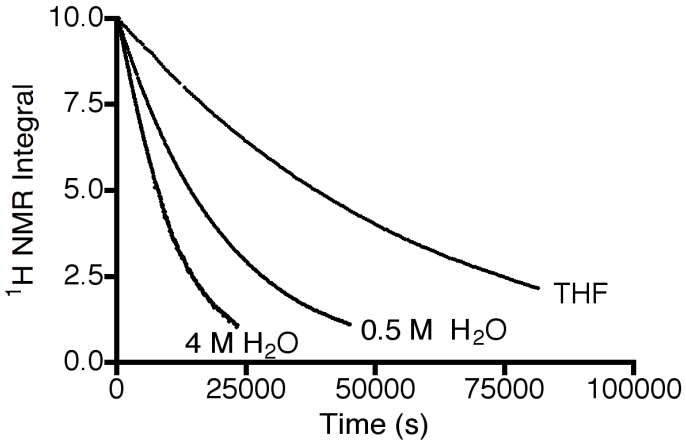


Figure 4.1. The decomposition rate of ruthenium methylidene complex **8** increases with increasing water concentrations.

Table 4.1. Effect of water on the decomposition rate of 0.023 M ruthenium methylidene complex **8** at 25 °C

Solvent	k_{obs} (s^{-1})	$t_{1/2}$ (h)
THF	$(1.78 \pm 0.01) \times 10^{-5}$	10.79 ± 0.09
0.5 M H_2O/THF	$(5.03 \pm 0.01) \times 10^{-5}$	3.83 ± 0.01
1 M H_2O/THF	$(6.59 \pm 0.02) \times 10^{-5}$	2.93 ± 0.01
2 M H_2O/THF	$(7.92 \pm 0.05) \times 10^{-5}$	2.43 ± 0.02
3 M H_2O/THF	$(8.78 \pm 0.05) \times 10^{-5}$	2.19 ± 0.01
4 M H_2O/THF	$(9.33 \pm 0.09) \times 10^{-5}$	2.07 ± 0.02
8 M H_2O/THF	$(15.7 \pm 0.1) \times 10^{-5}$	1.30 ± 0.01

As shown in Table 4.1, the rate constants for the decomposition of **8** rapidly increase from $(1.78 \pm 0.01) \times 10^{-5}$ s^{-1} in the absence of water to $(6.59 \pm 0.02) \times 10^{-5}$ s^{-1} in 1 M water/THF. Interestingly, the acceleration of the decomposition rate greatly diminishes at water concentrations greater than 1 M. The observed behavior is consistent with an exponential decay of this acceleration with respect to water concentration. Indeed, a plot of the measured half-lives versus water concentration, Figure 4.2, can be readily fit to a two-phase exponential decay with an R^2 value of 0.9998. From this fit, the extrapolated half-life of methylidene complex **8** in pure water, 55.5 M, is 143 s with a standard error of 4400 s. Despite the large error due to extensive extrapolation, these data clearly indicate that the decomposition of **8** in water is quite rapid at 25 °C. From these data, the order of water in the decomposition kinetics of complex **8** is unclear. However, as will be discussed later, this effect of water on the decomposition of **8** may be indicative of a direct interaction between water and complex **8**.

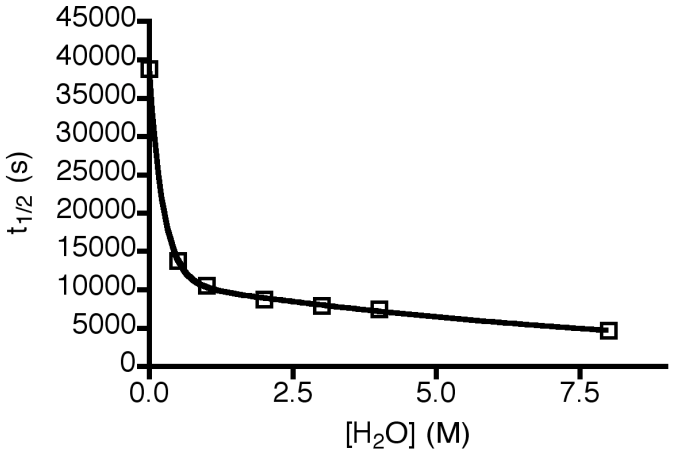


Figure 4.2. A plot of the decomposition half-life versus water concentration for 0.023 M of ruthenium methylidene complex **8** at 25 °C is nonlinear. The acceleration of **8**'s decomposition due to increasing water concentration can be fit to a two-phase exponential decay ($R^2 = 0.9998$).

As demonstrated in Figure 4.3, a plot of $\ln[\mathbf{8}]_0 - \ln[\mathbf{8}]$ versus time yields straight lines for the decomposition of **8** in pure THF and 0.5 and 4 M aqueous THF. These data are consistent with decomposition being first order in methylidene complex **8**. Measuring the decomposition of samples containing twice the initial concentration of **8** in 4 M water/THF readily confirms this kinetic order. Such samples do decompose twice as fast to yield a rate constant of $(1.16 \pm 0.01) \times 10^{-4}$ s^{-1} (initial rate = $\sim 5.3 \times 10^{-6}$ $M \cdot s^{-1}$) which is in reasonable agreement with the $(9.33 \pm 0.09) \times 10^{-5}$ s^{-1} rate constant (initial rate = $\sim 2.1 \times 10^{-6}$ $M \cdot s^{-1}$) obtained from earlier samples with lower initial concentrations of complex **8**.

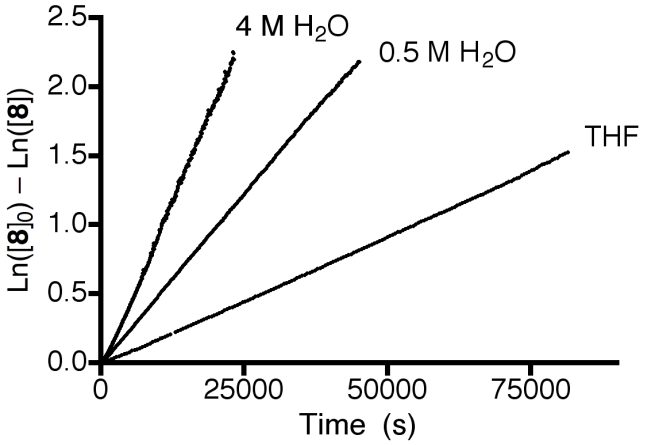
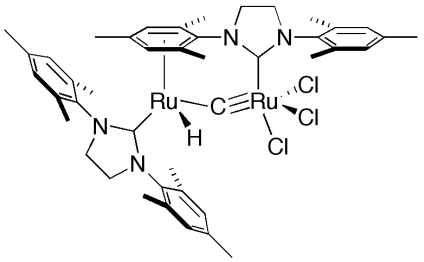


Figure 4.3. Plotting $\ln([\mathbf{8}]_0 - \ln([\mathbf{8}])$ versus time reveals that the decomposition of **8** is first order in itself in both the presence and absence of water.

The decomposition of **8** in THF and water/THF solvent mixtures produces black, opaque solutions. Spectroscopic examination of these solutions reveals that decomposition occurs through a variety of pathways. After decomposition in 0.5 M water, 7 peaks can be observed in the hydride region of the ^{1}H NMR spectrum between 0 and –30 ppm while only 4 of these peaks can be observed after decomposition in 4 M water. Peaks are not observed between 0 and –30 ppm in the ^{1}H NMR spectrum after decomposition in 8 M water.

One of the observed resonances in the ^{1}H NMR spectra is a doublet centered at –25.3 ppm. Removing the volatiles from a decomposed sample *in vacuo* and obtaining its ^{1}H and ^{31}P NMR spectra in deuterated dichloromethane reveals that this resonance is consistent with ruthenium hydride **10**.[19,20] This hydride is also observed for the decomposition of benzylidene compound **2** in the presence of methanol or other aliphatic alcohols.[19]



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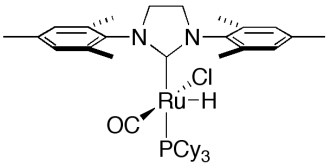

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At this time, the other six resonances in the hydride region of the ^{1}H NMR spectra have not been identified, although a singlet at –8.6 ppm is speculated to be the bimetallic hydride **9** as observed in the decomposition of **8** in benzene.[13] Regardless, all of these high-field resonances are actually minor peaks in the ^{1}H NMR spectra and represent relatively small amounts of material. Therefore, while ^{1}H NMR spectroscopy does not reveal any single dominant, ruthenium-based decomposition product, it does indicate the existence of a branch-point in the mechanism of **8**'s decomposition, which allows for the generation of the multiple products observed.

In contrast with the ^{1}H NMR spectra, the ^{31}P NMR spectra of solutions of decomposed **8** clearly show the presence of one dominant phosphorus-containing decomposition product at 34.8 ppm in all samples containing added water. In the absence of water, this peak is still the major phosphorus resonance, but other significant resonances are also observed. Suspecting the peak at 34.8 ppm to correspond to tricyclohexyl(methyl)phosphonium chloride salt (Cy_3PMeCl),[13] mild purification of multiple decomposed samples was accomplished by precipitation into ether to attain a black solid. High-resolution mass spectroscopy of this solid reveals the presence of the salt (calc: 295.2555, measured: 295.2552). Moreover, ^{1}H NMR and ^{1}H/^{31}P HMQC NMR spectroscopy confirm the assignment of the 34.8 ppm phosphorus resonance as

Cy_3PMeCl.[21] Therefore, while ^1H NMR reveals the presence of many decomposition pathways, ^{31}P NMR shows that pathways yielding Cy_3PMeCl tend to dominate the decomposition of ruthenium methylidene complex **8**.

Effect of additives on the decomposition of methylidene compound 8 in water. To develop a water-soluble analog of catalyst **2**, this issue of methylidene complex stability must be addressed. Therefore, experiments were designed to obtain information regarding the decomposition of methylidene complex **8** in the presence of water. Two components of **8** were identified as likely sources of complex instability—the ruthenium-chloride bonds and the fourteen-electron species generated upon phosphine dissociation (Scheme 4.1).

That the chloride ligands in complex **2** can be readily displaced by a variety of nucleophiles is well documented. Carboxylic acids,[22-24] various alcohols,[11,25,26] sulfonates,[23] and other halides[7] are all reported to displace the chloride ligands. Furthermore, research studying the formation and isomerization behavior of ruthenium hydrides generated by treating catalysts **1** and **2** with various protic solvents reveal a rate enhancement of ruthenium hydride formation upon the addition of base.[19,27] Therefore, these authors propose chloride displacement to generate hydrogen chloride as an early step in hydride formation. Furthermore, water is proposed to displace a chloride during deuterium exchange with the alkylidene hydrogen of bis(phosphine) complex **5** in deuterium oxide.[18] Given these observations, displacement of a chloride ligand of methylidene complex **8** by water is considered a potential step in catalyst decomposition (Table 4.2).

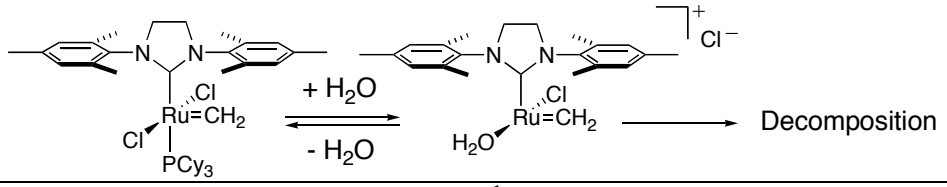
Measuring the effect of tetrabutylammonium chloride ($^{n}Bu_4NCl$) on the rate of **8**'s decomposition in 4M water/THF allows for the examination of potential chlorine displacement by water. By the common ion effect, the added chloride ions should inhibit or preclude the displacement of a chloride ligand by water. This should decrease the rate of complex decomposition assuming that chlorine displacement by water is an initial step in decomposition. However, the measured rate constant of $(8.7 \pm 0.2) \times 10^{-5}$ s^{-1} in the presence of 10 equivalents of excess chloride is only mildly slower than the rate constant of decomposition measured in the absence of the additive ($(9.33 \pm 0.09) \times 10^{-5}$ s^{-1}). Thus, displacement of the chloride ligand by water either does not occur under these conditions, is not involved in a major decomposition pathway or is a relatively rapid process occurring after the rate-determining step in the decomposition of ruthenium methylidene complex **8**.

Another aspect of complex **8** that may play a role in its decomposition is the stability of the fourteen-electron species generated upon phosphine dissociation. This dissociation serves as a catalyst initiation step within the context of the metathesis reaction[7,28] and is known to play a major role in the decomposition of some metathesis-active ruthenium bis(phosphine) complexes.[8] Along with freeing a ruthenium coordination site, phosphine dissociation greatly reduces the steric shielding around the methylidene carbon of **8**. Rates for decomposition pathways that require coordination to this newly available site and/or nucleophilic attack at the methylidene carbon should be greatly affected by the concentration of the fourteen-electron species.

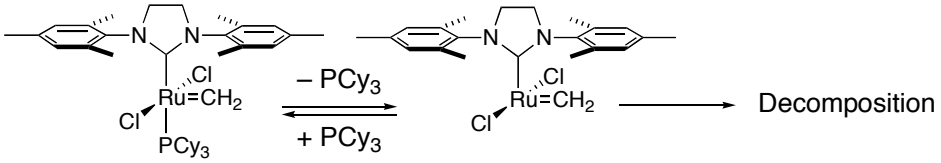
As phosphine dissociation is a reversible process for ruthenium-based metathesis catalysts,[7,28] the presence of excess free phosphine will lower the concentration of the

fourteen-electron species. Hence, the effect of excess phosphine on the rate of methylidene complex **8**'s decomposition should illuminate the possible role of the fourteen-electron species in this decomposition. An examination of **8**'s decomposition in 4 M water/THF in the presence of 10 equivalents of PCy_3 yields an observed rate constant of $(7.63 \pm 0.01) \times 10^{-5}$ s^{-1}, which is moderately slower than decomposition in the absence of excess phosphine ($(9.33 \pm 0.09) \times 10^{-5}$ s^{-1}). Increasing the amount of PCy_3 to 20 equivalents has a similar effect on the rate of complex **8**'s decomposition as compared to adding 10 equivalents of PCy_3 (Table 4.2).

Table 4.2. Effect of additives on the decomposition rate of 0.023 M ruthenium methylidene complex **8** in 4 M H_2O/THF at 25 °C



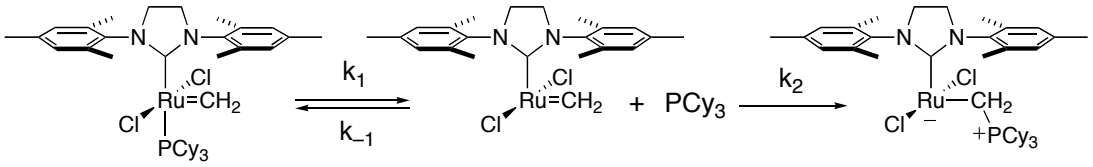
Additive (amount)	k (s^{-1})	$t_{1/2}$ (h)
None	$(9.33 \pm 0.09) \times 10^{-5}$	2.07 ± 0.02
$^{n}Bu_4NCl$ (10 equiv)	$(8.7 \pm 0.2) \times 10^{-5}$	2.22 ± 0.04



Additive (amount)	k (s^{-1})	$t_{1/2}$ (h)
PCy_3 (10 equiv)	$(7.63 \pm 0.01) \times 10^{-5}$	2.545 ± 0.005
PCy_3 (20 equiv)	$(7.16 \pm 0.02) \times 10^{-5}$	2.690 ± 0.007

As previously described, recent research examining the decomposition of ruthenium methylidene complex **8** in benzene demonstrated that PCy_3 plays an active role during decomposition by reacting with the methylidene carbon to form Cy_3PMeCl.[13,14] This salt may be the result of phosphine migration from the ruthenium atom in complex **8**

to its methylidene carbon or caused by nucleophilic attack on the methylidene carbon of the fourteen-electron species by PCy_3. Later steps are then responsible for the cleavage of the ruthenium-carbon bond and protonation to form the phosphonium salt. Consistent with this earlier research, the formation of Cy_3PMeCl is observed for the decomposition of **8** in THF in both the presence and absence of water.



8 **11** **12**

$$\frac{d[\mathbf{12}]}{dt} = k_2[\mathbf{11}][PCy_3] \tag{4.1}$$

$$[\mathbf{11}][PCy_3] = \frac{k_1[\mathbf{8}]}{k_{-1} + k_2} \quad \text{(steady - state approximation)} \tag{4.2}$$

$$\frac{d[\mathbf{12}]}{dt} = \frac{k_2 k_1[\mathbf{8}]}{k_{-1} + k_2} \tag{4.3}$$

The rate of complex **8**'s decomposition should be independent of phosphine concentration in the case of phosphine migration as the process is unimolecular. Assuming the steady-state approximation, decomposition by the nucleophilic attack of PCy_3 at the methylidene carbon is also expected to proceed with a rate independent of phosphine concentration as illustrated in eqs 4.1–4.3. Increasing the concentration of free phosphine has a moderate effect on the rate complex **8**'s decomposition. This effect can be understood as a mild breakdown of the steady-state approximation within the context

of nucleophilic attack by free PCy_3 on complex **8**'s fourteen-electron species' methylidene carbon.

Effect of water on complex initiation. Assuming that the described nucleophilic attack by free PCy_3 plays a prominent role in methylidene complex **8**'s decomposition, one explanation for water's effect on this decomposition is that water increases the rate of phosphine dissociation. Research shows that phosphine-containing, ruthenium-based metathesis catalysts initiate more rapidly in solvents with higher dielectric constants (Table 4.3, first three entries).[7] Moreover, the observed data indicates that initiation may occur through solvent-assisted pathways in coordinating solvents though a solvent coordinated complex is not observed.[7] Therefore, in the context of the current study, added water may be largely serving to increase the rate of phosphine dissociation by increasing the solution's dielectric and/or by participating in a solvent-assisted dissociation mechanism as exemplified in Scheme 4.3. To examine this possibility, ethyl vinyl ether-based kinetics were performed on compounds **2** and **8** in the presence and absence of water in THF at 25 °C.

Scheme 4.3.

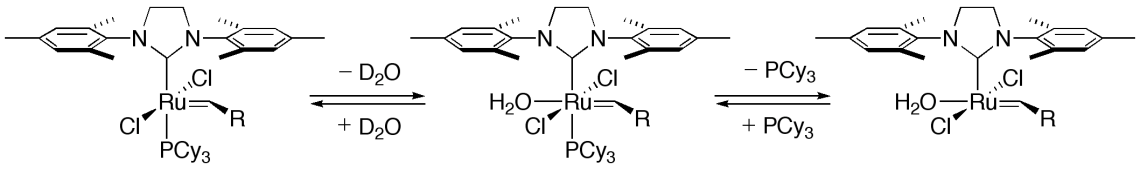
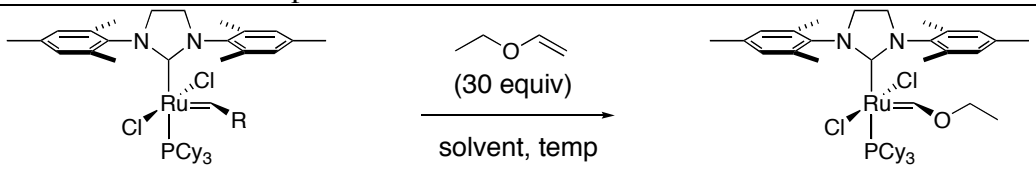


Table 4.3. ^{1}H NMR initiation kinetics for 0.017 M ruthenium complex and 0.5 M ethyl vinyl ether at the listed temperature and solvent



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Solvent	R	Temp (°C)	Dielectric Constant	k (s^{-1})	$t_{1/2}$ (min)
toluene[a]	Ph	35	2.38	$(4.6 \pm 0.4) \times 10^{-4}$	25 ± 2
Dichloromethane[a]	Ph	35	8.9	$(6.1 \pm 0.2) \times 10^{-4}$	18.9 ± 0.6
THF[a]	Ph	35	7.32	$(1.0 \pm 0.1) \times 10^{-3}$	12 ± 1
THF	Ph	25	7.32	$(2.377 \pm 0.004) \times 10^{-4}$	48.60 ± 0.08
4 M H_2O/THF	Ph	25	–	$(3.923 \pm 0.008) \times 10^{-4}$	29.45 ± 0.06
THF	H	25	7.32	7.0×10^{-5}	152
4 M H_2O/THF	H	25	–	1.7×10^{-4}	70

[a]These results are reported in reference 7. [b]These results are qualitative.

Ethyl vinyl ether reacts with complexes **2** and **8** to form the Fischer carbene, **13**.[29] In the presence of a large excess of the ether, this reaction was used by Grubbs and co-workers to measure the initiation activities of a variety of ruthenium-based metathesis catalysts (Table 4.3, first three entries).[7] Furthermore, the kinetics of this reaction were shown to equal the rate of phosphine exchange for these complexes as phosphine dissociation is the rate-determining step of catalyst initiation.[7] In this manner, ethyl vinyl ether is used in this study to examine the effect of water on the initiation/phosphine dissociation rates of complexes **2** and **8**.

Mixing ruthenium complex **2** or **8** with 30 equivalents of ethyl vinyl ether in the presence and absence of water in THF yields the initiation rate constants shown in Table 4.3 as measured by ^{1}H NMR spectroscopy. In 4 M water/THF, ruthenium benzylidene complex **2** initiates ~1.7 times faster than in water's absence. Water has the same effect on ruthenium methylidene complex **8**, which appears to initiate ~2 times faster in the presence of water. However, the results for complex **8**'s initiation should be treated as

qualitative. While >90% of **8** is observed to form Fischer carbene **13**, significant decomposition is also observed prohibiting the quantitative measurement of complex **8**'s initiation. While **8**'s initiation appears to roughly double in the presence of 4 M water, its rate of decomposition increases by a factor of ~5. Therefore, although water does increase the rate of phosphine dissociation and such likely contributes to complex **8**'s increased rate of decomposition, water appears to serve a more extensive role in **8**'s decomposition.

Mechanism of the decomposition of methylidene complex 8 in the presence of water. The decomposition mechanism of ruthenium methylidene complex **8** is complicated, as the observed decomposition products indicate multiple decomposition pathways. However, the decomposition of **8** is first order in itself, and most decomposition pathways involve the formation of Cy_3PMeCl. Therefore, many of the decomposition pathways likely share a single initiation step. From the effect of excess PCy_3 on complex **8**'s decomposition and the effect of water on complex initiation, this step is proposed to be phosphine dissociation. Nucleophilic attack on the the methylidene carbon of **8**'s fourteen-electron species by PCy_3 followed by fragmentation then yields the observed phosphonium salt (Scheme 4.4). These steps are already proposed to be part of the dominant pathway for the decomposition of **8** in anhydrous benzene.[13,14] In the same way, nucleophilic attack on the methylidene carbon of **8**'s fourteen-electron species by water may be an initial step in the formation of the observed ruthenium carbonyl hydride, **10**.

The effect of water on the decomposition of **8** can be considered as the aggregate result of two distinct causes. First, the addition of water changes the chemical

environment (i.e., dielectric constant). Clearly such changes should effect the rate of decomposition. Additionally, water may directly interact with **8** by coordinating to the metal center or a variety of other mechanisms.[30]

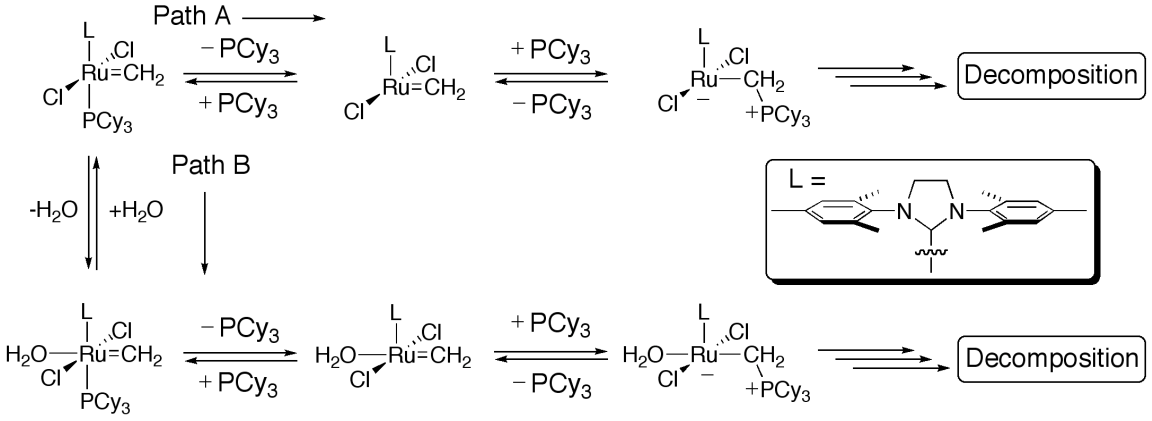
If water's impact on decomposition rates can be attributed entirely to its effect on the chemical environment, the effect of increasing the water concentration on decomposition rates should be approximately linear since environmental properties will be changing roughly linearly with increasing water concentration.[31-34] However, Figure 4.2 clearly shows that the relationship between increasing water concentration and the decomposition rate is nonlinear. Indeed, while increasing the water concentration from 0 to 1 M increases the decomposition rate constant by a factor of ~3.7, further increasing the water concentration to 4 M corresponds to a rate constant increase of only ~1.4.

The observed decomposition behavior appears indicative of a direct interaction between methylidene complex **8** and water under these conditions. However, the inability to directly observe such an interaction makes this proposition speculative, and a decomposition mechanism where water simply effects the chemical environment cannot be discounted at this time.

The current hypothesis regarding the speculated water/**8** interaction is that water may be reversibly coordinating to the ruthenium center to form a hexacoordinate complex, which may then decompose as illustrated in Scheme 4.4. The examined water concentrations are too high to determine the order of water in complex decomposition.[35] However, the proposed coordination is reasonable as other sigma-donating ligands, such as pyridines, are known to coordinate to ruthenium at that position,[36] and the negligible effect of chloride concentration on complex decomposition precludes the reversible

displacement of the chloride ligands by water before the rate-determining step. Unfortunately, evidence for water coordination cannot be directly observed by UV-Vis, NMR spectroscopy nor crystallography, which prevents a stronger endorsement for this conjecture. Even so, this is currently the favored explanation for the experimental results since an irreversible interaction should not cause the observed decrease in the acceleration of the decomposition rate of complex **8** at increased water concentrations (Figure 4.2).

Scheme 4.4.



Assuming a reversible coordination of water, the decomposition kinetics of ruthenium methylidene complex **8** can be interpreted as arising from the relative contributions of two competing decomposition pathways, A and B (Scheme 4.4). Pathway A involves decomposition of complex **8** absent any direct interaction between **8** and water during the initial decomposition steps while pathway B involves the coordination of water (Scheme 4.4). The relative contribution of pathway A to the total decomposition rate is then greater at lower water concentrations and diminishes at higher water concentrations as more of the water-coordinated species is formed. At sufficiently

high water concentrations, all decomposition occurs through pathway B involving the coordination of water to **8**'s ruthenium atom (Scheme 4.4). From Figure 4.2, the decomposition rate of **8** rapidly increases with increasing water concentration up to 1 M water. At these concentrations of water, both decomposition pathways A and B operate, and the large acceleration of decomposition is primarily due to the shunting of greater amounts of complex **8** through pathway B which is hypothesized to be more rapid. At water concentrations greater than 1 M, all decomposition occurs through pathway B and the slower rate of acceleration solely reflects the effect of the increasingly polar protic environment on pathway B's rate of decomposition.

At this point, it should be noted that PCy_3 is a good base, and it may deprotonate water to form hydroxide which is known to decompose ruthenium methathesis catalysts.[4] However, acid-base reactions always favor the formation of the weaker acid, and water (pKa = 15.7) is a weaker acid by several orders of magnitude than protonated PCy_3 (pka ~9.7).[37] Therefore, this process should be negligible. Even so, PCy_3 may be involved in other base-mediated decomposition pathways such as the deprotonation of ruthenium-coordinated water molecules.

Decomposition of ethylidene compex 7 in the presence of water. The observed data indicate that ruthenium methylidene complex **8** is not sufficiently stable toward water for productive aqueous metathesis. Also, an examination of the effect of additives on the decomposition rate does not yield immediate insights toward structural changes that may address this instability. Another approach to productive aqueous metathesis is to avoid ruthenium methylidene complex formation entirely by the appropriate choice of substrate. Obviously, internal olefins containing terminal phenyl groups make for ideal

substrates since they yield the relatively stable ruthenium benzylidene complex **2** during productive metathesis (Scheme 4.1). A second strategy is to employ substrates that contain internal olefins with terminal methyl groups. Such substrates have the advantage of being more synthetically available than their phenyl analogs. Productive metathesis reactions with these substrates produce ruthenium ethylidene complex **7** (Scheme 4.1). Therefore, examination of the decomposition of **7** in the presence of water should demonstrate the feasibility of this strategy. Additionally, as all productive metathesis reactions involve ruthenium alkylidene intermediates (Scheme 4.1), examination of ethylidene complex **7**'s decomposition can serve as a model for the general stability of ruthenium alkylidenes toward water.

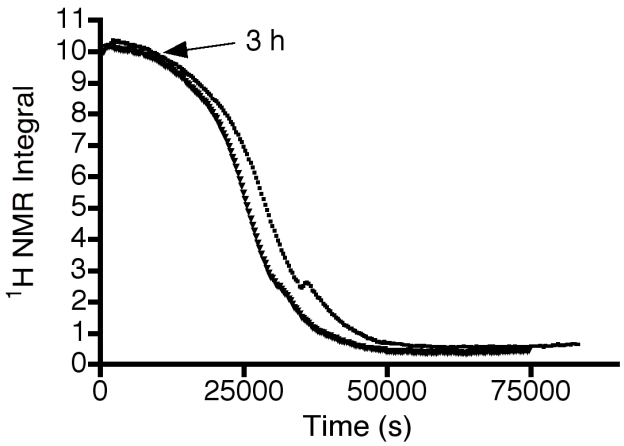


Figure 4.4. The decomposition of 0.023 M ruthenium ethylidene complex **7** in 4 M H_2O/THF at 25 °C occurs with ~3 hours of slow decomposition followed by rapid decomposition and with an observed half-life of ~7.5 hours. The two plots represent two separate trials.

Ruthenium ethylidene complex **7** can be readily synthesized by the reaction of **2** with *cis*-2-butene.[38] An examination of its decomposition in 4 M water/THF at 25 °C reveals the interesting decomposition behavior shown in Figure 4.4. There appears to be a

~3 hour period of slow decomposition followed by more rapid decomposition. Unfortunately, this behavior prohibits simple fitting of the data to an exponential decay to extract rate constants. However, ~6 hours are required for 75% decomposition of complex **8** in 4 M water/THF while ~11 hours are required to reach 75% decomposition for complex **7**. Therefore, ethylidene complex **7** is more stable toward water than methylidene complex **8**.

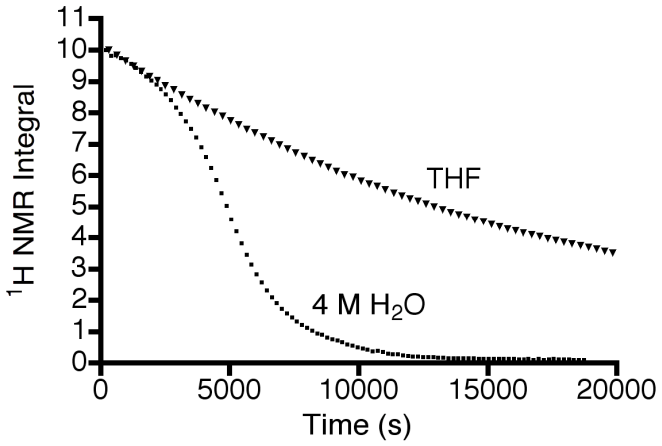


Figure 4.5. These plots represent the decomposition of 0.023 M ruthenium ethylidene complex **7** at 35 °C in the presence and absence of water.

Recently published work by Wagener and co-workers briefly examines the decomposition of complex **7** in benzene at 55 °C.[38] The published decomposition curves show far different behavior than that demonstrated in Figure 4.4. Therefore, the observed manner of decomposition may be due to the presence of water. To explore this possibility, the decomposition of **7** in THF and in 4 M water/THF was examined at 35 °C. As illustrated in Figure 4.5, in the absence of added water, complex **7** decomposes through a typical exponential decay ($k_{obs} = (5.87 \pm 0.03) \times 10^{-5}$ s^{-1} at 0.023 M). However, in the presence of 4 M water, curvature is observed at the beginning of the collected

decay, which is further evidence that water directly interacts with the ruthenium complex. Observation of **7**'s decomposition at 35 °C yielded two further interesting results.

As already described, ruthenium alkylidene and methylidene derivatives of bis(phosphine) complex **1** are known to decompose by very different mechanisms.[8] This is also believed to be true for metathesis catalysts containing NHC ligands.[7] The decomposition of ruthenium methylidene complexes, such as complex **8**, is known to be first order in the ruthenium methylidene complex.[8,13] However, the decomposition of ruthenium benzylidene and alkylidene complexes, such as complexes **2** and **7** respectively, is believed to be second order in the phosphine-dissociated fourteen-electron ruthenium complex.[8] To determine the kinetic order of ruthenium complex **7** in its decomposition under these conditions, the effect of doubling the concentration of **7** on its decomposition rate can be examined in both the presence and absence of 4 M water in THF (Figure 4.6).

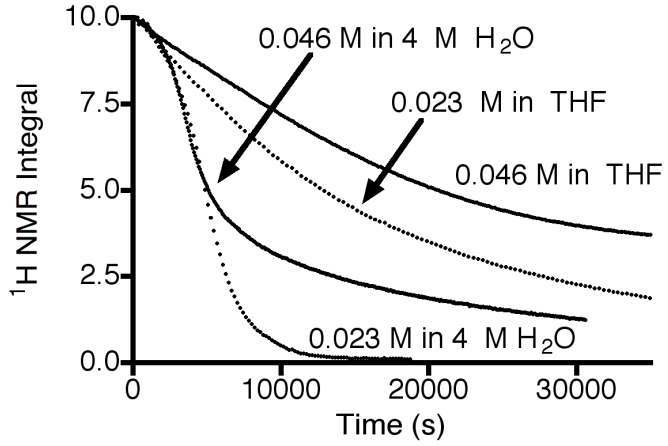
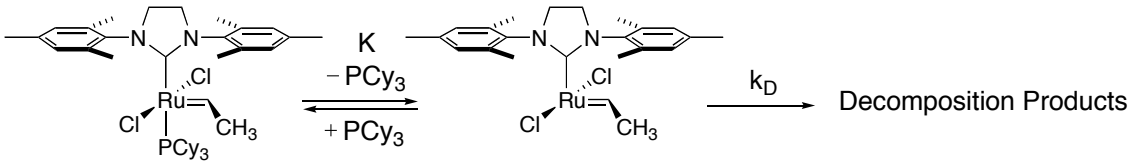


Figure 4.6. Doubling the initial concentration of ruthenium ethylidene complex **7** has a very different effect on its decomposition rate in the presence of water than in water's absence.



7 **14**

$$[\mathbf{14}] = \frac{K[\mathbf{7}]_t}{n([\mathbf{7}]_0 - [\mathbf{7}]_t)} \quad \text{(preequilibrium)} \quad (4.4)$$

$$\text{Decomposition\_Rate} = k_D\left[\frac{K[\mathbf{7}]_t}{n([\mathbf{7}]_0 - [\mathbf{7}]_t)}\right]^x \quad (4.5)$$

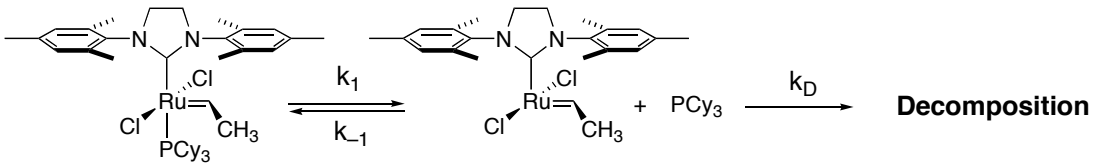
$$\text{Decomposition\_Rate}_y = k_D\left[\frac{K(1-y)[\mathbf{7}]_0}{n([\mathbf{7}]_0 - (1-y)[\mathbf{7}]_0)}\right]^x \quad \text{(rate at y percent decomposition)} \quad (4.6)$$

$$\text{Decomposition\_Rate}_y = k_D\left[\frac{K(1-y)}{ny}\right]^x \quad \text{(simplification)} \quad (4.7)$$

In the absence of water, the decomposition of ethylidene complex **7** is less than first order in **7** itself (Figure 4.6). This behavior is actually consistent with a decomposition pathway analogous to that proposed for the decomposition of the propylidene derivative of ruthenium bis(phosphine) **1**.[8] This mechanism involves a preequilibrium of the bis(phosphine) complex with its phosphine-dissociated fourteen-electron species followed by bimolecular decomposition. Assuming **7** similarly equilibrates with its fourteen-electron species, **14**, its decomposition can be represented by eqs 4.4 and 4.5. For these equations, $[\mathbf{7}]_t$ is the concentration of **7** at time "t." $[\mathbf{7}]_0$ Is the initial concentration of **7**. The variable "n" represents the fraction of PCy_3 actually present relative to the amount potentially present, and "x" is the fourteen-election species' decomposition kinetic order. Equations 4.6 and 4.7 demonstrate that given any

percentage of decomposition, "y," the rate of **7**'s decomposition (Decomposition_Rate$_y$) is independent of the concentration of **7**. Consistent with this analysis, with an initial concentration of 0.023 M in THF, the decomposition rate is ~1.0 × 10^{-5} M•s^{-1} at 10% decomposition of **7** while this rate is ~1.1 × 10^{-5} M•s^{-1} when the initial concentration is 0.046 M.

Doubling the initial concentration of complex **7** in the presence of 4 M water in THF has a very different effect on its rate of decomposition than in water's absence. Up to 50% decomposition, complex **7** appears to decompose twice as fast when the initial concentration is doubled, which is consistent with the decomposition being first order in **7**. Beyond 50% decomposition, the decomposition rate drastically reduces when **7**'s initial concentration is doubled (Figure 4.6).



7 **14**

$$\frac{d[\textbf{Decomposition}]}{dt} = k_D[\textbf{14}]^x \qquad (4.8)$$

$$[\textbf{14}] = \frac{k_1[\textbf{7}]}{k_{-1}[PCy_3] + k_D} \quad \text{(steady - state approximation)} \qquad (4.9)$$

$$\frac{d[\textbf{Decomposition}]}{dt} = k_D\left[\frac{k_1[\textbf{7}]}{k_{-1}[PCy_3] + k_D}\right]^x \qquad (4.10)$$

$$[PCy_3] = n([\textbf{7}]_0 - [\textbf{7}]_t) \qquad (4.11)$$

A cursory examination of the plots for the decomposition of ethylidene compound **7** in the presence of 4 M water indicates that it decomposes by a different mechanism in aqueous THF than in water's absence. Assuming that decomposition primarily involves the fourteen-electron species, **14**, and that PCy_3 is not immediately involved in **14**'s decomposition, the decomposition of **7** can be modeled with eqs 4.8–4.10. Equation 4.11 accounts for the processes that adsorb PCy_3 in later decomposition steps. The variables "n" and "x" are the same as defined for eqs 4.4–4.7.

The observed reduction of complex **7**'s decomposition rate when its initial concentration is 0.046 M can then be best explained by an examination of eq 4.10. Given that, in the presence of water, decomposition does not involve a preequilibrium, k_D is greater than k_{-1}. Assuming that k_D is sufficiently greater than k_{-1}, **7**'s decomposition rate will be independent of $[PCy_3]$ at low values of $[PCy_3]$. However, as the value of $[PCy_3]$ grows sufficiently large, the rate of **7**'s decomposition will decrease as the value of $k_{-1}[PCy_3]$ approaches the value of k_D. From Figure 4.6, the decomposition of a sample where **7**'s initial concentration is 0.023 M does not generate enough PCy_3 to retard the decomposition rate even after extensive decomposition. Consistent with this observation is the fact that the reduction of **7**'s decomposition rate for a sample with an initial concentration of 0.046 M does not occur until 50% of the sample has decomposed.

A second interesting result is the observation of a new alkylidene hydrogen resonance in the ^1H NMR spectra as ethylidene complex **7** decomposes, both in the presence and absence of water. This observation was also made by Wagener and co-workers upon examining the decomposition of complex **7** in benzene. They speculate that the identity of this new peak is ruthenium methylidene complex **8**.[38] Indeed, the new

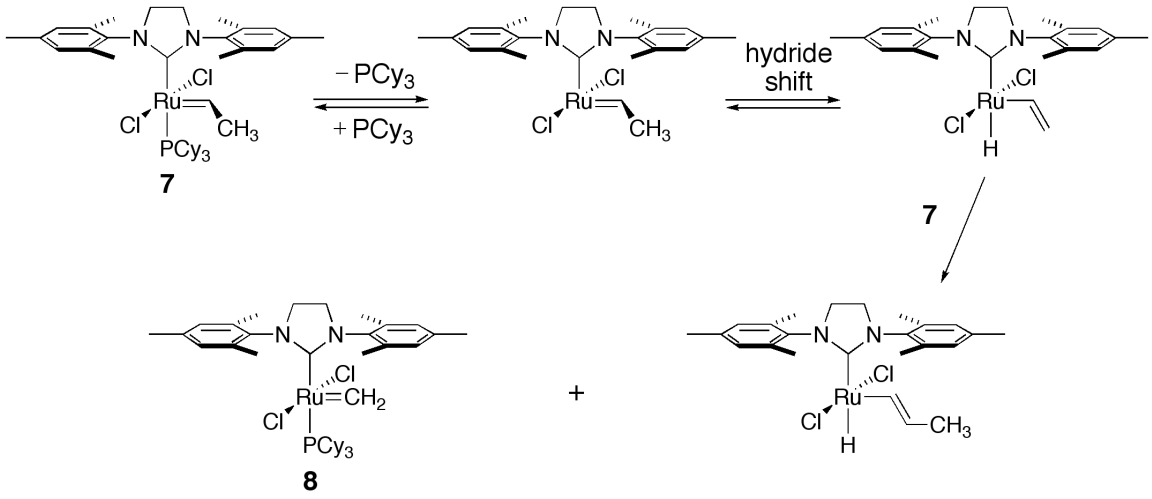
resonance appears at 17.8 ppm, which is identical with the chemical shift of **8**'s alkylidene hydrogen peak in THF. Moreover, an examination of the ^{31}P NMR spectra of **7** after decomposition at 35 °C reveals a major phosphorus resonance at 37.2 ppm, consistent with the phosphorus resonance of complex **8**. Additionally, the ^{31}P NMR spectrum reveals a large peak at 34.8 ppm matching the phosphorus resonance of Cy_3PMeCl whose presence would be expected from decomposition of the *in situ* generated **8**.

The decomposition of a sample containing known initial amounts of complexes **7** and **8** provides further confirmation of this identification. An examination of the ^{1}H NMR spectrum of this sample after brief decomposition reveals only two sharp alkylidene peaks at 18.5 and 17.8 ppm, corresponding to the alkylidene hydrogen resonances of **7** and **8** respectively. Had the newly observed compound not been **8**, three alkylidene hydrogen resonances should be present in this spectrum, or complex **8**'s alkylidene hydrogen resonance should have broadened or shown a shoulder. Therefore, the newly formed alkylidene hydrogen peak observed during **7**'s decomposition is confidently ascribed to the *in situ* generation of complex **8**.

The formation of ruthenium methylidene complex **8** during the decomposition of ethylidene compound **7** is likely indicative of a process like the one outlined in Scheme 4.5. A hydride shift to the ruthenium center from a carbon beta to the metal center is believed to play a role in the decomposition of ruthenium benzylidene complexes in the presence of various alcohols.[21,39] Similarly, a β-hydride shift from complex **7**'s alkylidene ligand's terminal methyl group to the ruthenium center is proposed to form a ruthenium hydride with a sigma-bound ethylene molecule (Scheme 4.5). This first step is proposed

to occur on the phosphine-dissociated fourteen-electron species, which contains an open coordination site appropriately positioned to accept a hydride ligand. Methylidene complex **8** is then produced by a metathesis reaction between the sigma-bound ethylene molecule and residual complex **7**.

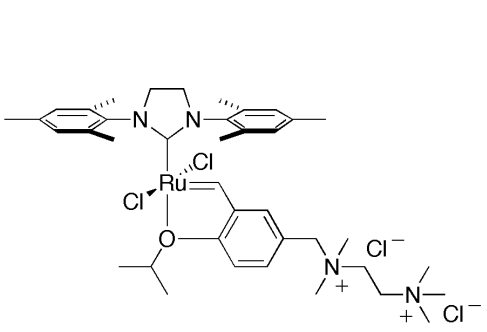
Scheme 4.5.



Ethylidene complex **7** is not overly stable at elevated temperatures in a polar environment. At 35 °C in THF, 50% of **7** decomposed in ~3.6 hours. In contrast, Wagener and co-workers extrapolate that 50% decomposition of **7** requires 100 hours at 55 °C in benzene.[38] In the presence of water, **7** is even less stable. In 4 M water/THF, 50% decomposition of **7** occurs after ~1.3 hours at 35 °C and ~7.5 hours at 25 °C. Unfortunately, these data indicate that the use of substrates containing internal olefins with terminal methyl groups is unlikely to be a successful strategy for aqueous metathesis at elevated temperatures. While not promising, the potential success of this strategy for aqueous metathesis at room temperature remains unclear.

Summary

To summarize, this research demonstrates that ruthenium benzylidene complex **2** is reasonably stable in the presence of water while ruthenium ethylidene complex **7** and ruthenium methylidene complex **8** show much lower stability. The decomposition of methylidene complex **8** is not significantly affected by added chloride ion and is only moderately affected by added PCy_3. An examination of the products arising from the decomposition of **8** reveals multiple decomposition pathways though most involve the generation of Cy_3PMeCl. The decomposition behavior of complex **8** in aqueous THF is first order in **8** itself and may indicate a direct interaction between **8** and water. While not approaching the stability of **2**, ethylidene complex **7** is more stable towards water than **8**. In 4 M water/THF, complex **7** shows a brief period of slow decomposition prior to a large increase in the decomposition rate. However, in the absence of added water, the decomposition rate of **7** follows a typical exponential decay. Finally, ethylidene complex **7** generates methylidene complex **8** during its decomposition.



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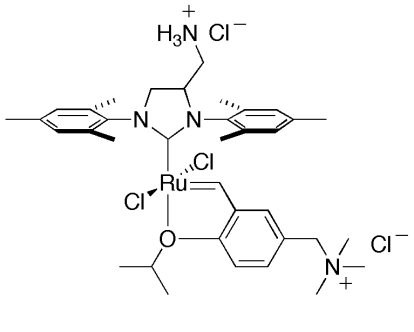

16

In conclusion, the successful generation of a ruthenium-based, water-soluble metathesis catalyst containing an NHC ligand must overcome the obstacles of the relative instabilities of methylidene and alkylidene ruthenium complexes toward water. The

formation of Cy_3PMeCl indicates that PCy_3 plays an active role in ruthenium methylidene complex **8**'s decomposition. Therefore, water-soluble compounds lacking a phosphine ligand may be better targets for an aqueous metathesis catalyst. Catalysts containing 2-isopropoxybenzylidene ligands, such as catalysts **15** and **16**, are thus attractive water-soluble catalyst targets. The successful development of these water-soluble metathesis catalysts is described in Chapter 5.

Acknowledgements

First and foremost, the author acknowledges the contributions of Dr. Soon Hyeok Hong to the research described in this chapter. He synthesized ruthenium complexes **7** and **8** and assisted with the described decomposition experiments. Drs. Scott Ross and Christine Thomas are gratefully acknowledged for their aid with solvent suppression and HMQC NMR spectroscopy respectively. Drs. Jonathan Owen, Sebastian Smidt, Joseph Samec, and Greg Beutner also contributed to this research with helpful discussions. The National Institute of Health funded this research (5R01GM068647).

Experimental

Materials and methods. All decomposition trials were measured on a Varian Inova 500 spectrometer (499.85 MHz for ^1H; 202.34 MHz for ^{31}P; 125.69 MHz for ^{13}C) under temperature control. Temperature calibration at elevated temperatures was accomplished with an ethylene glycol standard. All other NMR spectra were obtained on a Varian Mercury 300 spectrometer (299.817 MHz for ^1H, 75.4 MHz for ^{13}C, and 121 MHz for ^{31}P). ^1H NMR chemical shifts are reported in ppm relative to $SiMe_4$ ($\delta = 0$) and are internally referenced to residual solvent proton peaks. ^{31}P NMR spectra are externally

referenced to 98% phosphoric acid (δ = 0). With the exception of the initiation of complex **8**, all the reported decomposition or initiation measurements were performed at least twice, and the provided data is the average of all of the trials. Slow decomposition and time constraints prevented data collection over a period of more than two half-lives for the decomposition of methylidene **8** in THF. Otherwise, all decomposition and initiation collections were acquired over a period of at least three half-lives.

All samples, sans water, were prepared in a N_2-filled Vacuum Atmospheres glove box (O_2 < 3 ppm). Ruthenium benzylidene complex **2** was obtained from Materia and was used as received. Ruthenium ethylidene complex **7** and ruthenium methylidene complex **8** were made according to literature procedures.[37,7] Puriss water was purchased from Fluka (Aldrich). PCy_3 and zone-refined anthracene were obtained from Aldrich and used without further purification. Puriss $^{n}Bu_4NCl$ was acquired from Fluka (Aldrich) and dried under high vacuum at 90 °C for 2 days prior to storage and use in a glove box. Deuterated THF was purchased from Cambridge Isotopes Laboratories and dried over flame-activated 4 Å molecular sieves. Ethyl vinyl ether was acquired from Aldrich and distilled from CaH_2. All liquids were degassed by either 3 freeze, pump, and thaw cycles or a generous argon sparge.

Procedure for a typical decomposition measurement. In a N_2-filled glove box, ruthenium methylidene complex **8** (12.4 mg, 0.016 mmol) and anthracene (1 mg, 0.0056 mmol) were weighed into a 1-dram vial. Deuterated THF (650 μL) was used to transfer the sample to a screw-cap NMR tube. A septa-cap was used to seal the NMR tube before removing the tube from the glove box and reinforcing the seal with parafilm. The sample

was placed into the spectrometer and allowed to equilibrate at the probe temperature (25 °C) for 10 minutes prior to the injection of water (50 μL, 4 M) from an air-tight syringe. Mixing was accomplished by three tube inversions. The sample was reinserted into the spectrometer and rapidly locked and shimmed prior to collecting data through the use of a time-delayed array of ^{1}H NMR spectra (referred to as a preacquisition delay, PAD, by Varian software). A custom macro was used to export the time and integration data from the spectral array as a text file. These data were imported into GraphPad Prism 4.0b for Macintosh (trial version) and fitted to an exponential decay. The reported uncertainty represents the 95% confidence intervals of the fit.

Examination of the effect of additives. For PCy_3, the procedure is identical to that described above for measuring the decomposition of complex **8** except that the PCy_3 is also weighed into the sample vial. However, $^{n}Bu_4NCl$ was weighed directly into the NMR tube through the use of a weighing boat. Full dissolution of 10 equivalents of $^{n}Bu_4NCl$ occurred only upon the addition of water.

Procedure for a typical ethyl vinyl ether initiation experiment. In a N_2-filled glove box, ruthenium benzylidene complex **2** (10.1 mg, 0.012 mmol) and anthracene (1 mg, 0.0056 mmol) were weighed into a 1-dram vial. Deuterated THF (620 μL) was used to transfer the sample to a screw-cap NMR tube. The tube was sealed with a septa-cap and brought out of the box, and the seal was reinforced with parafilm. Water (50 μL, 4M) was injected using an air-tight syringe. The sample was inserted into the spectrometer and allowed to equilibrate at the probe temperature (25 °C) for 10 min. Sample locking and

shimming were performed just prior to the injection of ethyl vinyl ether (33.5 μL, 0.35 mmol, 29 equiv) with an air-tight syringe. Mixing was accomplished by three rapid tube inversions, and the sample was immediately reinserted into the spectrometer. Data collection and analysis waere accomplished as described for the decomposition of complex **8**. For the initiation of ruthenium methylidene complex **8** in the presence of water, a blank sample containing the appropriate amounts of deuterated THF, water, and ethyl vinyl ether was used to lock and shim the spectrometer. After temperature equilibration, both water and ethyl vinyl ether were injected into the methylidene sample followed by immediate data collection.

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Portions of this chapter have been published as: Jordan, J. P.; Hong, S. H.; Grubbs, R. H. *Organometallics* submitted, 2007.

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CHAPTER 5

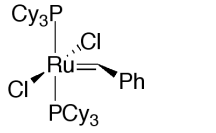
Water-Soluble Phosphine-Free Olefin Metathesis Catalysts Containing an *N*-Heterocyclic Carbene Ligand

Abstract

Two water-soluble, ruthenium-based olefin metathesis catalysts containing an *N*-heterocyclic carbene ligand are described. Both catalysts are phosphine-free and utilize ammonium salts to achieve solubility in water. The ability of these catalysts to mediate ring-opening metathesis polymerization, ring-closing metathesis and cross metathesis as homogenous reactions in water is examined. Both catalysts competently mediate ring-opening polymerization and ring-closing metathesis reactions in water, though their ability to enable aqueous cross metathesis is limited.

Introduction

Olefin metathesis, the metal-mediated exchange of double-bond substituents, has become a prominent reaction of contemporary chemistry.[1] Ruthenium catalysts **1**–**6** allow for the metathesis-mediated synthesis of small molecules,[1-3] macromolecules,[1,4,5] and even supramolecular complexes (Chapter 1).[6-8] While already a powerful tool in synthetic chemistry, the potential of olefin metathesis has yet to be fully realized. The desire to expand the utility of this reaction has served and still serves as motivation to develop transition metal catalysts that better enable this transformation. This chapter describes the synthesis and activity of two water-soluble metathesis catalysts that contain an *N*-heterocyclic carbene (NHC) ligand.



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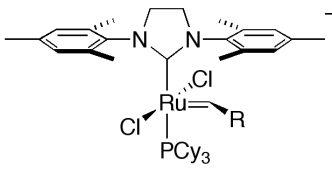

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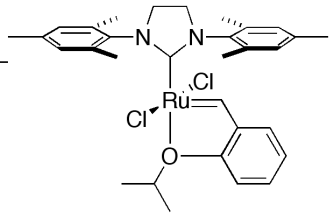

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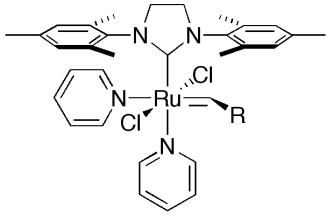

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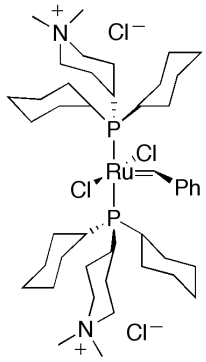

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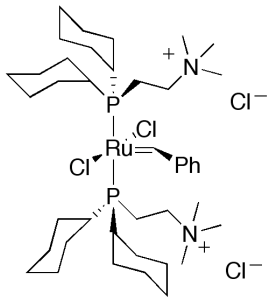


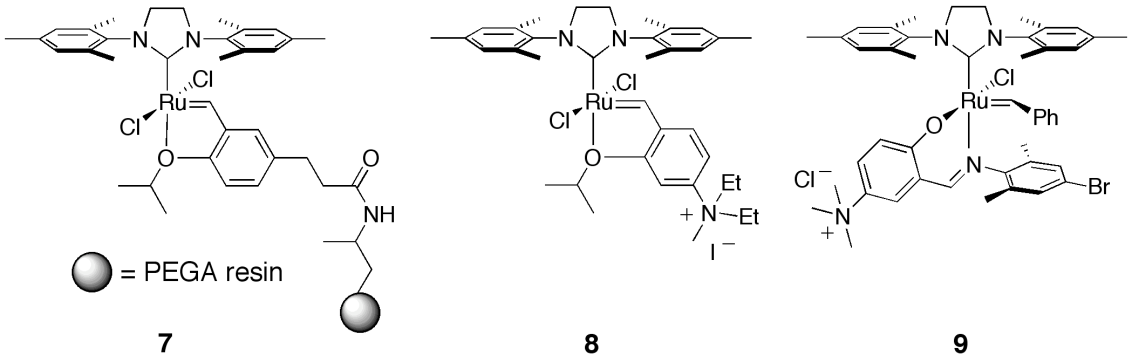
6

Earlier research by Lynn, Mohr, and Grubbs produced electron-rich phosphine ligands displaying water-soluble ammonium functional groups.[9] Incorporation of these

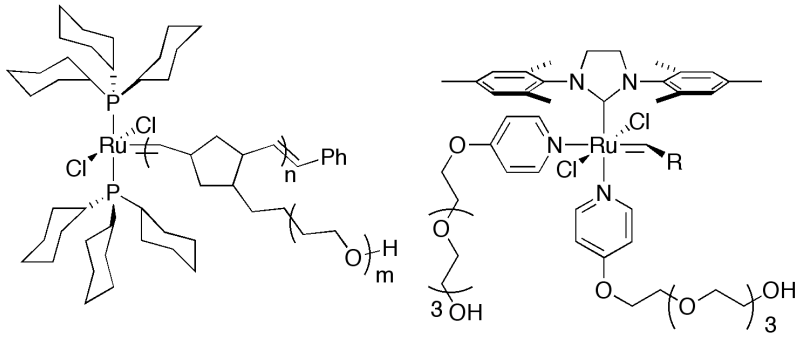
ligands onto ruthenium gave water-soluble catalysts **5** and **6**.[9-11] These catalysts were capable ROMP initiators and would polymerize water-soluble norbornene monomers in a living manner.[10,11] Moreover, these complexes were also capable of catalyzing ring-closing metathesis (RCM) in protic solvents, including water, with substrates that avoid the formation of intermediate ruthenium methylidene complexes, [Ru]=CH_2.[12] Unfortunately catalysts **5** and **6**, particularly their methylidene derivatives, were unstable in water, which limited their utility in aqueous environments.[11-13] Even so, these complexes were the first well-defined, active water-soluble metathesis catalysts, and they demonstrated the potential for ruthenium-based metathesis catalysts to mediate the metathesis of acyclic substrates in water.

A variety of methods and catalysts targeting metathesis in water have been produced since the introduction of the water-soluble bis(phosphine) catalysts.[14-25] A few reports have demonstrated that surfactants can be used to perform metathesis in water.[14-16] Catalysts **1** and **2** can also be occluded within a polydimethylsiloxane membrane to be used in methanol/water mixtures.[17] Furthermore, derivatives of catalyst **3** were anchored to a solid support to give catalysts such as complex **7**, a catalyst active in methanol and water though catalysis was believed to occur within the pores of the gel.[18,19] Also, Grela and co-workers synthesized analogs of **3** that displayed a single ammonium salt such as a pyridinium salt[20] or a tetraalkyl ammonium salt (**8**),[21] which showed ring-closing activity in methanol/water mixtures. Similarly, Blechert and co-workers have examined the ability of catalyst **3** and a couple of derivatives of **3** to perform metathesis in DMF/water and methanol/water mixtures.[22] A different approach was taken by Raines and co-workers who incorporated an ammonium-salt-containing salicylaldimine ligand onto a

ruthenium complex supported by an NHC ligand to produce catalyst **9**, which was active in methanol/water mixtures.[23] Finally, catalysts explicitly designed to be used in neat water include two macroinitiators that incorporate poly(ethylene glycol) (PEG) chains to form water-soluble analogs of catalyst **1** (**10**) and **4** (**11**) for ROMP in an aqueous environment.[24,25] Unfortunately, none of these systems effectively catalyzed the metathesis of hydrophilic acyclic substrates in neat water.



7 **8** **9**

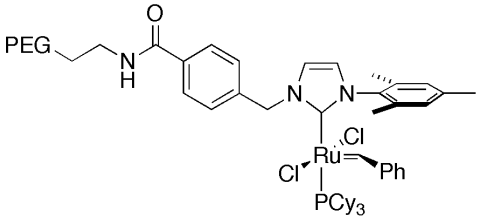


10 **11**

Desiring a water-soluble olefin metathesis catalyst with improved stability and activity relative to catalysts **5** and **6**, we synthesized catalyst **12**, which displays a PEG chain from a nitrogen substituent of an unsaturated NHC ligand (Chapter 2).[26] The hypothesis was that NHC ligands would impart the same increase in stability and activity onto water-soluble metathesis catalysts as observed with catalysts **2** and **3**.[27-29] Indeed, catalyst **12** did show increased ROMP activity over bis(phosphine) catalyst **6**. However,

12 was not sufficiently stable for the efficient mediation of ring-closing and cross-metathesis reactions in water (Chapter 2).[26]

A careful consideration of catalyst **12** revealed structural weaknesses that could be addressed to produce catalysts with greater stability and activity in water (Chapter 3). This analysis inspired the ruthenium-complex templates shown in Figure 5.1 as promising targets for the production of the desired catalyst. However, an examination of the decomposition of the methylidene derivative of catalyst **2** showed that nucleophilic attack at the carbon double-bonded to the ruthenium center by free tricyclohexylphosphine (PCy_3) is a major path of complex decomposition.[27,28] Moreover, examining the effect of water on the decomposition of the methylidene derivative of **2** indicated that pathways involving the nucleophilic attack by PCy_3 at this carbon also dominated its decomposition in aqueous environments (Chapter 4).[30] Therefore, the targeted catalysts should be phosphine-free (templates **B**–**D**, Figure 5.1). Because of the greater stability of catalysts containing isopropoxybenzylidene ligands,[31,32] complexes modeled from template **B** (Figure 5.1) are particularly attractive as potentially stable and active water-soluble catalysts.



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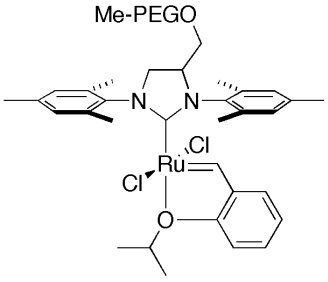

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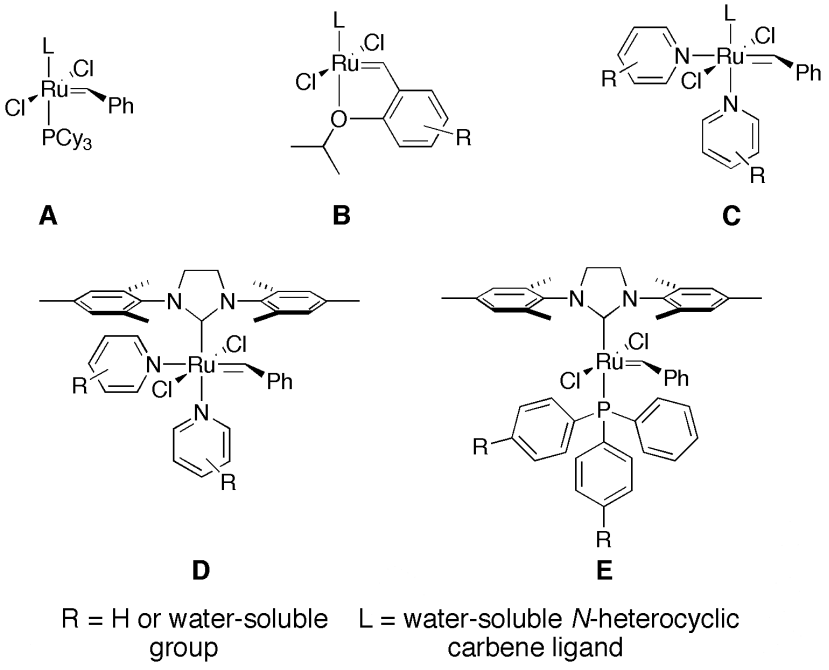


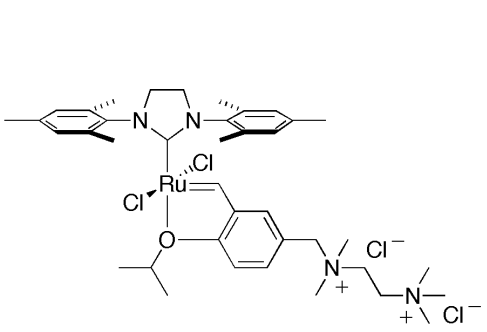
Figure 5.1. Water-soluble groups can be incorporated onto NHC ligands and/or ligands that dissociate during metathesis reactions to produce NHC-containing olefin metathesis catalysts that are soluble in water.

Two strategies can be employed to render analogs of catalyst **3** soluble in water. Like catalyst **12**, the first strategy utilizes PEG to achieve solubility in water. Indeed, Grubbs and Hong followed this strategy to produce catalyst **13**, which showed greater activity for ROMP, ring-closing, and cross-metathesis reactions in water than earlier catalysts.[32] However, catalysts that incorporate PEG are inherently polydisperse and are amenable to limited structural characterization. Furthermore, a long PEG chain may interact with substrate molecules or with the catalyst itself in manners affecting catalyst structure and activity. For example, catalyst **13** forms aggregates resembling micelles in water.[32] Therefore, the strategy employed by the research presented in this chapter pursues the synthesis of small-molecule catalysts. Such complexes are amenable to full

characterization by both X-ray and spectroscopic techniques and avoid any potential complications arising from a large pendant group.

Results and Discussion

Catalyst synthesis and characterization. The ammonium functional group was used to produce discrete, water-soluble catalysts. This functionality was chosen based both on its ease of synthesis and the prior use of ammonium salts to successfully generate water-soluble analogs of catalyst **1**.[9,11] Earlier research has shown that at least two ionic functional groups must be incorporated to yield water-soluble metathesis catalysts containing an NHC ligand.[33] Therefore, catalysts **14** and **15**, which each contain two ammonium functional groups, were synthesized. While catalyst **14** displays both ammonium groups from its 2-isopropoxybenzylidene ligand, catalyst **15** includes only one ammonium salt on its benzylidene ligand. A second ammonium group is attached to this complex through its NHC ligand.



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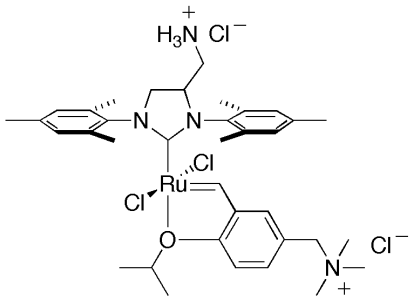

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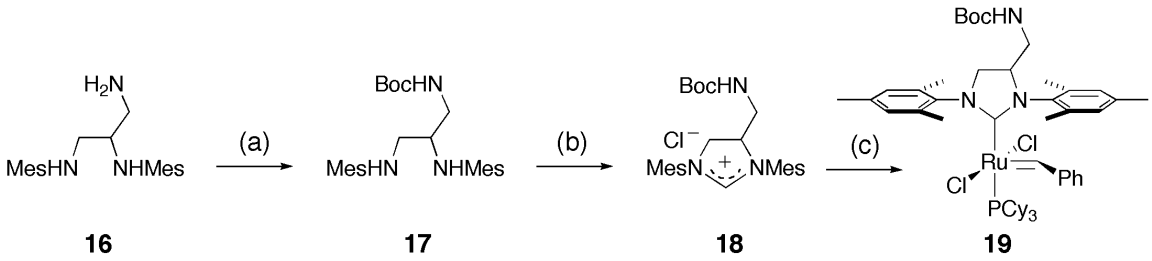
The syntheses of the ruthenium starting material and the 2-isopropoxystyrenes used to construct catalysts **14** and **15** are shown in Schemes 5.1 and 5.2. The synthesis of ruthenium complex **19** is straightforward and is described in more detail in Chapter 3

(Scheme 5.1). Also, the syntheses of the 2-isopropoxystyrenes are chromatography free and readily allow for the rapid production of multiple grams of both styrenes **23** and **25**.

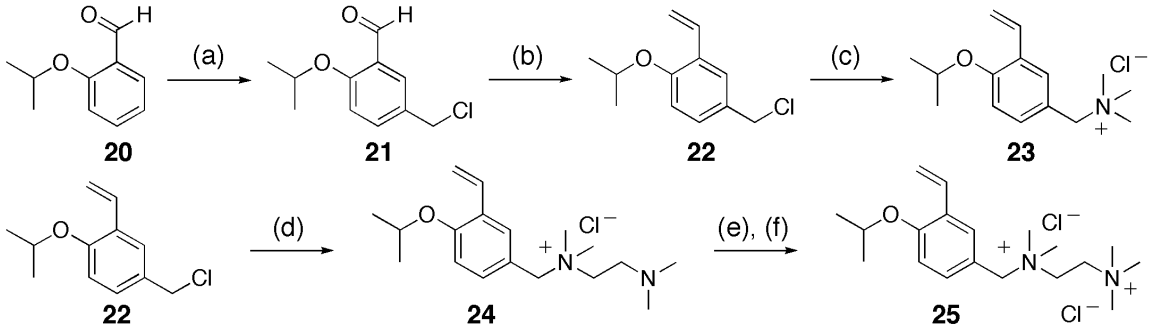
Scheme 5.1.



Reagents and conditions: (a) Boc_2O, DMAP, CH_2Cl_2, rt, 2 h (86%), (b) $(EtO)_3CH$, NH_4Cl, 120 °C, 16 h (90%), (c) ^tBuOK, **1**, THF, rt, 17 h (61%). Boc: *tert*-butoxycarbonyl

The syntheses of styrenes **23** and **25** used to produce catalysts **14** and **15** are shown in Scheme 5.2. Chloromethylation followed by Wittig olefination of readily synthesized benzaldehyde **20** provides benzyl chloride **22** in moderate yield. Amination with trimethylamine then yields isopropoxystyrene **23**. Amination of **22** with N,N,N',N'-tetramethylethylenediamine followed by methylation and ion exchange gives isopropoxystyrene **25**.

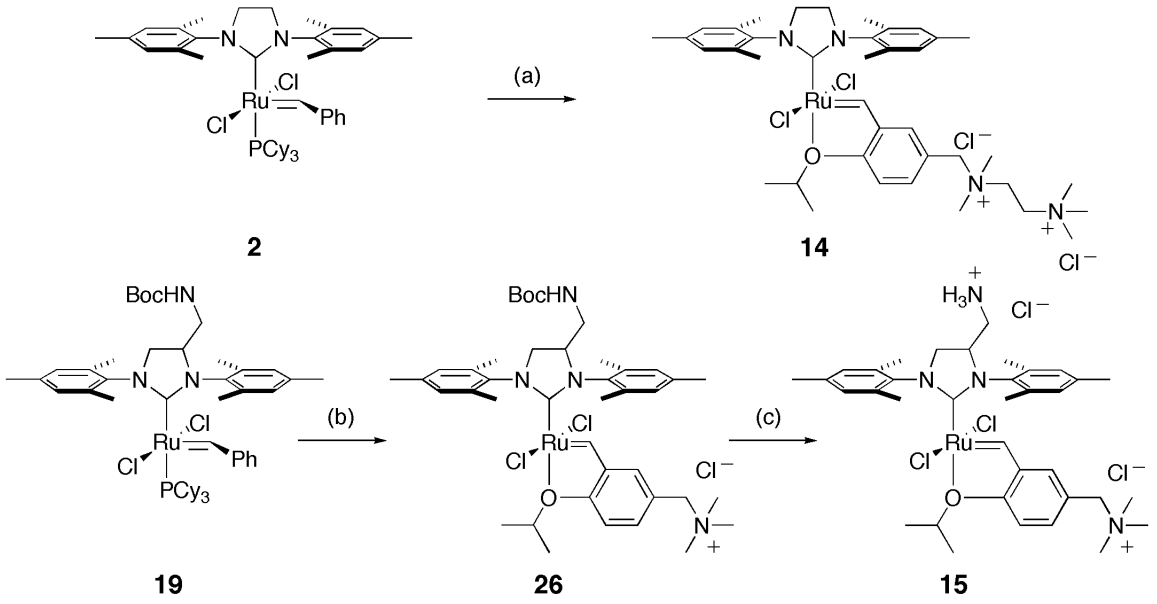
Scheme 5.2.



Reagents and conditions: (a) CH_2O, HCl(aq), HCl(g), 50 °C, 3h (66%), (b) $BrCH_3PPh_3$, KO^tBu, THF, –60 – 15 °C, 2 h (78%), (c) NMe_3, MeCN, 0 °C – rt, 12 h (81%), (d) $MeN(CH_2)_2NMe_2$, MeCN, rt, 24 h (90%), (e) MeI, CH_2Cl_2, rt, 7 h, (f) Amberlite IRA-400(Cl), H_2O, 12 h (performed 3 times) (81%, 3 steps).

Catalyst **14** and ruthenium complex **26** can be readily assembled by mixing ruthenium complexes **2** and **19** with 2-isopropoxystyrenes **25** and **23** in the presence of copper(I)chloride (Scheme 5.3). The deprotection of **26**'s primary amine with a freshly prepared solution of hydrogen chloride in benzene then yields catalyst **15**. Interestingly, catalyst **14** is also produced by mixing styrene **25** with ruthenium bis(pyridine) complex **4** in dry, degassed DMF at 30 °C. However, because the reactions in DMF gave lower conversions to product **14**, this route was abandoned..

Scheme 5.3.



Reagents and conditions: (a) **25**, CuCl, CH_2Cl_2, 45 °C, 1 h (46%), (b) **19**, CuCl, CH_2Cl_2, 40 °C, 1 h, (c) HCl, C_6H_6, rt, 1 h (67%, 2 steps).

The isolation of catalysts **14** and **15** was challenging as both the desired catalysts and the impurities were highly polar. As neither catalyst ran on silica gel and recrystallizations of crude material were ineffective, chromatography on alumina was explored. The anaerobic passage through two neutral Brockman grade V alumina

columns followed by a single neutral Brockman grade III alumina column provided **14** in sufficient purity that its recrystallization from methanol with diethyl ether yielded pure catalyst. To obtain catalyst **15**, ruthenium complex **26** was passed through a single neutral Brockman grade III alumina column prior to its deprotection with hydrogen chloride in benzene. After this deprotection, trituration with dichloromethane followed by recrystallization from methanol with diethyl ether gave pure catalyst **15**.

The structures of catalysts **14** and **15** are readily confirmed by spectroscopic analysis. The ^{1}H NMR spectra of **14** and **15** each display a resonance at 16.8 ppm, which is consistent with phosphine-free benzylidene complexes containing an NHC ligand.[31,34] Similarly the ^{13}C NMR spectra of **14** and **15** contain the expected resonances corresponding to their two carbene carbons, 295.3 and 209.4 ppm for **14** and 306.1 and 210.8 ppm for catalyst **15**.[31,34] Finally, the composition of catalysts **14** and **15** was further confirmed by high resolution mass spectrometry.

Additionally, the diffusion of diethyl ether into a relatively dilute solution of **14** in methanol yields crystals suitable for X-ray analysis. The crystal structure reaffirms the assigned structure of **14** (Figure 5.2). X-ray quality crystals of catalyst **15** have not been obtained at this time.

Interestingly, the water-solubility properties of catalysts **14** and **15** are quite different. Catalysts **15** readily dissolves in water to form homogenous solutions. In contrast, complex **14** is only moderately soluble in water. Full dissolution of catalyst **14** only occurs under highly dilute conditions though it is sufficiently soluble to be observed in deuterium oxide by ^{1}H NMR spectroscopy. For reactions run with five mol% catalyst

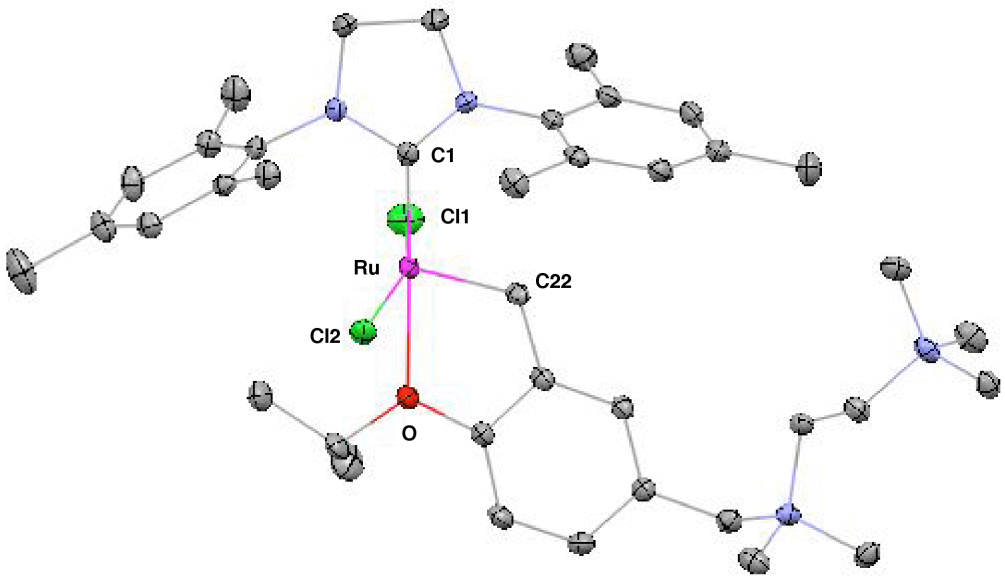


Figure 5.2. The structure of catalyst **14** has been confirmed by X-ray crystallographic analysis. Solvent molecules and the chloride counter-ions are omitted for clarity. Selected bond lengths (Å) and angles (°) for catalyst **14**: Ru-C22 1.8266(16), Ru-C1 1.9683(17), Ru-O 2.2601(12), Ru-Cl1 2.3378(4), Ru-Cl2 2.3459(5), C22-Ru-C1 101.68(7), C22-Ru-O 79.64(6), C1-Ru-O 178.65(5), C22-Ru-Cl2 97.14(5), C1-Ru-Cl2 96.62 (5), O-Ru-Cl2 82.94(3), Cl1-Ru-Cl2 158.086(18).

and 0.2 M substrate, the standard conditions for most reactions described in this chapter, catalyst **15** will form a homogenous solution while catalyst **14** does not fully dissolve. Many of the differences in the activity of catalysts **14** and **15** are likely related to these differences in their solubility properties.

Both catalysts are quite stable in water in the absence of substrate. For example, catalyst **15** has a decomposition half-life of over one week under inert conditions in deuterium oxide. Interestingly, the benzylidene hydrogen of these compounds does not appear to participate in deuterium exchange with deuterium oxide. Such an exchange process is rapid for water-soluble bis(phosphine) catalysts **5** and **6**.[13,35]

ROMP in water with catalysts 14 and 15. The ability to ROMP challenging, water-soluble *endo*-norbornene monomer **27** has been used to compare the activity of PEG-

catalyst **11** with water-soluble bis(phosphine) catalyst **6**.[26] Therefore, as an initial screen of their aqueous metathesis activity, the ability of catalysts **14** and **15** to polymerize **27** in water was examined. As shown in Figure 5.3, both **14** and **15** successfully polymerize monomer **27** in less than three hours. The ability of parent catalysts **2** and **3** to polymerize **27** in water was also examined to determine whether either catalyst would show activity in water. Neither catalyst **2** nor **3** demonstrated any ROMP activity in water, neither showing any visible reaction when mixed with monomer **27**.

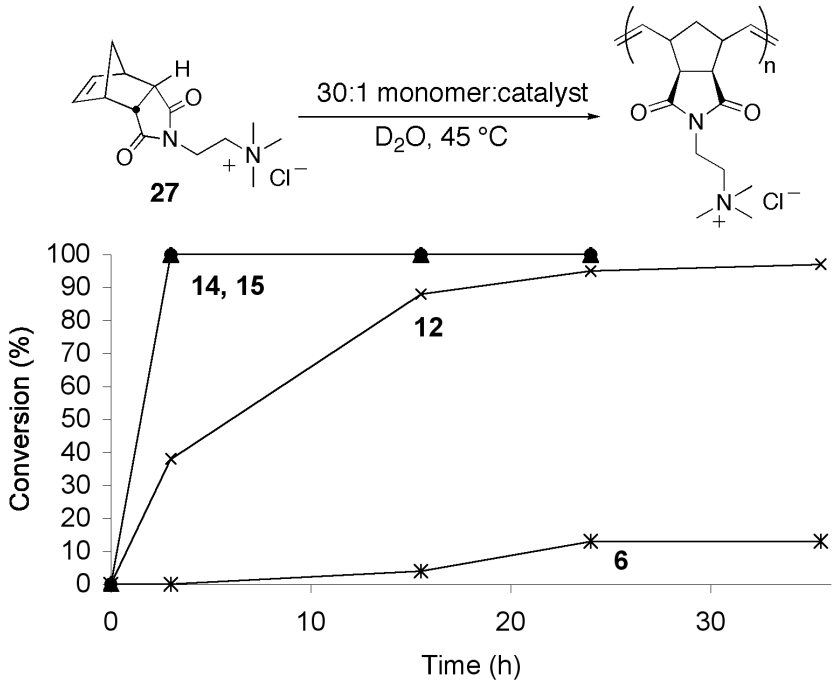
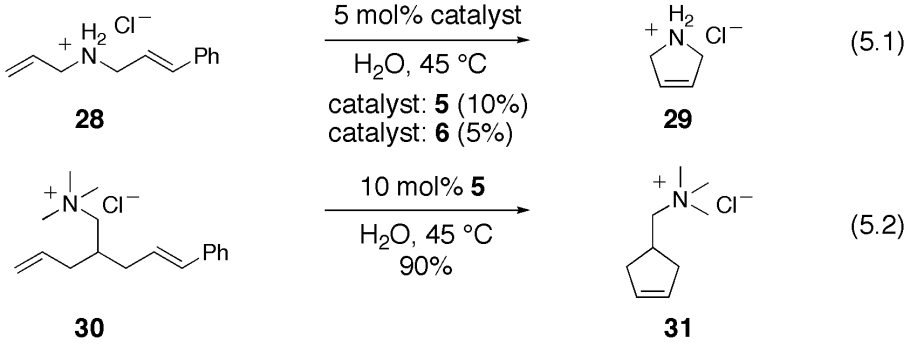


Figure 5.3. Following the ROMP of monomer **27** by ^{1}H NMR spectroscopy provided a measure of the relative activities of catalysts **6**, **12**, **14**, and **15** in water. For catalysts **5** and **11** the polymerization was run in the presence of one equivalent of deuterium chloride (versus catalyst) for increased activity. (The data for catalysts **14** and **15** overlap.)

The ROMP of monomer **27** does indicate increased activity for catalysts **14** and **15** in water relative to earlier water-soluble catalysts. Even so, the ROMP of norbornene monomers in water is one of the oldest reactions for ruthenium-based metathesis

catalysts.[36-38] Of greater interest is the ability of these catalysts to mediate metathesis reactions in water involving acyclic substrates, such as ring-closing or cross-metathesis reactions. Most prior research in ring-closing and cross-metathesis reactions in water with catalysts containing an NHC ligand either involved mixed solvent systems[20-23] or heterogenous systems where catalysis was believed to occur in organic pores.[17,24,25] Therefore, the ability of catalysts **14** and **15** to enable aqueous ring-closing metathesis and cross metathesis as homogenous reactions in water is of particular interest.

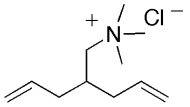
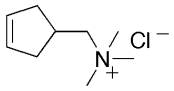
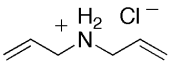
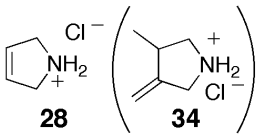
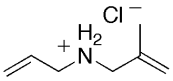
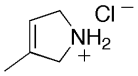
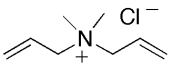
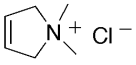
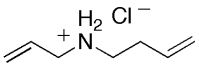
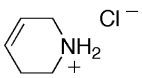
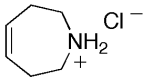
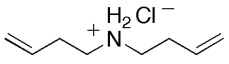
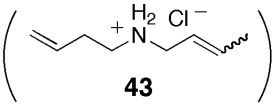
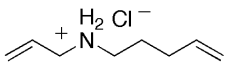
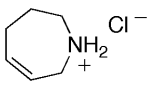
Ring-closing metathesis in water with catalysts 14 and 15. Prior to PEG-catalyst **13**, there are only three examples of homogenous ring-closing metathesis reactions in neat water. Water-soluble catalysts **5** and **6** mediate the ring-closing metathesis of substrate **28** (eq 5.1). Additionally catalyst **6** also ring-closes substrate **30** (eq 5.2).[12] Note that both substrates contain one terminal olefin and one internal olefin with a terminal phenyl group. This substrate composition is required to inhibit the formation of the highly unstable bis(phosphine) ruthenium methylidene derivative for these reactions to be successful.[12,39,40] However, as the substrates are more synthetically accessible and the reactions more atom efficient, the ring-closing of α,ω-dienes is preferred. Currently, catalysts **13** through **15** are the only catalysts capable of performing homogenous, RCM reactions of α,ω-dienes in neat water.



28 **29** (5.1)

30 **31** (5.2)

Table 5.1. Ring-closing metathesis of α,ω-dienes in water with catalysts **13**–**15**[a]

Entry (Catalyst)	Substrate	Time (h)	Product	Conversion (%)
1 (**13**)[b]		12		>95%
2 (**14**)		24		>95%
3 (**15**)	**32**	0.5	**31**	>95%
4 (**13**)[b]		36		67 (+28)
5 (**14**)		24		>95
6 (**15**)	**33**	4	**28** **34**	36 (+59)
7 (**13**)[b]		24		42
8 (**14**)		24		70
9 (**15**)	**35**	6	**36**	26
10 (**13**)[b]		24		<5
11 (**14**)		24		<5
12 (**15**)	**37**	24	**38**	<5
13 (**13**)[b]		24		>95
14 (**14**)		24		>95
15 (**15**)	**39**	4	**40**	84
16 (**13**)[b]		24		68 (+14)
17 (**14**)		24	**42**	77
18 (**15**)	**41**	4	 **43**	36 (+30)
19 (**13**)[c]		24		39
20 (**14**)		24		45
21 (**15**)	**44**	4	**45**	9

[a]Reactions were performed at 30 °C with 5 mol% of catalyst and an initial substrate concentration of 0.2 M in deuterium oxide. Reaction times were not optimized, and the conversions represent the maximum conversion for the reaction. All conversions were measured by ^{1}H NMR and are the average of two trials. [b]Reactions were performed at room temperature. These data are from reference 41. [c]These data are from reference 41.

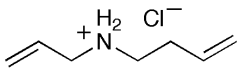
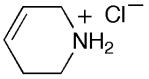
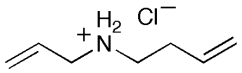
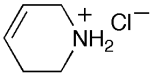
Table 5.1 lists the results of the RCM of several α,ω-dienes in water with catalysts **14** and **15**. The reported results for the RCM of these substrates with catalyst **13** are also provided for comparison.[32,41] As shown, all three catalysts are capable of ring-closing α,ω-diene substrates to form five-membered ring (entries 1–9), six-membered ring (entries 13–15), and seven-membered ring (entries 16–21) products in good to moderate yields. Moreover, like catalyst **13**, catalysts **14** and **15** show sufficient activity to ring-close substrate **35** to yield **36**, which contains a trisubstituted olefin (entries 7–9). Finally, ring-closing the fully symmetric substrate **46** to form seven-membered ring **47** occurs far more readily with all three catalysts than the cyclization of the analogous unsymmetrical substrate **49** (entries 16–21).

Both catalysts **13** and **15** produce a significant amount of isomerized product **34** when ring-closing substrate **33** (entries 4–6). Significant isomerization is also observed during the ring-closing metathesis of substrate **41** with catalyst **15** (entry 18). These isomerized products are believed to be the results of reactions with ruthenium hydrides formed upon catalyst decomposition.[24,32,27,42-46]

Table 5.1 clearly indicates that catalyst **14** has a greater aqueous ring-closing activity than catalyst **15**. To gain a better insight into this apparent difference in activity, the aqueous ring-closing metathesis of substrate **39** with both catalysts was examined after short reaction times. As shown in Table 5.2, after 30 minutes, catalyst **14** has cyclized 53% of **39** while **15** has ring-closed 78% of the substrate. However, allowing the reactions to proceed for an additional 30 minutes allows catalyst **14** to ring-close an additional 23% of **39** to give a conversion of 76%. In contrast, in that same period of time, catalyst **15** is only able to ring-close an additional 4% of **39** yielding an 82%

conversion. Finally, as listed in Table 5.1, after extended reaction times, catalysts **14** will fully cyclize **39** while catalyst **15** gives a maximum conversion of 88%.

Table 5.2. The ring-closing metathesis of substrate **39** with catalysts **14** and **15**[a]

Catalyst	Substrate	Time (h)	Product	Conversion (%)
14		0.5		53
15	**39**	0.5	**40**	78
14		1		76
15	**39**	1	**40**	82

[a]Reactions were performed at 30 °C with a 5 mol% catalyst loading and an initial substrate concentration of 0.2 M in deuterium oxide. Conversions were determined by ^{1}H NMR spectroscopy and represent the average of two trials.

The data in Table 5.2 suggest that catalyst **15** is the more kinetically reactive and less stable than catalyst **14**. While slower than **15**, the increased stability of catalyst **14** allows it to ring-close more substrate prior to decomposition. The increased stability of catalyst **14** over **15** is also reflected in the aqueous ring-closing of substrates **38** and **46** where catalyst **15** yields a greater amount of isomerized product (Table 5.1, entries 5, 6, 17, and 18).

The differences in their water-solubility are believed to dominate the kinetic reactivity and stability of catalysts **14** and **15**. Catalyst **15** dissolves in water to form a homogenous solution. This allows catalyst **15** to be more accessible to substrate molecules and, therefore, the more kinetically reactive catalyst. For the same reason, catalyst **15** is the least stable catalyst as it is the most accessible to water, which is a solvent known to be harmful to the stability of ruthenium metathesis catalysts.[30,47,48]

Under the shown reaction conditions, catalyst **14** only partially dissolves in water, leaving a solid reservoir of catalyst. The low concentration of dissolved catalyst is likely responsible for **14**'s lower kinetic reactivity relative to catalyst **15**. However, the low solubility of **14** is probably also responsible for its increased stability, as catalyst consumed during the reaction can be replenished from the solid reservoir. This may serve to minimize the amount of **14** that decomposes prior to performing any productive metathesis. The low concentration of catalyst **14** in water may also increase its stability by decreasing the rate of decomposition pathways involving two metal centers. Such pathways are known to play a role in the decomposition of metathesis-active ruthenium alkylidene complexes.[49]

At this point it is important to note the likelihood for microphase behavior with these catalysts during metathesis reactions. Solubility changes during the course of metathesis reactions may cause catalysts **14** and **15** to form microphases. Ruthenium metathesis catalysts containing an NHC ligand require at least two ionic groups to dissolve in water.[33] With catalyst **14**, both groups are displayed by its isopropoxybenzylidene ligand while catalyst **15** contains only one ionic group on its isopropoxybenzylidene ligand. However, this ligand is freed from the ruthenium center during productive metathesis.[31,50] Hence, the only water-soluble group on catalyst **14**'s alkylidene derivative is that provided by the water-soluble substrate while **14**'s methylidene derivative lacks a water-soluble functional group (Figure 5.4). Catalyst **15**'s alkylidene derivative will display two water-soluble groups, one from its NHC ligand and that provided by the water-soluble substrate and is likely fully soluble in water. However, **15**'s methylidene derivative relies entirely on the ionic NHC ligand for dissolution in

water (Figure 5.4). Therefore, the formation of microphases by catalysts **14** and **15** during metathesis reactions is plausible.

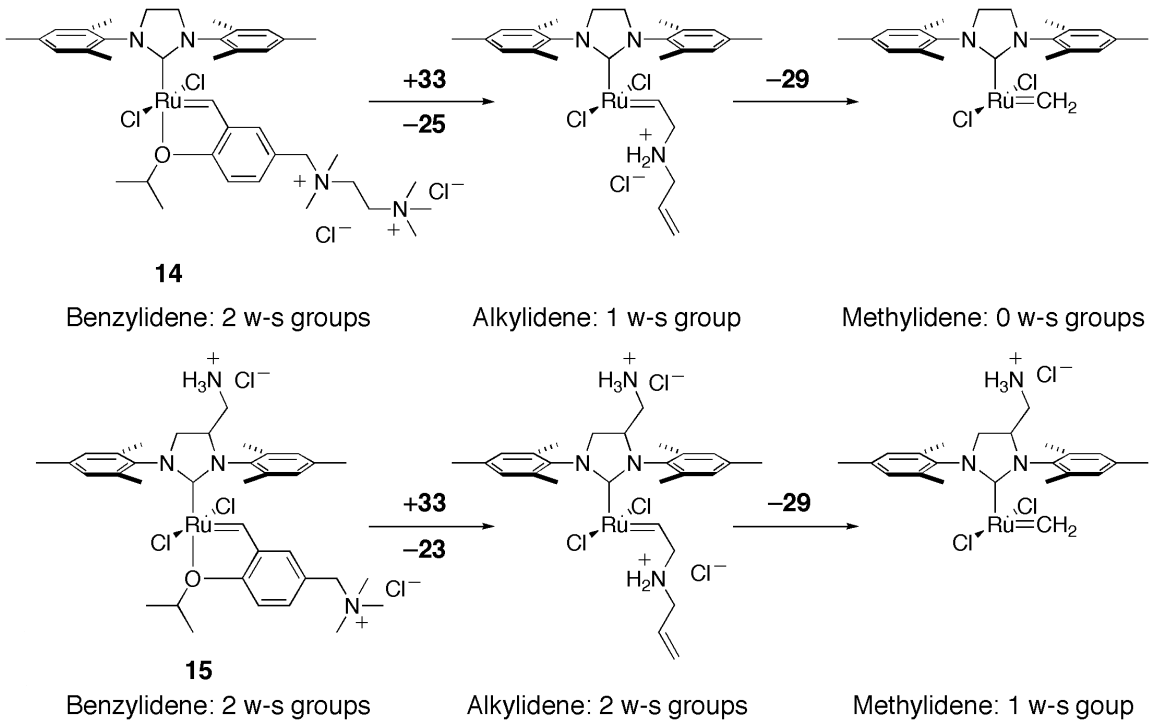


Figure 5.4. The alkylidene and methylidene derivatives formed during the ring-closing metathesis of substrate **33** with catalysts **14** and **15** are shown. Provided below each structure is the number of water-soluble (w-s) functional group(s) that each complex contains.

Tolerance of water-soluble functional groups. There exist a variety of functional groups commonly encountered in water and not in organic media. Such groups include the sulfate, sulfonate, carboxylate, phosphate and guanidinium functional groups. The ability of ruthenium-based metathesis catalysts to tolerate these groups is of interest as this tolerance is required for substrates containing such functionality.

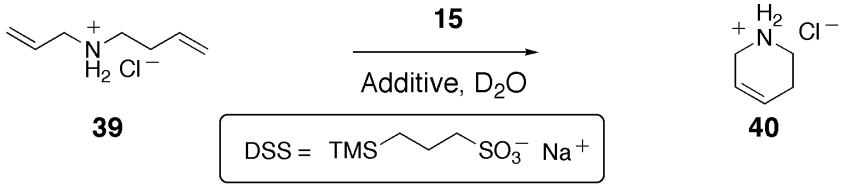
The RCM of substrate **39** with catalyst **15** was utilized to examine the tolerance of ruthenium-based metathesis catalysts for the listed functional groups. This reaction was chosen because catalyst **15** is fully soluble in water, which removes many concerns

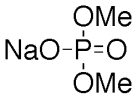
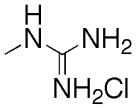
regarding mass transfer. Furthermore, **15** does not isomerize nor fully cyclize **39** making RCM reactions with this substrate an excellent platform for comparing the effect of various additives on catalyst **15**. The chosen additives each display a functional group of interest. These reactions provide a good method for judging the effect of various functional groups on ruthenium-based metathesis catalysts.

Table 5.3 lists the results of ring-closing 0.2 M of substrate **39** with 5 mol% of catalyst **15** in deuterium oxide in the presence of 0.2 M of an additive of interest. While the sulfonate group dramatically reduces the ability of **15** to ring-close **39**, the sulfate group only has a moderate effect on conversion though it appears to cause complex decomposition over time (entries 2 and 3). Neither phosphate nor guanidinium groups have much of an effect on this reaction though the guanidinium-containing additive significantly retards the rate of **15**'s dissolution in water (entries 4 and 5). Interestingly, while the carboxylate group completely shuts down the reaction to give an orange solution, the corresponding acid does not significantly effect catalyst **15** though it promotes the formation of a minor, unidentified side-product (entries 6 and 7).

The additives that had the largest impact on the shown reaction, sodium acetate and 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt (DSS)**,** both contain functional groups that are known to displace the chloride ligands of ruthenium-based metathesis catalysts.[51-54] Therefore, these additives likely displace one or more of **15**'s chloride ligands to yield a complex that is less stable and/or active than catalyst **15**. As would be expected from this theory, when DSS is the additive, an insoluble green precipitate is formed. This is consistent with replacing **15**'s chloride ligand(s) with a greasy trimethysilylpropyl group of DSS to yield a water-insoluble complex(es).

Table 5.3. The effect of various functional groups on the ring-closing of substrate **39** with catalyst **15**[a]



Entry	Additive	Conversion (%)	Comments
1	None	88	--
2	DSS	18	MOST of **15** rapidly forms a water-insoluble complex.
3	Na_2SO_4	72	Dissolution of **15** is noticeably retarded. Decomposition to an orange complex and a precipitate are observed.
4		83	Only a minor effect on catalysis is observed.
5		90	Dissolution of **15** is noticeably retarded.
6	NaOAc	< 5	**15** rapidly decomposes to an orange complex.
7	AcOH	94	A minor side-product is observed.

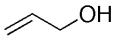
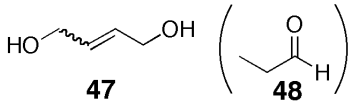
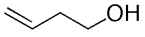
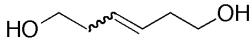
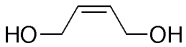
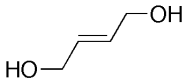
[a]Reactions were performed at 30 °C with a 5 mol% catalyst loading and initial substrate and additive concentrations of 0.2 M in deuterium oxide. Conversions were determined after 4 h by ^{1}H NMR spectroscopy and represent the average of two trials.

Catalyst cross-metathesis activity in water. As shown, catalysts **14** and **15** are able to mediate ROMP in water and are competent catalysts for RCM in an aqueous environment. Another prominent metathesis transformation is the cross-metathesis reaction. This is a challenging reaction in water that earlier water-soluble catalysts failed to catalyze.[11,26]

The homodimerization of various substrates was used as an initial examination of the ability of catalysts **14** and **15** to perform cross-metathesis in water. As shown in Table 5.4, both catalysts successfully homodimerized allyl and homoallyl alcohol. The catalysts

were also able to isomerizes *cis*-2-butene-1,4-diol. Again, the reported results for catalyst **13** with these substrates are also provided for comparison.[32,41]

Table 5.4. Homodimerization in water with catalysts **13**–**15**[a]

Entry (Catalyst)	Substrate	Time (h)	Product	Conversion (%)	E:Z
1 (**13**)[b]	 **46**	12	 **47** **48**	>95	15:1
2 (**14**)		24		82 (+4)	13:1
3 (**15**)		6		69 (+12)	19:1
4 (**13**)[c]	 **49**	12	 **50**	83	8:1
5 (**14**)		24		81	9:1
6 (**15**)		6		70	4:1
7 (**13**)[b]	 **51**	12	 **52**	94	--
8 (**14**)[d]		24		92	--
9 (**15**)[d]		2		94	--

[a]Reactions were performed at 45 °C with 5 mol% of catalyst and an initial substrate concentration of 0.2 M in deuterium oxide. Conversions were determined by ^{1}H NMR spectroscopy and represent the average of two trials. Reactions times were not optimized. [b]These data are from reference 41. [c]Reaction was performed at room temperature. These data are from reference 41. [d]Reaction was performed at 30 °C.

That catalysts **14** and **15** homodimerize allyl alcohol and homoallyl alcohol raises an interesting possibility. Both allyl and homoallyl alcohol can coordinate to the ruthenium center through their oxygen atoms to form a four- and five-membered chelate respectively (Figure 5.5). In contrast, such substrates as *O*-allyl tyrosine hydrochloride, allyl amine hydrochloride and (4-vinylbenzyl)trimethyl ammonium chloride, which lack a well-placed coordinating group, do not show any noticeable reaction with these catalysts. This inspires the hypothesis that productive cross metathesis in water requires a coordinating group that can chelate to the ruthenium center and stabilize the ruthenium alkylidene formed during the reaction. To test this hypothesis, we examined the homodimerization of 2-*O*-allyl-*β*-glucopyranoside, 3-butenoic acid, 4-pentenoic acid, 3-

butenamide and 4-pentenamide, which all contain reasonably well-placed coordinating groups. Unfortunately, these substrates also fail to homodimerize, though some isomerization was observed during attempts to homodimerize the olefins displaying sugar or carboxylic acid functionalities. Therefore, while a well-placed coordinating group may be required for successful cross metathesis in water, the mere presence of such functionality is not sufficient for successful aqueous cross metathesis.

Figure 5.5. Four- and five-membered ring chelate complexes might be formed during the homodimerization of allyl alcohol (**A**) and homoallyl alcohol (**B**) respectively.

Admittedly, the cross-metathesis activity of catalysts **14** and **15** is limited. Even so, the reactions shown in Table 5.4 represent the first examples of successful cross metathesis in water. Moreover, Kuo and Grubbs have used catalyst **14** to mediate cross-metathesis reactions between olefin-displaying ruthenium dyes and a few different cross partners.[41] Two examples of these reactions are provided in Figure 5.6. While the yields are low to moderate, the cross-metathesis reactions of Kuo and Grubbs are the only examples of successful cross metathesis between two different substrates in water.

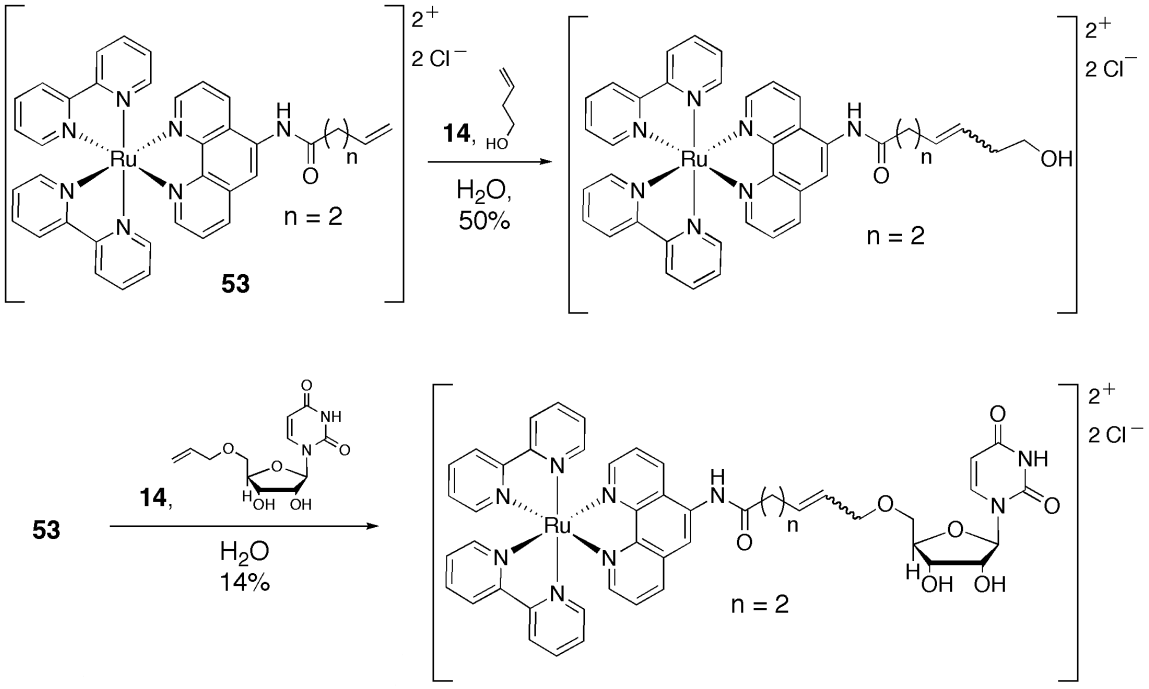


Figure 5.6. Catalyst **14** is able to cross terminal olefins onto ruthenium dye complex **53**.[41]

Summary

Water-soluble catalysts **14** and **15**, containing an NHC ligand, were synthesized. Both catalysts are phosphine-free and utilize ammonium salts to achieve solubility in water. While **14** is only moderately soluble, catalyst **15** readily dissolves in water. Both catalysts show superior ROMP activity over earlier water-soluble bis(phosphine) catalysts. Also, catalysts **14** and **15** are able to ring-close α,ω-dienes in water to form five-, six-, and seven-membered ring products in good to moderate conversions. Furthermore, though their aqueous cross-metathesis activity is limited, these catalysts are able to homodimerize allyl and homoallyl alcohol in good conversion.

Acknowledgements

The author is grateful to Dr. Soon Hyeok Hong and Professor Louis Kuo for their collaboration in developing aqueous metathesis catalysts. Also, Dr. Soon Hyeok Hong generously provided substrates **35** and **39**. Dr. Ian Stewart and Professor Tobias Ritter are acknowledged for helpful conversations. Dr. Mona Shahgholi generously assisted with mass spectometry, and Drs. Larry M Henling and Michael W. Day are thanked for their assistance with X-ray crystallography. Finally, the National Institute of Health (5R01GM068647) is acknowledged for funding.

Experimental

General considerations. All glove-box manipulations were performed in a N_2-filled Vacuum Atmospheres glove box (O_2 < 2.5 ppm). Otherwise reactions run under dry, degassed conditions were performed using standard Schlenk techniques under an atmosphere of dry argon using flame or oven-dried glassware. All NMR spectra were recorded on a Varian Mercury 300 (299.817 MHz for ^{1}H, 75.4 MHz for ^{13}C, and 121 MHz for ^{31}P) and reported in parts per millon (ppm) downfield from trimethylsilane as referenced to residual protio solvent peaks. Multiplicity abbreviations used when reporting ^{1}H NMR spectra are: s = singlet, d = doublet, ψd = pseudo-doublet, ψt = pseudo-triplet, dd = doublet of doublets, sept = septet, m = multiplet, and br = broad. All thin-layer chromatography (TLC) of organic compounds was accomplished on silica-gel 60 F254 percoated plates with a fluorescent indicator and visualized by UV light and/or by standard potassium permanganate stains. All flash chromatography of organic compounds was performed with silica-gel 60 (230–400 mesh). Neutral Brockman grade III alumina was generated by mixing 6% water (by mass) with neutral Brockman grade I

alumina (~150 mesh). For anaerobic chromatography, columns are first purged with argon, and all eluant is degassed with a generous argon sparge (at least 30 minutes). Product is then eluted under argon and collected in a round-bottom flask already purged with argon and equipped with a magnetic stir bar while under a stream of argon. Eluant is then removed *in vacuo*, not by rotary evaporation.

Materials. All deuterated solvents were purchased from Cambridge Isotope Laboratories. Deuterated dichloromethane was dried over 4 Å molecular sieves, and deuterated methanol was dried over calcium sulfate. Deuterated methanol and deuterated dichloromethane were degassed by three freeze, pump, and thaw cycles while deuterium oxide was degassed by a generous argon sparge. Anhydrous methanol was purchased from Aldrich and degassed with a generous argon sparge. Anhydrous DMF was purchased from Acros Organics and degassed with a generous argon sparge. Acetonitrile was purchased from Aldrich. All other solvents were purchased from Fischer Scientific. Solvents were dried by passage through purification columns packed with alumina and degassed by a generous argon sparge. All commericial materials were used as obtained. Ruthenium complexes **1**, **2**, and **3** were gifts from Materia. The syntheses of compounds **16**–**18** and ruthenium complex **19** was described in Chapter 3. Benzaldehyde starting material, **20**,[55] homoallyl amine,[56] and *N*-(*tert*-butoxycarbonyl)allylamine[57] were made following literature procedures. Substrates and products **27**,[26] **28**,[58] **29**,[59] **30**,[11] **31**,[60] **32**,[32] **34**,[24] **35**,[32] **36**,[59] **39**,[32] **40**,[61] **50**,[62,63] **52**,[64] *O*-allyl tyrosine hydrochloride,[65] 2-*O*-allyl-*β*-glucopyranoside,[66] 3-butenamide,[67] 4-pentenamide,[67] (4-vinylbenzyl)trimethyl ammonium chloride,[68] and 5-hexenoyl chloride[69] have already been reported. Substrate

33 was purchased from TCI America. Compounds **37**, **46**, **49**, **50**, triphenyl(methyl)phosphonium bromide, di-*tert*-butyl dicarbonate, homoallyl bromide, 60% sodium hydride, sodium hydride, 5-bromo-1-pentene, 3-butenoic acid, 4-pentenoic acid, 4 M HCl in dioxane, *N*,*N*,*N*',*N*'-tetramethylethylenediamine, trimethylamine gas, Amberlite IRA-400(Cl) ion-exchange resin were purchased from Aldrich. Sulfuric acid was purchased from Fischer Scientific. Ammonium chloride, hydrochloric acid, sodium hydroxide, sodium chloride, sodium bicarbonate, and magnesium sulfate were purchased from Malinkrodt. Sodium sulfate was purchased from EMS.

5-(Chloromethyl)-2-isopropoxybenzaldehyde (21). A two-neck round-bottom flask, equipped with a stir bar, was charged with compound **20** (10.0 g, 61 mmol), aqueous formaldehyde (37%, 13.6 mL, 180 mmol, 3.0 equiv), and concentrated hydrochloric acid (40 mL). The reaction mixture was heated to 50 °C prior to sparging with hydrogen chloride. (Hydrogen chloride was generated by slowly dripping 10 equivalents of sulfuric acid onto 10 equivalents of ammonium chloride.) The reaction was allowed to continue for 3 hours with a constant hydrogen chloride sparge at 50 °C. The produced dark-red, biphasic reaction mixture is cooled to 0 °C and diluted with diethyl ether. This mixture is made basic by the slow addition of 15% aqueous sodium hydroxide, and the resulting precipitate was removed by vacuum filtration. The filtrate is transferred to a separatory funnel and rinsed with water (2×) and brine (2×). The organic layer is dried over magnesium sulfate and evaporated to give a yellow solid. Recrystalization from petroleum ether yields 8.50 g (66%) of a white, crystalline product. ^{1}H NMR ($CDCl_3$, ppm): δ 10.46 (s, 1H), 7.83 (d, J = 2.4 Hz, 1H), 7.56 (dd, *J* = 8.7 Hz, 2.4 Hz, 1H), 6.99 (d,

J = 8.1 Hz, 1H), 4.70 (sept, *J* = 6.0 Hz, 1H), 4.55 (s, 2H), 1.41 (d, *J* = 6.0 Hz, 6H). ^{13}C NMR ($CDCl_3$, ppm): δ 189.8, 160.7, 136.2, 129.8, 128.6, 125.6, 114.5, 71.5, 45.6, 22.1. HRMS (EI+) *m*/*z* calc for $C_{11}H_{13}O_2Cl$: 212.0604, found 212.0600.

4-(Chloromethyl)-1-isopropoxy-2-vinylbenzene (22). A flame-dried, three-neck round-bottom flask, equipped with a stir bar and an addition funnel and purged with argon, was charged with triphenyl(methyl)phosphonium bromide (8.23 g, 23 mmol, 1.2 equiv), dry, degassed THF (157 mL), and potassium *tert*-butoxide (3.11 g, 28 mmol, 1.5 equiv) to give a bright-yellow solution. This solution was allowed to stir at room temperature under a positive argon pressure for 2 hours prior to cooling to ~ –60 °C. A solution of compound **21** (4.00 g, 19 mmol) in dry, degassed THF (78 mL) was slowly added over a period of 30 minutes while maintaining the temperature at ~ –60 °C. The reaction was then allowed to continue under a positive argon pressure while slowly warming to ~15 °C (~2 hours). Upon reaction completion, this mixture was diluted with diethyl ether, transferred to a separatory funnel and rinsed with a saturated aqueous solution of sodium bicarbonate (2×) and with brine (2×). The organic layer was dried over sodium sulfate and evaporated. The product was then passed through a plug of neutral alumina with 5% ethyl acetate in hexanes to obtain 3.07 g (78%) of clear, colorless liquid product of sufficient purity for use (~90% pure). For improved purity, the product can be eluted from a short flash column with 5% ethyl acetate in hexanes. However, the yield is significantly lowered (~50% yield) by the instability of **22** on silica-gel 60. The characterization data are of pure material. ^{1}H NMR ($CDCl_3$, ppm): δ 7.48 (d, *J* = 2.1 Hz, 1H), 7.21 (dd, *J* = 8.2 Hz, 2.2Hz, 1H), 7.02 (dd, *J* = 11 Hz, 18 Hz, 1H), 6.84 (d, *J* = 8.7

Hz, 1H), 5.74 (dd, *J* = 18 Hz, 1.8 Hz, 1H), 5.25 (dd, *J* = 11 Hz, 1.5 Hz, 1H), 4.55 (s, 2H), 4.53 (sept, *J* = 6.0 Hz, 1H), 1.34 (d, *J* = 6.0 Hz, 6H). ^{13}C NMR ($CDCl_3$, ppm): δ 155.4, 131.7, 129.6, 129.3, 128.2, 127.3, 114.8, 114.2, 71.1, 46.6, 22.3. HRMS (EI+) *m*/*z* calc for $C_{12}H_{15}OCl$: 210.0811, found 210.0814.

1-(4-Isopropoxy-3-vinylphenyl)-*N*,*N*,*N*-trimethylmethanaminium chloride (23). A round-bottom flask was equipped with a stir bar and a cold-finger filled with a dry-ice/acetone bath. The flask was charged with compound **22** (501 mg, 2.4 mmol) and acetonitrile (12.0 mL) and cooled to 0 °C prior to a 5 minute sparge with trimethylamine gas. The reaction was allowed to continue overnight (~12 hours) while slowly warming to room temperature. Upon reaction completion, the reaction mixture was sparged generously with air to remove excess trimethylamine. The acetonitrile was removed by rotary evaporation and the acquired solid dissolved in dichloromethane. Precipitation from diethyl ether followed by isolation by vacuum filtration yielded 520 mg (81%) of product as a white powder. ^{1}H NMR ($CDCl_3$, ppm): δ 7.60 (d, *J* = 2.4 Hz, 1H), 7.47 (dd, *J* = 8.7 Hz, 2.4 Hz, 1H), 6.88 (dd, *J* = 11 Hz, 18 Hz, 1H), 6.79 (d, *J* = 8.7 Hz, 1H), 5.73 (dd, *J* = 18 Hz, 1.2 Hz, 1H), 5.19 (dd, *J* = 11 Hz, 1.2 Hz, 1H), 4.88 (s, 2H), 4.50 (sept, *J* = 6.0 Hz, 1H), 3.32 (s, 9H), 1.28 (d, *J* = 6.0 Hz, 6H). ^{13}C NMR ($CDCl_3$, ppm): δ 156.8, 133.7, 131.3, 130.9, 128.1, 119.2, 115.9, 113.6, 70.7, 68.8, 52.4, 22.1. HRMS (FAB+) *m*/*z* calc for $C_{15}H_{24}NO$: 234.1858, found 234.1854.

2-(Dimethylamino)-N-(4-isopropoxy-3-vinylbenzyl)-*N*,*N*-dimethylethanaminium chloride (24). A round-bottom flask equipped with a stir bar was charged with compound

22 (3.04 g, 14 mmol), *N*,*N*,*N*',*N*'-tetramethylethylenediamine (15.2 mL, 100 mmol, 7.1 equiv), and acetonitrile (72.0 mL). This reaction mixture was allowed to stir at room temperature for 14 hours. Upon reaction completion, the acetonitrile was removed by rotary evaporation, and the product was dissolved in dichloromethane. Precipitation from –78 °C diethyl ether followed by vacuum filtration yields 4.26 g (90%) of product as a white powder that rapidly forms an oil in the presence of moisture (extremely hygroscopic). A solid is obtained by extensive drying under high vacuum. The sample for NMR spectroscopy was prepared in a N_2-filled glove box with dry, degassed deuterated dichloromethane. ^{1}H NMR (CD_2Cl_2, ppm): δ 7.74 (d, *J* = 3.0 Hz, 1H), 7.54 (dd, *J* = 9.0 Hz, 2.7 Hz, 1H), 6.96 (dd, *J* = 11 Hz, 18 Hz, 1H), 6.88 (d, *J* = 9.3 Hz, 1H), 5.80 (dd, *J* = 18 Hz, 1.8 Hz, 1H), 5.24 (dd, *J* = 12 Hz, 1.8 Hz, 1H), 5.03 (s, 2H), 4.57 (sept, *J* = 6.0 Hz, 1H), 3.81 (t, *J* = 5.4 Hz, 2H), 3.27 (s, 6H), 2.73 (t, *J* = 5.4 Hz, 2H), 2.23 (s, 6H), 1.31 (d, 6.6 Hz, 6H). ^{13}C NMR (CD_2Cl_2, ppm): δ 157.0, 134.4, 132.0, 131.5, 128.2, 120.0, 115.7, 113.9, 71.1, 68.4, 60.6, 54.3, 49.7, 45.6, 22.2. HRMS (FAB+) *m*/*z* calc for $C_{18}H_{31}N_2O$: 291.2436, found 291.2424.

***N*-(4-Isopropoxy-3-vinylbenzyl)-*N*,*N*,*N'*,*N'*,*N'*-pentamethylethane-1,2-diaminium chloride (25).** A round-bottom flask equipped with a stir bar was charged with compound **24** (4.26 g, 13 mmol), dichloromethane (65.0 mL), and iodomethane (7.00 mL, 110 mmol, 8.6 equiv). The reaction was allowed to stir at room temperature for 7 hours. Precipitation of the reaction mixture from diethyl ether yields an ivory solid. This solid was allowed to stir in diethyl ether overnight prior to isolation by vacuum filtration to yield a white solid, which rapidly forms an oil in the presence of moisture (highly

hygroscopic). The material was dissolved in water (433 mL) followed by the addition of 65 g of Amberlite IRA-400(Cl) resin. This mixture was allowed to stir for 12 hours prior to removing the resin by vacuum filtration. 65 g of fresh resin was then added to the filtrate and the mixture was stirred for 12 hours prior to the resin's removal by vacuum filtration. This process was repeated one more time. Water was removed by rotary evaporation at elevated temperature, and the product was triturated 3 times with benzene. Drying under high vacuum for an extended period of time (~16 h) at 50 °C yields 3.97 g (81%) of product as a white powder (highly hygroscopic). ^{1}H NMR (DMSO-d_6, ppm) δ 7.87 (d, J = 1.8 Hz, 1H), 7.55 (dd, J = 8.5 Hz, 1.8 Hz, 1H), 7.12 (d, J = 8.7 Hz, 1H), 6.93 (dd, J = 11 Hz, 18 Hz, 1H), 5.88 (dd, J = 18 Hz, 1.5 Hz, 1H), 5.30 (dd, J = 11 Hz, 1.5 Hz, 1H), 4.76 (s, 2H), 4.70 (sept, J = 6.0 Hz, 1H), 4.41 (br s, 2H), 4.24 (br s, 2H), 3.31 (s, 9H), 3.14 (s, 6H), 1.29 (d, J = 6.0 Hz). ^{13}C NMR (DMSO-d_6, ppm): δ 155.9, 134.0, 131.5, 130.9, 126.7, 119.3, 115.7, 113.7, 70.1, 66.1, 56.8, 55.4, 52.6, 49.1, 21.8. HRMS (FAB+) m/z calc for $C_{19}H_{34}N_2OCl$: 341.2360, found 341.2361.

Ruthenium complex 14. In a N_2-filled glove box, a flame-dried round-bottom flask, equipped with a stir bar, was charged with ruthenium complex **2** (200 mg, 0.24 mmol), compound **21** (133 mg, 0.35 mmol, 1.5 equiv), and copper(I)chloride (47 mg, 0.48 mmol, 2.0 equiv) and capped with a septum. The flask was brought out of the glove box, and its seal was reinforced with Teflon tape. Dry, degassed dichloromethane (6 mL) was added, and the reaction was heated to 45 °C. The reaction was stirred at 45 °C for 1 hour. Upon reaction completion, the product mixture was passed through a plug of celite, and the dichloromethane was removed by rotary evaporation. Purification was accomplished by

running 2 anaerobic (as previously described in the general considerations section), long, approximately gravimetric neutral Brockman grade V alumina columns with 20% methanol in dichloromethane. (The material was loaded with dichloromethane, and the green band is product.) These columns are followed by a single anaerobic, long ~gravimetric neutral Brockman grade III alumina column with 20% methanol in dichloromethane. (The material was loaded with CH_2Cl_2.) The product is then dissolved in dry, degassed methanol (~0.02 M solutuion) and layered with 5–6 volume equivalents of dry, degassed diethyl ether and allowed to crystallize overnight. The brown supernatant is decanted from the dark green crystals, which are then rinsed with diethyl ether (3×). The product is dried under high vacuum at ~45 °C for ~20 hours to yield 90 mg (46%) of a green, crystalline product. The sample for NMR spectroscopy was prepared in a N_2-filled glove box with dry, degassed deuterated methanol. The NMR spectra for this complex are provided in Appendix 1. The X-ray crystal data for this complex are provided in Appendix 2. ^{1}H NMR (CD_3OD, ppm): δ 16.81 (s, 1H), 7.91 (dd, J = 8.6 Hz, 2.2 Hz, 1H), 7.19 (d, J = 8.7 Hz, 1H), 7.15 (d, J = 2.1 Hz, 1H), 7.09 (s, 4H), 5.01 (sept, J = 6.2 Hz, 1H), 4.78 (s, 2H), 4.20 (s, 4H), 4.20–4.05 (br, 4H), 3.32 (s, 9H), 3.14 (s, 6H), 2.44 (s, 18H), 1.24 (d, J = 6.3 Hz, 6H). ^{13}C NMR (CD_3OD, ppm): δ 295.3, 209.4, 155.5, 147.1, 140.5, 135.7, 130.6, 127.0, 122.3, 115.5, 78.1, 69.4, 59.1, 57.8, 54.7, 52.9, 50.5, 50.0, 21.8, 21.6, 20.0. HRMS (FAB+) *m*/*z* calc for $C_{39}H_{58}N_4OCl_3Ru$: 807.2731, found 807.2747.

Ruthenium complex 15. In a N_2-filled glove box, a flame-dried round-bottom flask, equipped with a stir bar, was charged with copper(I)chloride (62 mg, 0.63 mmol, 2.4

equiv), compound **19** (90 mg, 0.33 mmol, 1.3 equiv), and ruthenium complex **25** (253 mg, 0.26 mmol) and capped with a septum. This flask was removed from the glove box, and its seal was reinforced with Teflon tape. Dry, degassed dichloromethane (7.7 mL) was added, and the reaction was heated to 45 °C. The reaction was allowed to continue for 1 hour at 45 °C. Upon reaction completion, the reaction was allowed to cool, and the dichloromethane was removed by rotary evaporation. The dark-green material was passed through a plug of celite with benzene and precipitated from diethyl ether. The green solid was isolated from diethyl ether by centrifugation (rinsing with diethyl ether (2x)), and eluted from a long, neutral Brockman grade III alumina column with 7% methanol in dichloromethane to obtain ruthenium complex **26** as a dark-green solid. A flame-dried round-bottom flask, equipped with a stir bar, was charged with ruthenium complex **26** and purged with argon. Freshly prepared hydrogen chloride/benzene solution (13 mL) was added to give a green suspension. (The hydrogen chloride/benzene solution was generated by sparging dry, degassed benzene (~20 mL) with hydrogen chloride gas for 1 hour. The hydrogen chloride gas was produced by slowly dripping sulfuric acid onto an equivalent (versus sulfuric acid) of ammonium chloride.) The reaction was allowed to stir for 45 minutes at room temperature. The product was isolated from benzene by centrifugation, rinsing with dichloromethane (2×). This green solid is dispersed in ~500 mL of degassed, reagent-grade dichloromethane in a round-bottom flask and allowed to stir overnight (~16 hours) under a positive argon pressure. The fine, green powder was isolated by vacuum filtration through a medium frit. The product was dissolved in dry, degassed methanol (~0.2 M solution) in a 20 mL vial. This vial was brought into a N_2-filled glove box and placed in a reservoir of dry, degassed diethyl ether

to recrystalize by liquid/vapor diffusion. The light-green supernatant was decanted from the green crystals, which were rinsed with diethyl ether (3x). The product was dried under high vacuum at 45 °C for ~20 hours to obtain 138 mg (67%, 2 steps) of green, crystalline material. The NMR sample was prepared under an inert atmosphere using degassed deuterium oxide (generous argon sparge). Dry, degassed methanol was used as an internal standard for the ^{13}C-NMR spectrum. The NMR spectra for this complex are provided in Appendix 1. ^{1}H NMR (D_2O, ppm): δ 16.83 (s, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.31–7.15 (m, 4H), 7.05 (s, 1H), 5.09–4.86 (m, 2H), 4.58 (ψt, J = 11.1 Hz, 1H), 4.47 (s, 2H), 4.19 (ψt, J = 10.0 Hz, 1H), 3.48 (ψt, J = 11.2 Hz, 1), 3.39–3.31 (m, 1H), 3.03 (s, 9H), 2.51 – 2.20 (m, 18H), 1.16 (ψt, J = 6.4 Hz, 6H). ^{13}C NMR (D_2O, ppm): δ 306.1, 210.8, 154.4, 146.1, 141.3, 141.0, 139.7, 136.6, 130.8, 130.5, 130.2, 130.1, 126.5, 122.5, 115.2, 77.9, 68.9, 61.7, 52.6, 42.4, 21.2, 20.9, 20.8, 19.0. HRMS (FAB+) *m*/*z* calc for $C_{36}H_{51}N_4OCl_2Ru$: 727.2484, found 727.2490.

Dibut-3-enylammonium chloride (41). A flame-dried round-bottom flask, equipped with a condenser, was charged with homoallyl amine (551 mg, 7.7 mmol, 2 equiv), dry, degassed THF (4 mL), and homoallyl bromide (0.4 mL, 3.82 mmol). The reaction mixture was heated to reflux and allowed to continue at reflux for 20 hours under a positive argon pressure. Upon reaction completion, the reaction was allowed to cool, and the THF was removed by rotary evaporation. The product was dissolved in water, and the mixture was made acidic with 3 M hydrochloric acid prior to transferring the solution to a separatory funnel. The water layer was rinsed with diethyl ether (3×) and made basic with solid potassium hydroxide. The basic solution was extracted with diethyl ether (4×), and

the combined ether layers were rinsed with water (6×) and with brine (1×). The organic fraction was dried over magnesium sulfate, and the volatiles were removed by rotary evaporation. To purify, the crude material was protected by stirring in the presence of di-*tert*-butyl dicarbonate (834 mg, 3.8 mmol, 1 equiv) in dichloromethane (19 mL) overnight (~16 hours) at room temperature. The volatiles were removed by rotary evaporation, and the product was eluted from a flash column using 10% ethyl acetate in hexanes. The product was stirred in a solution of hydrochloric acid in methanol (3 M, 19 mL) overnight (~16 h). The volatiles were removed by rotary evaporation and the product was dried under high vacuum to obtain 171 mg (52%) of white, solid product **41**. ^{1}H NMR (CD_2Cl_2, ppm): δ 9.70 (s, 2H), 5.89–5.75 (m, 2H), 5.21–5.10 (m, 4H), 3.03–2.98 (m, 4H), 2.69–2.62 (m, 4H). ^{13}C NMR (CD_2Cl_2, ppm) δ 133.5, 118.4, 47.3, 30.5. HRMS (ES+) *m*/*z* calc for $C_8H_{16}N$: 126.1283, found 126.1291.

***N*-allylpent-4-en-1-aminium chloride (44).** A flame-dried round-bottom flask was charged with *N*-(*tert*-butoxycarbonyl)allylamine (1.21 g, 7.7 mmol), anhydrous DMF (15 mL), and 60% sodium hydride (619 mg, 16 mmol, 2.1 equiv). After stirring for 20 minutes at room temperature under a positive argon pressure, 5-bromo-1-pentene (2.3 mL, 18.5 mmol, 2.4 equiv) was added, and the reaction mixture was heated to 80 °C. The reaction was allowed to continue at 80 °C under a positive argon pressure for 16 hours. After being allowed to cool to room temperature, the product mixture was diluted with diethyl ether and rinsed with water (6×) and with brine (1×). The organic fraction was dried over magnesium sulfate, and the volatiles were removed by rotary evaporation. Flash chromatography with 10% ethyl acetate in hexanes yielded 1.25 g (72%) of a clear,

colorless liquid product. Substrate **44** was obtained by stirring this liquid (1.05 g, 4.65 mmol) in a solution of hydrochloric acid in methanol (3 M, 8 mL) for 8 hours. The volatiles were removed by rotary evaporation, and the crude material was dissolved in water made acidic with hydrochloric acid. This aqueous solution was rinsed with diethyl ether (3×), made basic with solid potassium hydroxide and extracted with diethyl ether (4×). The combined dietyl ether extracts of the basic solution were dried over magnesium sulfate, and the diethyl ether was removed by rotary evaporation. A solution of this material in diethyl ether was cooled to -78 °C prior to the drop-wise addition of 4 M hydrogen chloride in dioxane to yield an acidic solution. The white precipitate produced was isolated by vacuum filtration and dried under high vacuum to obtain 367 mg (49%, 35% over the 2 steps) of compound **44** as a hygroscopic white solid. ^{1}H NMR ($CDCl_3$, ppm): δ 9.66 (s, 2H), 6.14–6.00 (m, 1H), 5.79–5.66 (m, 1H), 5.50–5.42 (m, 2H), 5.09–4.97 (m, 2H), 3.57 (d, J = 6.9 Hz, 2H), 2.90–2.85 (m, 2H), 2.18–2.11 (m, 2H), 2.02–1.92 (m, 2H). ^{13}C NMR ($CDCl_3$, ppm): δ 136.4, 128.0, 124.1, 116.5, 49.7, 46.0, 30.8, 25.0. HRMS (ES+) m/z calc for $C_8H_{16}N$: 126.1283, found 126.1284.

General procedure for ROMP, RCM, and cross-metathesis reactions with catalyst 14. In an N_2-filled glove box, catalyst **14** (5 mg, 5.9 μmol, 0.05 equiv) was weighed into a 1-dram vial. This vial was equipped with a stir bar, sealed with a septa-cap and removed from the glove box. The vial's seal was reinforced with Teflon tape, and the vial was charged with a 0.2 M solution of substrate in degassed deuterium oxide (0.6 mL). (The substrate stock solution was prepared under inert conditions with degassed deuterium oxide and stored under argon. A sufficient amount of the stock solution was

prepared to allow for at least 3 trials.) The vial was heated to the appropriate temperature and allowed to continue for 24 hours under a positive argon pressure. After 24 hours, the reaction mixture is transferred to an NMR tube and its conversion was determined by ^{1}H NMR spectroscopy.

For ROMP with **14**, in a N_2-filled glove box, catalyst **14** (1.9 mg, 2.3 μmol, 0.034 equiv) was weighed into a 1-dram vial which was equipped with a stir bar and sealed with a septa-cap. This vial was brought out of the box, and its seal was reinforced with Teflon tape. A 0.095 M stock solution of monomer **32** in degassed deuterium oxide (0.7 mL) was added, and the reaction was heated to 45 °C. (The monomer stock solution was prepared under inert conditions and stored under argon.) The reaction was monitored by the ^{1}H NMR spectroscopy of reaction-mixture aliquots.

General procedure for ROMP, RCM, and cross-metathesis with catalyst 15. In an N_2-filled glove box, catalyst **15** (4.8 mg, 6.0 μmol, 0.05 equiv) was weighed into a 1-dram vial. The vial was sealed with a septa-cap and removed from the glove box. A screw-cap NMR tube was also sealed with a septa-cap and removed from the glove box. The seals of both the vial and the NMR tube were reinforced with Teflon tape. A 0.2 M solution of substrate in degassed deuterium oxide (0.6 mL) was added to the vial, and full dissolution of **15** was accelerated with brief (~5–60 seconds) sonication. (The substrate solution was prepared under inert conditions with degassed deuterium oxide and stored under argon. A sufficient amount of substrate stock solution was prepared to allow for at least 3 trials.) The solution was transferred to the NMR tube by a air-tight syringe, and the reaction was heated to 30 °C. The reaction was monitored by ^{1}H NMR spectroscopy.

For ROMP, catalyst **15** (1.7 mg, 2.12 μmol, 0.032 equiv) was weighed into a 1-dram vial, which was sealed with a septa-cap. The vial and a septa-cap-sealed NMR tube were removed from the glove box, and their seals were reinforced with Teflon tape. A 0.095 M stock solution of monomer **27** in degassed deuterium oxide (0.7 mL) was added. (The monomer stock solution was prepared under inert conditions and stored under argon.) After brief sonication, the reaction mixture was transferred to the NMR tube using an air-tight syringe, and the reaction was heated to 45 °C. The reaction was monitored by ^{1}H NMR spectroscopy.

Newly Characterized Materials from RCM Reactions

(*Z*)-2,3,6,7-tetrahydro-1*H*-azepinium chloride (42). ^{1}H NMR (D_2O, ppm): δ 5.82 (t, *J* = 3.2 Hz, 2H), 3.19 (t, *J* = 5.2 Hz, 4H), 2.42 (ψd, *J* = 5.1 Hz, 4H). ^{13}C NMR (D_2O, methanol internal standard, ppm): δ 130.0, 45.4, 24.8. HRMS (ES+) *m*/*z* calc for $C_6H_{12}N$: 98.0970, found 98.0973.

(*E*)-*N*-(but-3-enyl)but-2-en-1-aminium chloride (43). (Note: while both E and Z isomers were observed, the provided characterization is for the major isomer, the Z isomer.) ^{1}H NMR (D_2O, ppm): δ 6.03–5.95 (m, 1H), 5.83–5.72 (m, 1H), 5.57–5.50 (m, 1H), 5.26–5.16 (m, 2H), 3.58 (d, *J* = 7.2 Hz, 2H), 3.09 (t, *J* = 7.0 Hz, 2H), 2.47–2.39 (m, 2H), 1.74–1.71 (m, 2H). ^{13}C NMR (D_2O, methanol internal standard, ppm): δ 137.6, 133.5, 120.2, 119.5, 49.6, 46.0, 30.6, 17.9. HRMS (ES+) *m*/*z* calc for $C_8H_{16}N$: 126.1283, found 126.1290.

(*Z*)-2,3,4,7-tetrahydro-1*H*-azepinium chloride (45). ^{1}H NMR (D_2O, ppm): δ 6.25–6.17 (m, 1H), 5.81–5.73 (m, 1H), 3.77 (d, J = 5.7 Hz, 2H), 3.42 (t, J = 5.8 Hz, 2H), 2.43–2.36 (m, 2H), 1.96–1.88 (m, 2H). ^{13}C NMR (D_2O, methanol internal standard, ppm): δ 138.7, 122.7, 50.1, 44.7, 27.2, 23.8. HRMS (ES+) m/z calc for $C_6H_{12}N$: 98.0970, found 98.0967.

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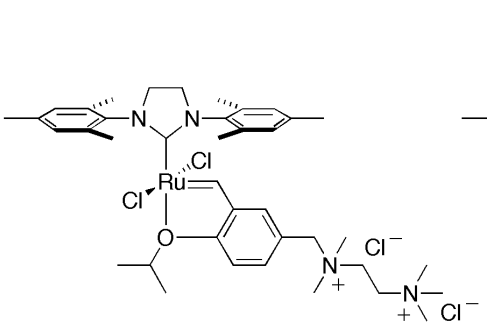
CHAPTER 6

Research Opportunities in Aqueous Olefin Metathesis

Opportunities for Catalyst Development



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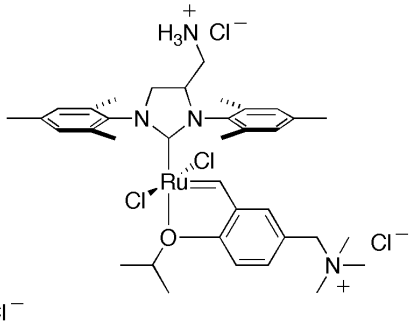

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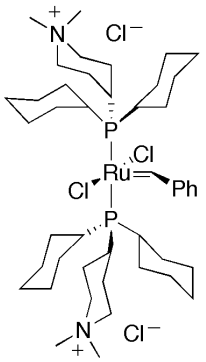

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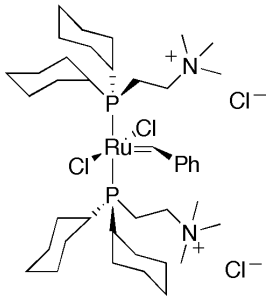


4

The research presented in this thesis has established that olefin metathesis catalysts containing an *N*-heterocyclic carbene (NHC) ligand (**1** and **2**) are more stable and active in water than their bis(phosphine) counterparts (**3** and **4**). Indeed, the development of catalysts **1** and **2** represent significant progress in the ability to perform homogenous metathesis in water. As described in Chapter 5, catalysts **1** and **2** are competent at mediating ring-opening metathesis polymerization (ROMP) and ring-closing metathesis in water, yet their ability to catalyze cross-metathesis is limited. Therefore, further research is still required to generate a catalyst that fully mirrors in water the activity of olefin metathesis catalysts in organic solvents.

In all metathesis reactions, as with all catalyzed reactions, at least two processes compete: productive catalysis (reactivity) and catalyst decomposition (stability). Therefore, metathesis reactions are improved by increasing the rate of productive catalysis relative to the rate of catalyst decomposition. Two strategies are available to accomplish this objective, improve the rate of catalysis or decrease the rate of catalyst decomposition. Ideally, catalysts that are both more stable and more reactive are desired, but goals to improve one of these metrics are more realistic. Also, there is usually a trade-off between reactivity and stability in catalysis. More stable catalysts are typically less catalytically reactive and vice versa, and whether strategies that favor greater catalyst reactivity or stability are pursued depends on the targeted process. Examples of both strategies are proposed for aqueous olefin metathesis.

Improving the reactivity of water-soluble metathesis catalysts. One promising method to increase the rate of productive catalysis for olefin metathesis is to decrease the steric bulk around the metal, which allows substrates greater access to the catalytically active center.[1,2] This is the strategy employed by Grubbs and co-workers to develop catalysts **5**–**8**.[1,2] The goal of these catalysts is the facile ring-closing of geminal-disubstituted olefins to form a tetrasubstituted olefin, which is a challenging transformation in olefin metathesis (Figure 6.1).[3-8] Catalyst **8** is a particularly good catalyst for these transformations because it couples the ability to form tetrasubstituted olefins with reasonable complex stability, being more stable than catalysts **5**–**7**.[2]

Producing a water-soluble analog of catalyst **8** should be straightforward. Mixing ruthenium complex **7**[2] with isopropoxystyrene **9**[9] in the presence of copper(I)chloride should yield catalyst **10**, whose solubility properties should echo those of catalyst **1**. This

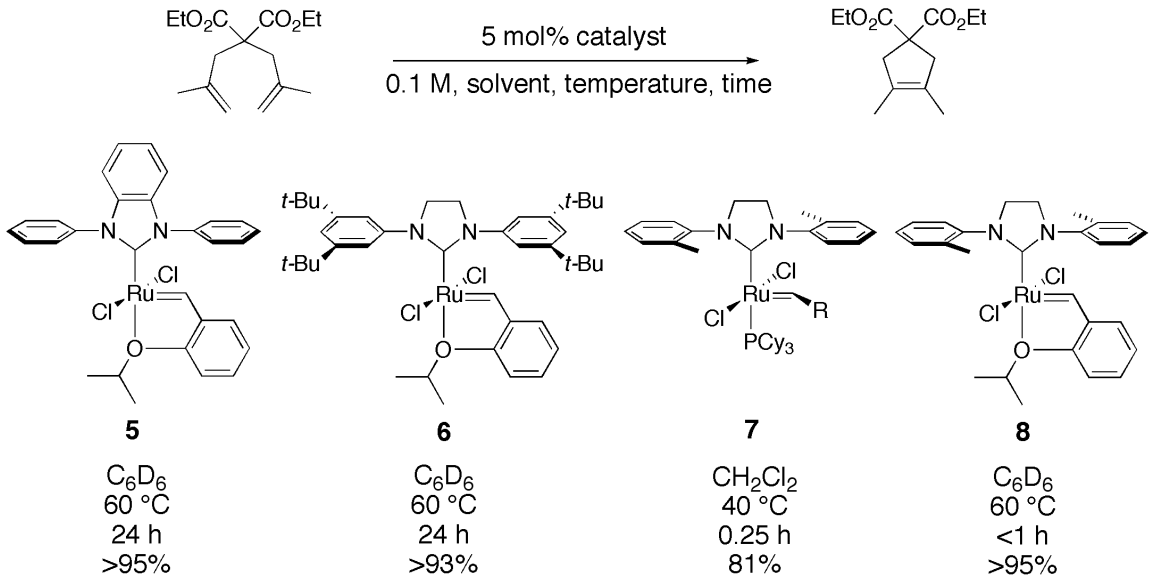
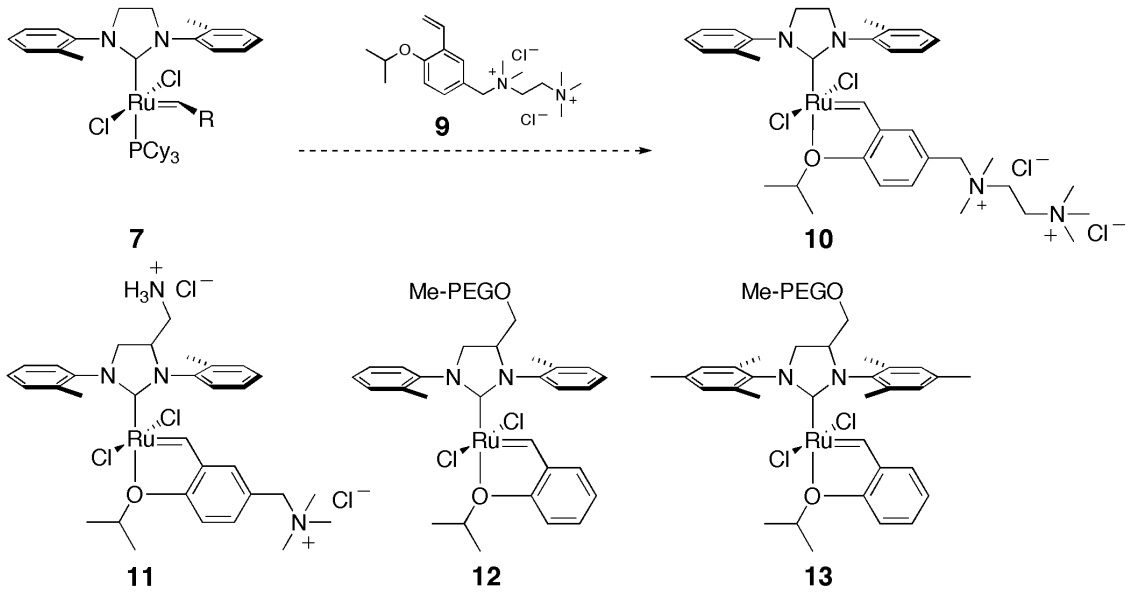


Figure 6.1. Reducing the steric bulk surrounding the ruthenium center produces more reactive metathesis catalysts, which are able to ring-close α,ω-dienes to produce tetrasubstituted olefins. The solvent, temperature, time, and conversion for the specified reaction is shown below each catalyst.

route provides a rapid method to examine this strategy for improved rates of catalysis in water. Should challenging aqueous cross-metathesis reactions with the proposed catalyst be successful, then the more-involved production of complexes **11** and **12**, analogs of water-soluble catalysts **2** and **13**,[10] may be warranted (PEG = poly(ethylene glycol)).

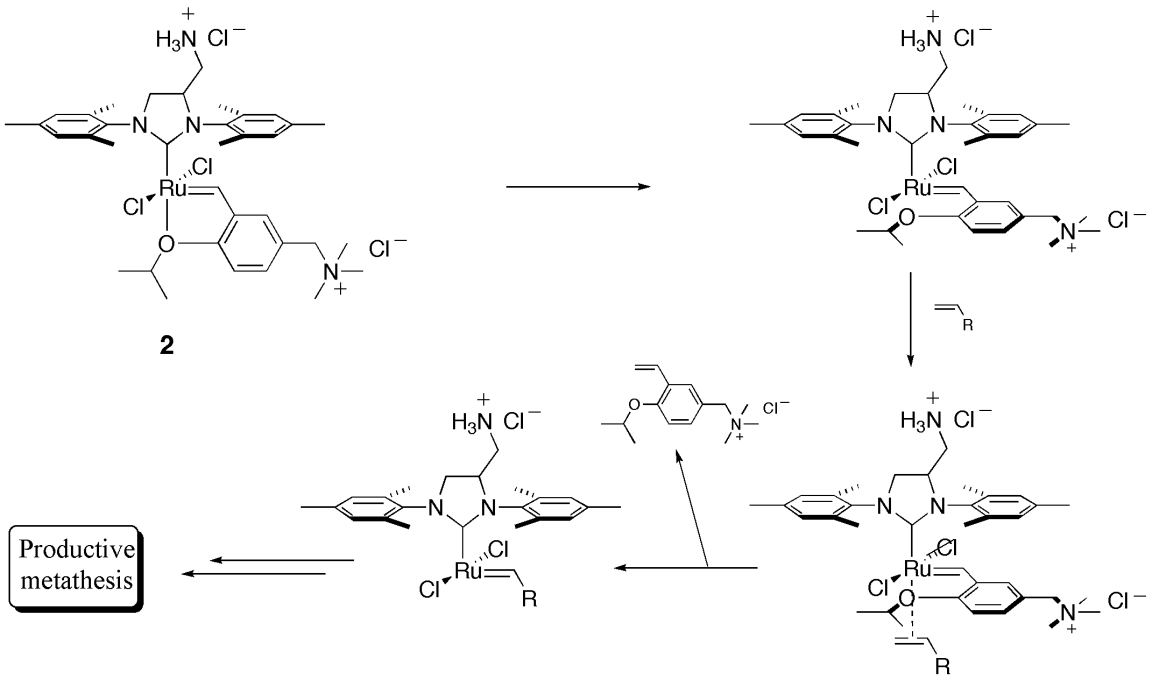


While the described method for improving catalyst reactivity can be rapidly examined, this author believes that the more promising strategy is to stabilize the catalyst against decomposition in water. Increased catalyst activity arises from increasing the ratio of the rate of productive catalysis over the rate of catalyst decomposition. The research reported in Chapters 4 and 5 shows that metathesis catalysts decompose more rapidly in water than in organic solvents. Therefore, in water, greater increases in the rate of productive catalysis are required to attain the same improvements in catalyst activity as observed for lesser rate increases in organic solvents. Also, the high stability of metathesis catalysts in organic solvents can accommodate a moderate increase in the rate of catalyst decomposition. However, for aqueous metathesis, the rate of decomposition is often similar to and even greater than the rate of productive metathesis, particularly for aqueous cross metathesis. In contrast, an increase in catalyst stability may provide aqueous metathesis reactions with sufficient time to progress to completion at a lesser rate.

Improving the stability of water-soluble metathesis catalysts. Chapters 4 and 5 reveal that the ruthenium benzylidene complexes, especially isopropoxybenzylidene complexes **1** and **2**, are highly stable toward water. However, Chapter 4 also indicates that ruthenium menthylidene and alkylidene complexes decompose rapidly in the presence of water. The limited capabilities of catalysts **1** and **2** to perform aqueous cross metathesis is further evidence for this conclusion. Therefore, strategies that increase the stability of the methylidene and alkylidene complexes may produce catalysts with increased activities in water.

The first step of productive metathesis is the dissociation of the ligand trans to the NHC.[11,12] For catalysts **1** and **2**, this ligand is the isopropoxybenzylidene's ether group. During productive metathesis, the isopropoxybenzylidene is released from the catalyst upon the reaction of the catalyst with substrate (Scheme 6.1),[13,14] and the ether group is insufficiently coordinating to stabilize the catalyst in the absence of chelation. Consequently, the methylidene and ethylidene analogs of catalysts **1** and **2** lack a ligand that can coordinate to the metal and stabilize these complexes against decomposition. Therefore, catalysts that provide such a ligand may show increased activities in water. Acknowledging the active role of phosphine in methylidene decomposition,[15,16] these catalysts should be phosphine-free.

Scheme 6.1.



A promising ligand scaffold that satisfies the stated requirements supports the catalyst with a chelating ligand that coordinates to the ether and chloride positions of

catalysts like **1** and **2** (Figure 6.2). The dissociating ligand of such catalysts remains coordinatively linked to the metal center and can serve to stabilize the methylidene and alkylidene complexes. Reported research for this type of system has produced catalysts **14**–**18** (Figure 6.2) whose dissociating ligands all chelate to the ruthenium center.[17-21]

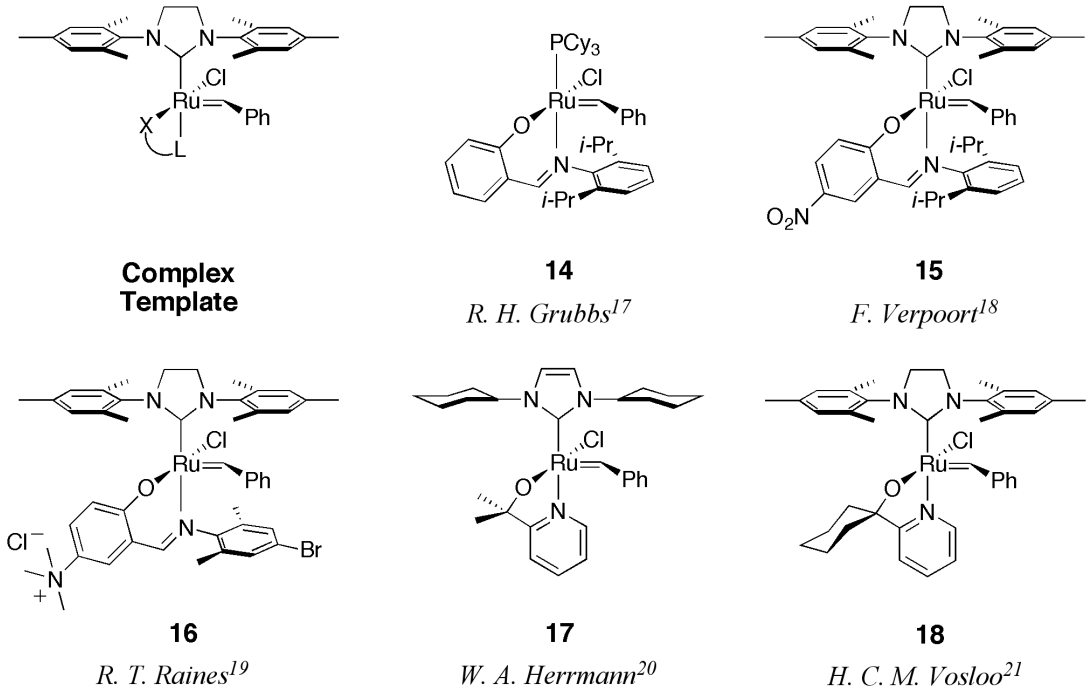


Figure 6.2. Ruthenium complexes based on the shown **Complex Template** are very stable olefin metathesis catalysts.

The first metathesis catalyst utilizing the proposed ligand scaffold was complex **14**, which employs a salicylaldimine ligand.[17] After 12 hours at 40 °C in methanol, catalyst **14** cyclizes the hydrogen chloride salt of diallylamine to the product five-membered ring in 95% conversion. This is the first example of ring-closing an α,ω-diene in a protic solvent and is the first demonstration of the potential for the proposed ligand scaffold in a polar protic environment.

More recent research has focused on incorporating chelating ligands onto ruthenium metathesis catalysts that contain an *N*-heterocyclic carbene ligand (**15**–**18**).[18-21] Catalysts reported by Verpoort and Raines include salicylaldimine ligands[18,19] while Herrmann and Vosloo describe catalysts supported by 2-pyridylcarbinols.[20,21] These catalysts are all highly stable. However, as may be expected, these catalysts are also far less reactive than catalysts containing isopropoxybenzylidene ligands and require high temperatures and/or long reaction times to mediate metathesis reactions.[18-21]

Slow dissociation of the ligand *trans* to the NHC is responsible for the poor reactivities observed with catalysts **15**–**18**.[19,20] However, the rate of catalyst initiation increases in more polar solvents,[11] and Chapter 4 shows that ruthenium complexes initiate more rapidly in the presence of water. Consequently, initiation with catalysts **15**–**18** may be sufficiently rapid in water to mediate metathesis at more moderate temperatures. Indeed, with catalyst **16**, Raines and co-workers show that catalyst activity for these systems is much higher in methanol/water mixtures than in nonpolar solvents.[19] Therefore, while the described ligand scaffold produces catalysts with poor reactivity in organic solvents, catalysts containing such ligands may strike the correct balance between stability and reactivity for aqueous metathesis.

The proposed chelating ligands are 2-pyridylcarbinols where the coordinated oxygen is presented as a phenoxide containing an ammonium salt *para* to the oxygen (Figure 6.3). 2-Pyridylphenols were chosen mainly due to salicylaldimine ligands being unstable toward water.[19] The indicated phenoxide is proposed for its increased acidity relative to alkoxides[22] and as a vehicle for incorporating a water-soluble functional group. Also, the pyridine rings of these ligands may be modified to increase complex initiation

by incorporating electron-withdrawing groups and/or steric bulk *ortho* to the nitrogen (Figure 6.3).

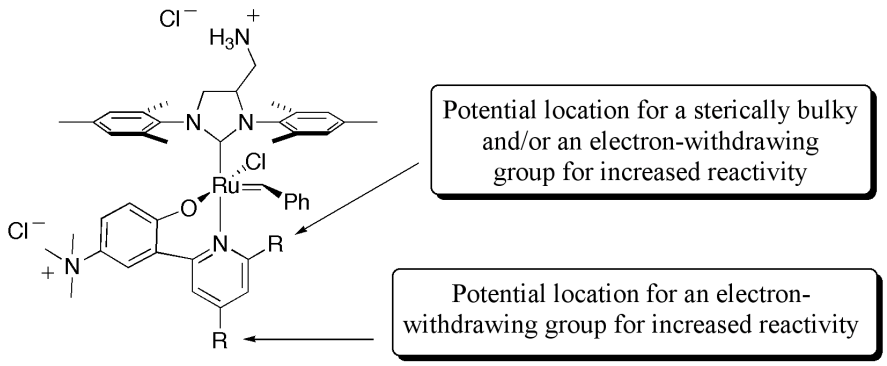
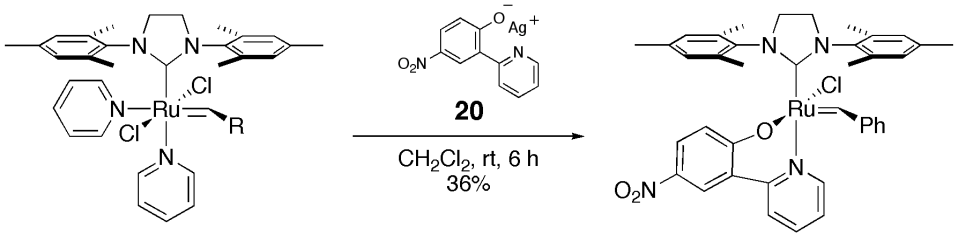


Figure 6.3. 2-Pyridylphenol supported ruthenium complexes are proposed as potentially stable water-soluble metathesis catalysts.

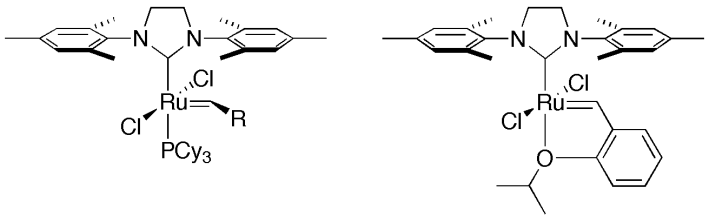
Results supporting this strategy. Preliminary research exploring the synthesis of a ruthenium complex containing the described ligand scaffold produced ruthenium complex **19**. Mixing the silver salt of 2-pyridylphenol **20**[23] with ruthenium bis(pyridine) complex **21**[24] in dichloromethane for three hours at room temperature gives **19** as a red solid. The ^{1}H NMR spectrum of **19** shows a single benzylidene resonance at 17.95 ppm, which is in excellent agreement with the published values for benzylidene resonances of NHC-containing catalysts supported by a 2-pyridylcarbinol.[20,21] This catalyst is very stable and is capable of ring-closing diethyl diallylmalonate in reagent grade dichloromethane, open to air to 85% conversion after 54 hours at 45 °C. To be applied to aqueous metathesis, complex **19** needs to be modified to incorporate water-soluble ionic groups.



21 19

Potential Biological Applications of Aqueous Metathesis

Olefins are orthogonal to the functional groups displayed by the natural amino acids. Furthermore, techniques exist for the site-specific incorporation of unnatural amino acids displaying double bonds.[25-28] Therefore, olefin metathesis has the potential to provide a unique and useful method for the regioselective modification of proteins. However, polypeptides of biological interest are often only soluble in water, a solvent that does not dissolve commonly used, moisture-tolerant catalysts **22** and **23**. Because of their solubility and good activity in water, catalyst **1** and **2** provide the capability required to initiate an exploration of the potential for olefin metathesis in this area.

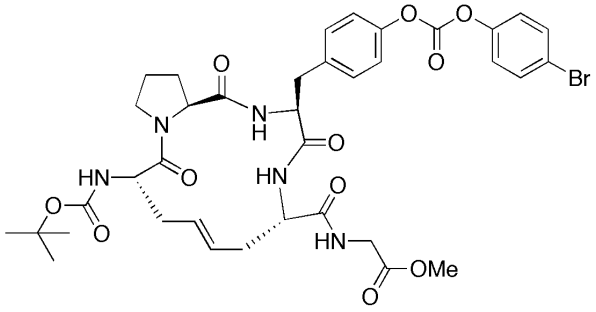


22 23

Before venturing further, the impact of one aspect of protein research on the use of olefin metathesis in this field needs to be addressed. Solutions of proteins are usually very dilute with concentrations often ranging from nM to μM. These concentrations are much lower than the substrate concentrations employed in more traditional olefin

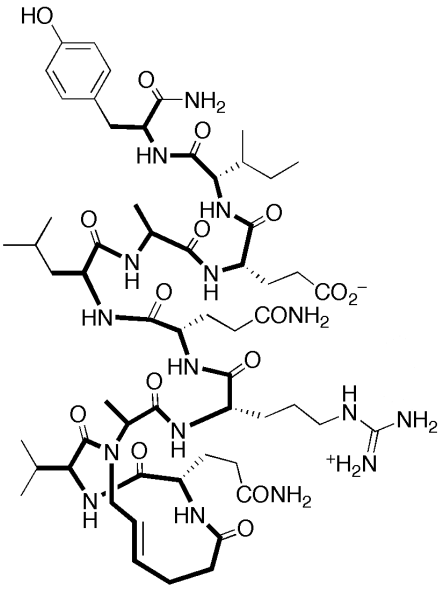
metathesis reactions.[2-8,29,30] The immediate implications of these low concentrations are twofold. First, metathesis reactions on proteins may require extended reaction times, which can place an increased emphasis on catalyst stability. However, this pressure on catalyst stability is moderated by the second implication of low protein concentrations, which is that water-soluble catalysts can be used in stoichiometric quantities for this application. More than that, the dilute concentrations of protein solutions even allow for the metathesis "catalyst" to be used in heavy excess for these transformations without committing exorbitant quantities of catalyst.

Stabilized peptide β-turn:



R. H. Grubbs[31]

Stabilized peptide α-helix:



P. S. Arora[38]

Figure 6.4. Olefin metathesis has been used to stabilize β-turn and α-helical secondary structures of short peptide chains.

Stabilizing protein secondary structure by olefin metathesis. Two general applications of catalysts **1** and **2** to modify protein structure will be presented. First, Chapter 1

discusses the use of olefin metathesis to stabilize two secondary structure motifs of short peptides, β-turns and α-helices (Figure 6.4).[31-38] The solubility of catalysts **1** and **2** in water allows for this application of metathesis in biology on olefin-dsplaying proteins as opposed to the model peptides used in the reported research. As these reactions can be considered examples of ring-closing metathesis, the demonstrated competency of catalysts **1** and **2** for this transformation in water makes this a particularly enticing application for the currently available catalysts.

Modifying proteins with probe molecules by olefin metathesis. Another potential application of catalysts **1** and **2** in protein modification is the use of olefin metathesis to regioselectively incorporate probes onto proteins (Figure 6.5). These probes may include chromophores for improved protein detection or molecules like biotin for simpler protein isolation.

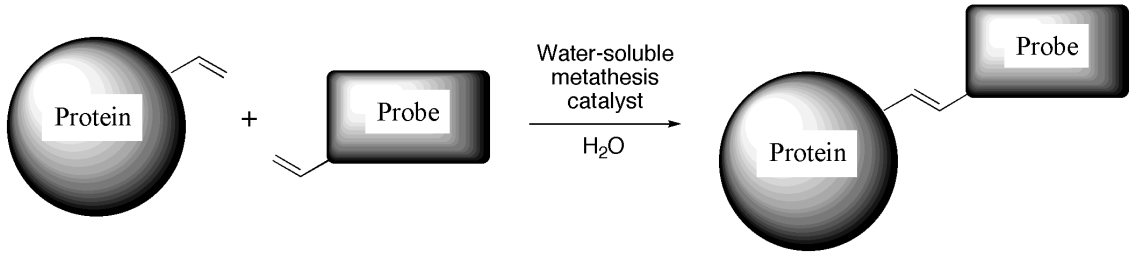


Figure 6.5. Olefin metathesis in water can potentially regioselectively modify proteins with probe molecules.

This application presents two challenges for aqueous metathesis. First, efficient modification reactions will likely require excess quantities of the probe molecule. Consequently, probe dimerization may decrease the efficiencies of the desired transformation by enabling catalyst decomposition pathways that are avoided by the stable, uninitiated isopropoxybenzylidene complex.[9] This hurdle can likely be overcome

by using probe molecules that contain olefins that participate in cross-metathesis reactions but do not homodimerize or homodimerize very slowly.[29]

The low protein concentrations commonly encountered in this area of research presents a second challenge for regioselectively incorporating probes onto proteins. The results presented in Chapter 5 reveal that isopropoxybenzylidene complexes **1** and **2** are quite stable in water. However, as already mentioned, the limited aqueous cross-metathesis activity of catalysts **1** and **2** indicates that the alkylidene complexes formed by the reaction between these catalysts with a terminal olefin are not stable in water. Successfully crossing probe molecules onto proteins requires the alkylidene complex produced by the reaction of the protein with the catalyst to persist for an extended period of time. The most direct solution to this obstacle is to develop a more stable aqueous metathesis catalyst. Even so, a different strategy may allow the use of already-developed water-soluble catalysts **1** and **2**.

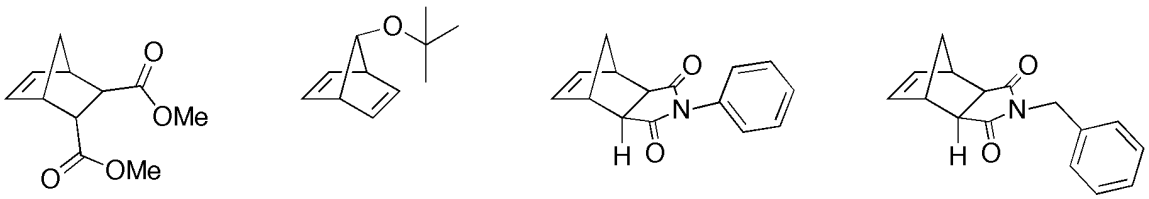
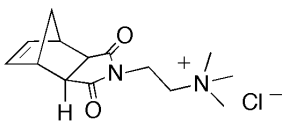


Figure 6.6. Monomers that Khosravi and co-workers have shown to chelate to ruthenium during their ROMP with catalyst **22**.[41,42]

Norbornene monomers containing esters have long been thought to coordinate to ruthenium catalysts during ROMP.[39-47] For example, Khosravi and co-workers have reported observing NMR evidence for chelating alkylidenes during the ROMP of various oxygen containing norbornene monomers (Figure 6.6).[41,42] Furthermore, Grubbs and co-workers observed that alkylidenes formed during the ROMP of *exo*-norbornene monomer

24 with catalysts **3** and **4** is stable for three months in the presence of monomer,[43] though both catalysts rapidly decompose in water in the absence of substrate.[44,45] Also, as described in Chapter 2, the alkylidene formed during the ROMP of *endo*-norbonene monomer **25** with catalyst **26** is stable for at least two days in water.[46,47] Such chelation events may serve to stabilize the alkylidene complexes formed during the modification of proteins with catalysts **1** and **2**.



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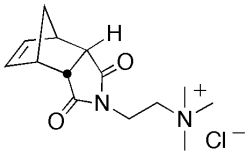

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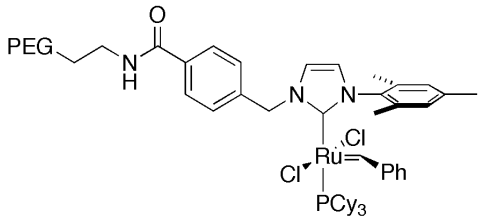


26

Results that support the described strategy of protein modification. A particularly attractive probe olefin that dimerizes slowly is an acrylamide.[29,48] Preliminary research has shown that these olefins do show activity for aqueous metathesis. NMR and mass-spectral analysis reveal that catalyst **1** can cross allyl alcohol onto acylamide in water, though not catalytically. Therefore, catalysts **1** and **2** should be able to cross acrylaminde-containing probe molecules onto proteins.

Also, further evidence supporting the hypothesis that norbornenes stabilize ruthenium alkylidenes has been obtained. During the ROMP of **27** with catalyst **22** a new alkylidene resonance is observed in the ^{1}H NMR spectrum while the ^{31}P NMR only contains resonances for free tricyclohexylphosphine and uninitiated catalyst **22**. The chemical shift of this alkylidene resonance, 17.25 ppm, is consistent with similar

complexes containing a chelating alkylidene such as complex **23** (Figure 6.7(A)).[13,49-51]

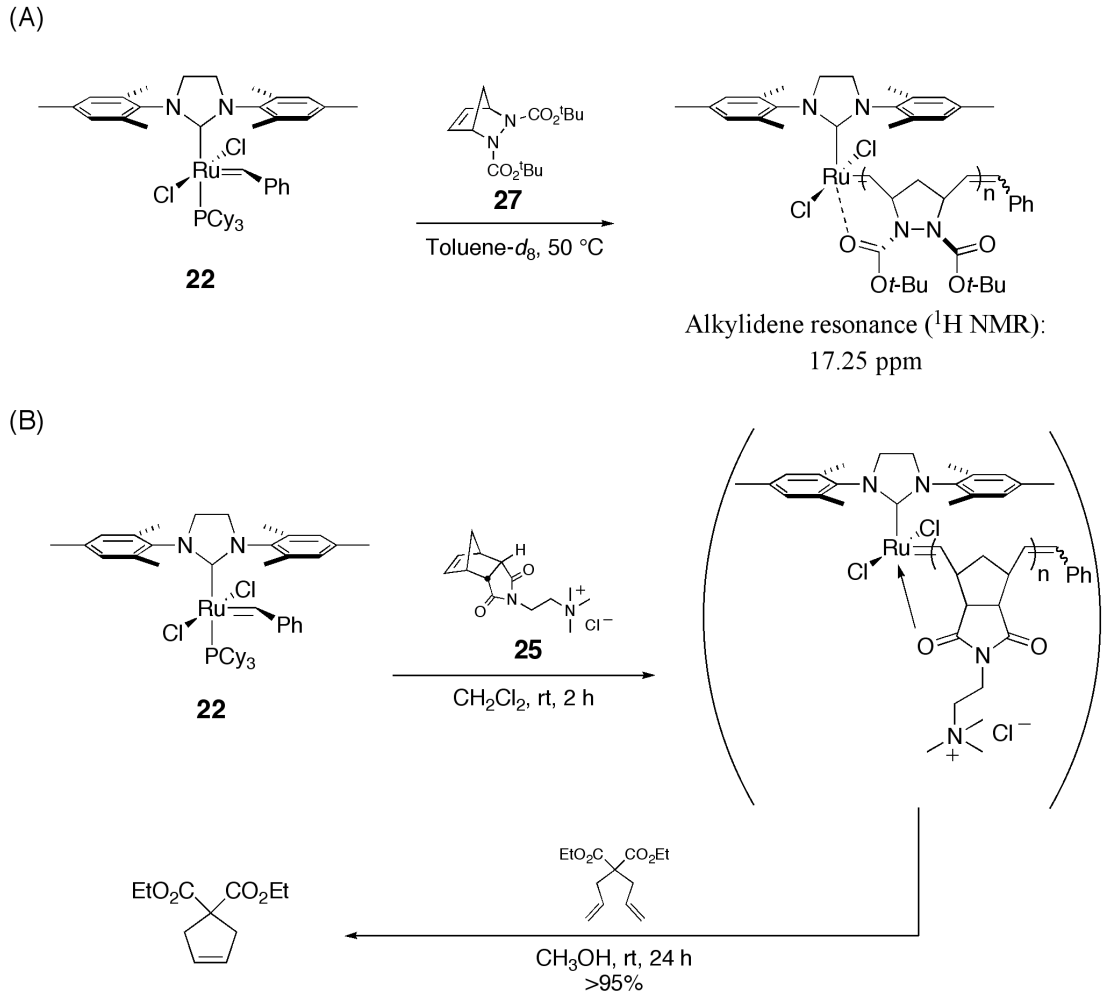


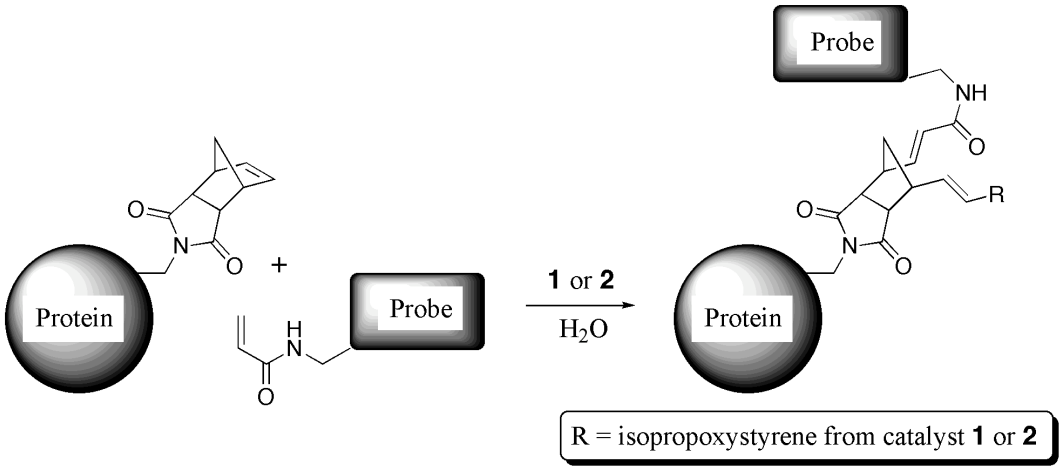
Figure 6.7. (A) NMR spectral analysis indicates that the propagating alylidene formed during the ROMP of monomer **27** with catalyst **22** is stabilized by chelation. (B) The reaction of catalyst **22** with monomer **25** produces an isolable mixture of complexes that ^{31}P NMR indicates is phosphine-free. This mixture of complexes is able to quantitatively ring-close diethyl diallylmalonate in methanol within 24 hours at room temperature.

Additionally, the reaction of catalyst **22** with monomer **25** in dichloromethane produces a stable mixture of complexes that can be isolated (Figure 6.7(B)). Interestingly, while the ^{1}H NMR spectrum of this product mixture contains four alkylidene resonances, the ^{31}P NMR spectrum indicates the absence of any species containing phosphorus. Therefore,

the produced complexes are phosphine-free and are likely stabilized by a chelating oxygen (Figure 6.7(B)). These complexes are soluble in methanol and water and are capable of quantitatively ring-closing diethyl diallylmalonate in methanol within 24 hours at room temperature. As a whole, this evidence suggests that norbornenes containing coordinating oxygens may sufficiently stabilize alkylidene complexes formed with catalyst **1** or **2** to allow for their application to the modification of proteins.

Proposed method for using catalysts 1 and 2 to incorporate probe molecules onto proteins. The complete strategy for regioselectively incorporating probe molecules onto proteins is presented in Scheme 6.2. A water-soluble olefin metathesis catalyst such as complex **1** or **2** could be used to cross an acrylamide-containing probe molecule onto a protein displaying a norbornene, which contains coordinating oxygens.[52] The choice of protein and probe molecules can be varied as desired. However, bovine serum albumin (BSA) provides a readily available platform to examine the viability of this strategy.

Scheme 6.2.



Bovine serum albumin is a heavily researched protein present in cow blood, which is available in large quantities from commercial sources.[53,54] BSA contains a single cysteine that does not participate in a disulfide bridge.[53,54] This thiol group can be used

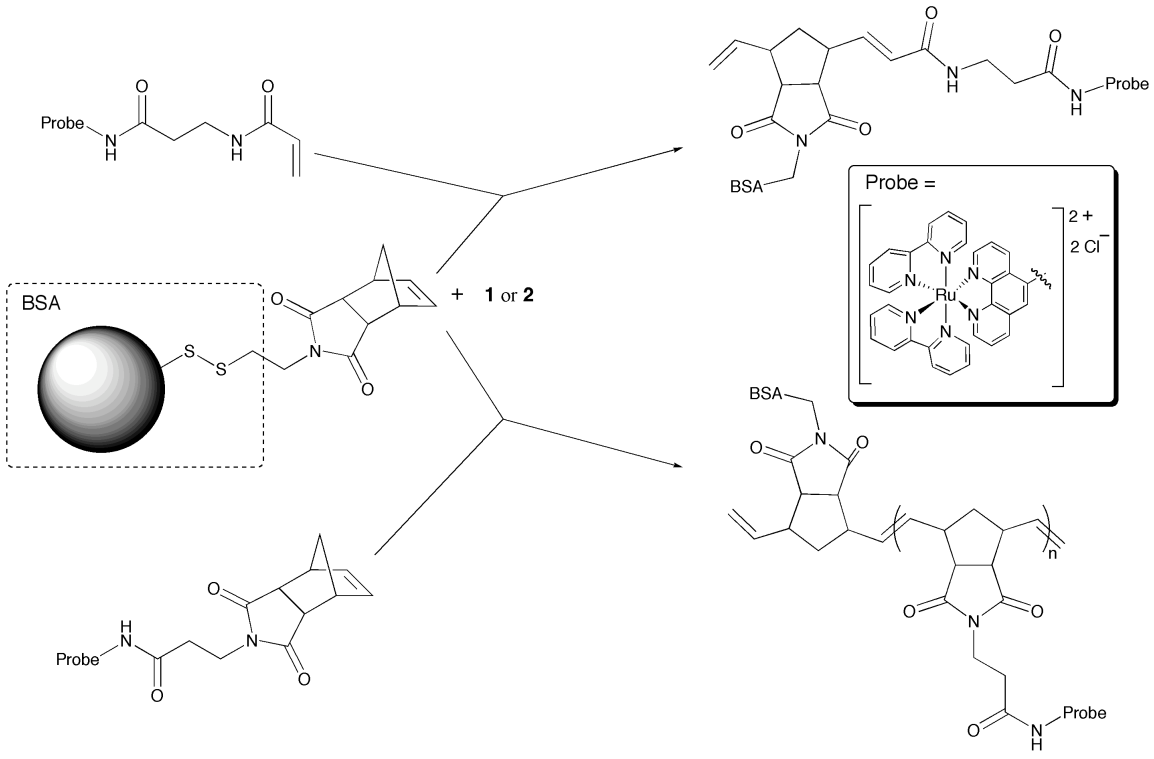


Figure 6.8. Crossing ruthenium dyes onto the protein BSA is proposed as a system for proof-of-concept research on the described strategy for employing water-soluble catalysts **1** and **2** to the regioselective modification of proteins.

to decorate BSA with various molecules by the formation of a disulfide bond. For example, Maynard and co-workers have recently used this thiol to incorporate atom transfer radical polymerization initiators onto BSA, which they employed to grow polymers from this protein.[55] The same methodology could be utilized to include the desired norbornene molecule onto BSA (Figure 6.8). Water-soluble catalysts **1** and **2** may then mediate metathesis reactions between this protein with an acrylamide-displaying

probe molecule. Acrylamide-displaying analogs of the ruthenium dyes used by Kuo and Grubbs in aqueous cross metathesis can readily serve as probe molecules for these experiments (Figure 6.8).[56] Alternatively, norbornenes can also be covalently attached to these ruthenium dyes. The propagating alkylidene produced during the ROMP of this probe norbornene can react with the norbornene-containing BSA to incorporate multiple probe molecules onto a single protein. If these proof-of-concept experiments succeed, methods for site-specifically incorporating unnatural amino acids displaying a "coordinating norbornene" need to be developed for this strategy to have practical utility for protein modification.

Summary

The development of catalysts **1** and **2** represent significant progress in the ability to perform homogenous metathesis in water. However, their limited ability to mediate aqueous cross metathesis presents an opportunity for future catalyst development. Reducing the steric bulk around the ruthenium center may produce catalysts with increased reactivity in water. Alternatively, 2-pyridylphenol ligands may be used to improve the stability of catalysts in water.

Despite their limited activity in aqueous cross metathesis, catalysts **1** and **2** might be used to modify the structure of proteins. Aqueous ring-closing reactions on proteins containing unnatural amino acids, which present carbon-carbon double bonds, may be used to stabilize such protein structural motifs as β-turns and α-helices. Also, appropriately modifying protein and probe molecules with well-chosen olefins may allow catalysts **1** and **2** to incorporate the probe molecule onto the protein, and BSA provides an excellent platform to examine this strategy of protein modification.

In conclusion, catalysts **1** and **2** provide a glimpse of the potential for olefin metathesis in water, which is a field rich in possibility. Catalysts capable of competently mediating the full range of metathesis transformations in water appear to be an attainable goal. Once developed, a variety of applications exist for such catalysts, particularly in biology. Therefore, olefin metathesis in water will surely be the subject of future research.

Acknowledgements

The author wishes to thank Professor Brian Connell for his generous donation of 2-pyridylphenol **20** and helpful discussions. Professor Louis Kuo is also acknowledged for his helpful discussions regarding biological research. Dr. Mona Shahgholi is thanked for mass spectroscopic analysis. This research was financially supported by a grant from the National Institute of Health (5R01GM068647).

Experimental

General considerations. All glove-box manipulations were performed in a N_2-filled Vacuum Atmospheres glove box (O_2 < 2.5 ppm). Otherwise reactions run under dry, degassed conditions were performed using standard Schlenk techniques under an atmosphere of dry argon using flame or oven-dried glassware. NMR spectral analysis of the products for the cross-metathesis reaction between acrylamide and allyl alcohol and the ROMP of **27** with catalyst **22** was performed on an Inova 500 (499.85 MHz for ^{1}H; 202.34 MHz for ^{31}P; 125.69 MHz for ^{13}C). All other NMR spectra were recorded on a Varian Mercury 300 (299.817 MHz for ^{1}H, 75.4 MHz for ^{13}C, and 121 MHz for ^{31}P) and reported in parts per millon (ppm) downfield from trimethylsilane as referenced to

residual protio solvent peaks. Multiplicity abbreviations used when reporting ^{1}H NMR spectra are: s = singlet, and br = broad.

Materials. All deuterated solvents were purchased from Cambridge Isotope Laboratories. Deuterated dichloromethane and deuterated toluene were dried over 4 Å molecular sieves, and deuterated methanol was dried over calcium sulfate. Deuterated methanol and deuterated dichloromethane were degassed by three freeze, pump, and thaw cycles while deuterium oxide and deuterated toluene were degassed by a generous argon sparge. Anhydrous methanol was purchased from Aldrich and degassed with a generous argon sparge. All other solvents were purchased from Fischer Scientific. Solvents were dried by passage through purification columns packed with alumina and degassed by a generous argon sparge. All commericial materials were used as obtained. The synthesis of ruthenium complexes **1** and **2** and isopropoxystyrene **9** were described in Chapter 5. Ruthenium complex **22** was a gift from Materia Inc. The syntheses of *endo*-norbornene monomer **25** and ruthenium complex **26** were described in Chapter 2. Sodium methoxide, neutral Brockman grade I alumina, acrylamide, and allyl alcohol were purchased from Aldrich. Silver nitrate was purchased from Strem. Diethyl diallylmalonate was purchased from Avocado. 2-Pyridylphenol **20** was the gift of Prof. Brian Connell. Monomer **27**,[57] and ruthenium bis(pyridine) complex **21**[24] were synthesized according to literature procedures.

Ruthenium complex 19. A flame-dried round-bottom flask, containing compound **20** (304.2 mg, 1.4 mmol), was brought into a N_2-filled glove box, charged with sodium

methoxide (79.1 mg, 1.5 mmol, 1.1 equiv), equipped with a stir bar and sealed with a septum. This flask was removed from the glove box, brought under a positive argon pressure and cooled to 0 °C. Dry, degassed methanol (5 mL) was slowly added by syringe, and the reaction mixture was stirred at 0 °C for 10 minutes, warmed to room temperature, and stirred for an additional 2.5 hours. Upon reaction completion, the volatiles were removed by rotary evaporation. The brown solid product was dissolved in water (3 mL), and silver nitrate (505.9 mg, 3.0 mmol, 2.1 equiv) was added. This reaction mixture was stirred for 10 minutes. The silver salt, which precipitates during the reaction, is isolated by vacuum filtration and generously rinsed with water, benzene, and diethyl ether in that order. The product was dried under high vacuum to obtain 389.4 mg (86%) of the silver salt as a brown solid. (Note: this salt is light sensitive.) In a N_2-filled glove box, the silver salt of 2-pyridylphenol **20** (10.2 mg, 0.032 mmol) and ruthenium bis(pyridine) complex **21** (23.4 mg, 0.032 mmol, 1.0 equiv) were weighed into a 1-dram vial. This vial was equipped with a stir bar, charged with dry, degassed deuterated dichloromethane (0.77 mL) and sealed with a septa-cap. The reaction mixture was stirred for 6 hours before removing the vial from the glove box. The product mixture was passed through a short column of neutral alumina with dichloromethane, rinsed with *n*-pentane, and dried under high vacuum to obtain 8.2 mg (36%) of complex **19** as a dark-red solid. ^{1}H NMR (CD_2Cl_2, ppm, benzylidene resonance): δ 17.95 (s).

Ring closing diethyl diallylmalonate with catalyst 19. Catalyst **19** (8.2 mg, 0.011 mmol, 0.052 equiv) was dissolved in reagent grade deuterated dichloromethane (0.7 mL) and transferred to an NMR tube. Diethyl diallylmalonate (50 μL, 0.21 mmol) was

injected by syringe, and the reaction mixture was heated to 45 °C. The reaction conversion was followed by ^{1}H NMR spectroscopy.

Stoichiometric cross metathesis of allyl alcohol and acrylamide in water with catalyst 1. In a N_2-filled glove box, a 1-dram vial was charged with catalyst **1** (5.6 mg, 0.0066 mmol, 1.1 equiv), equipped with a stir bar and sealed with a septa-cap. The vial was removed from the glove box and brought under a positive argon pressure. An aliquot (0.15 mL) of a solution of allyl alcohol (10 mL) and acrylamide (16.3 mg) in degassed deuterium oxide (2.9 mL) was added to this vial by syringe. (Actual reaction contained 0.0063 mmol of allyl alcohol and 0.012 mmol (1.9 equiv) of acrylamide.) The reaction was stirred at 30 °C for 16 hours under a positive argon pressure, and the product mixture was examined by ^{1}H NMR and mass spectral analysis. The cross-product was estimated to form in 36% conversion from the ^{1}H NMR spectrum.

ROMP of monomer 27 with catalyst 22. In a N_2-filled glove box, a screw-cap NMR tube was sealed with septa-cap, and monomer **27** was weighed into a round-bottom flask, which was then sealed with a septum. This flask and the NMR tube were brought out of the glove box, and a positive argon pressure was applied to the monomer-containing flask. Dry, degassed deuterated toluene was transferred to the monomer-containing flask using standard Schlenk techniques to produce a 0.6 M monomer solution. An aliquot (0.6 mL) of this solution was thermostated at 55 ºC for 10 minutes in the NMR spectrometer prior to the addition of an aliquot (0.10 mL) of a solution of catalyst **22** (25 mg) in dry, degassed deuterated toluene (0.25 mL). The reaction mixture was mixed by three tube

inversion and reinserted into the NMR spectrometer. The reaction progress was followed by ^{1}H NMR spectroscopy.

Complex mixture formed by the ROMP monomer 25 with catalyst 22. In a N_2-filled glove box, ruthenium complex **22** (29.6 mg, 0.035 mmol) and monomer **25** (50.2 mg, 0.18 mmol, 5.1 equiv) were weighed into a 1-dram vial. The vial was equipped with a stir bar and charged with dry, degassed dichloromethane (2 mL). The reaction mixture was allowed to stir for 2 hours before removing the vial from the glove box and isolating the product by centrifuge. Drying under high vacuum provides 54.7 mg of a brown, solid product. ^{1}H NMR (CD_3OD, ppm, benzylidene resonances): δ 18.86 (br, relative integral 1.00), 18.09 (br, relative integral 1.03), 18.02 (br, relative integral 0.39), 17.93 (br, relative integral 2.03). Mixing this solid (15 mg) with diethyl diallylmalonate (50 μL, 0.21 mmol) in dry, degassed methanol (0.6 mL) yields 95% conversion of the ring-closed product after 24 hours at room temperature.

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(23) This 2-pyridylphenol was the generous gift of Professor Brian Connell.

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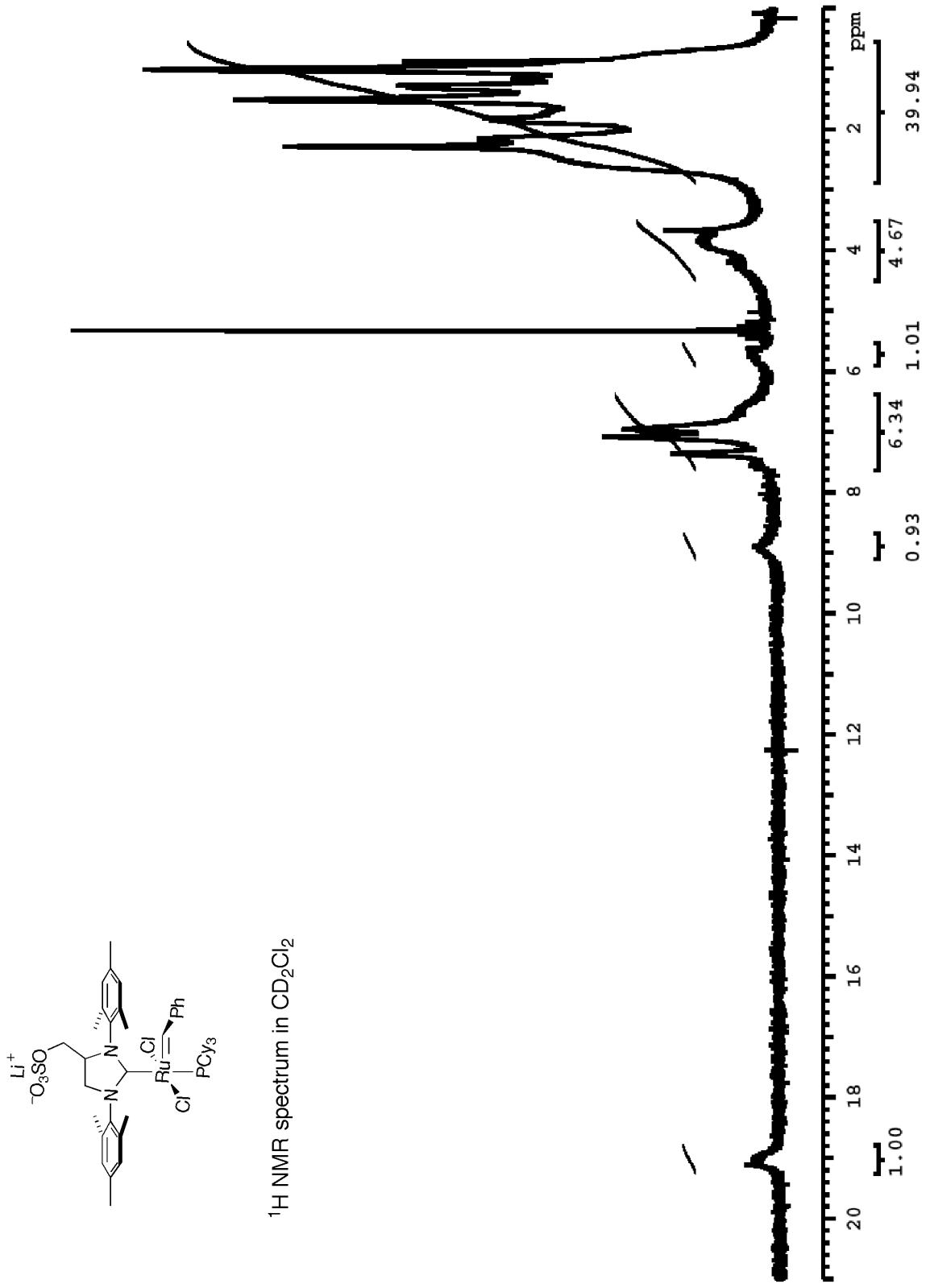
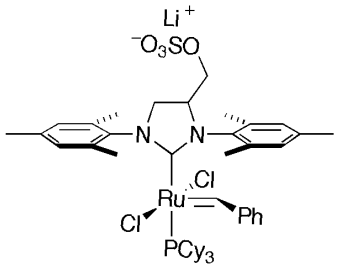
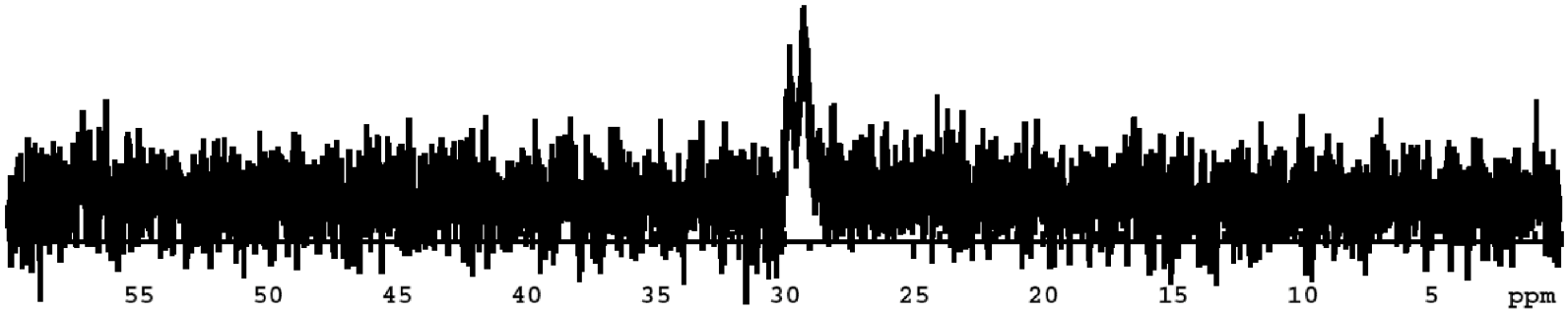
APPENDIX 1

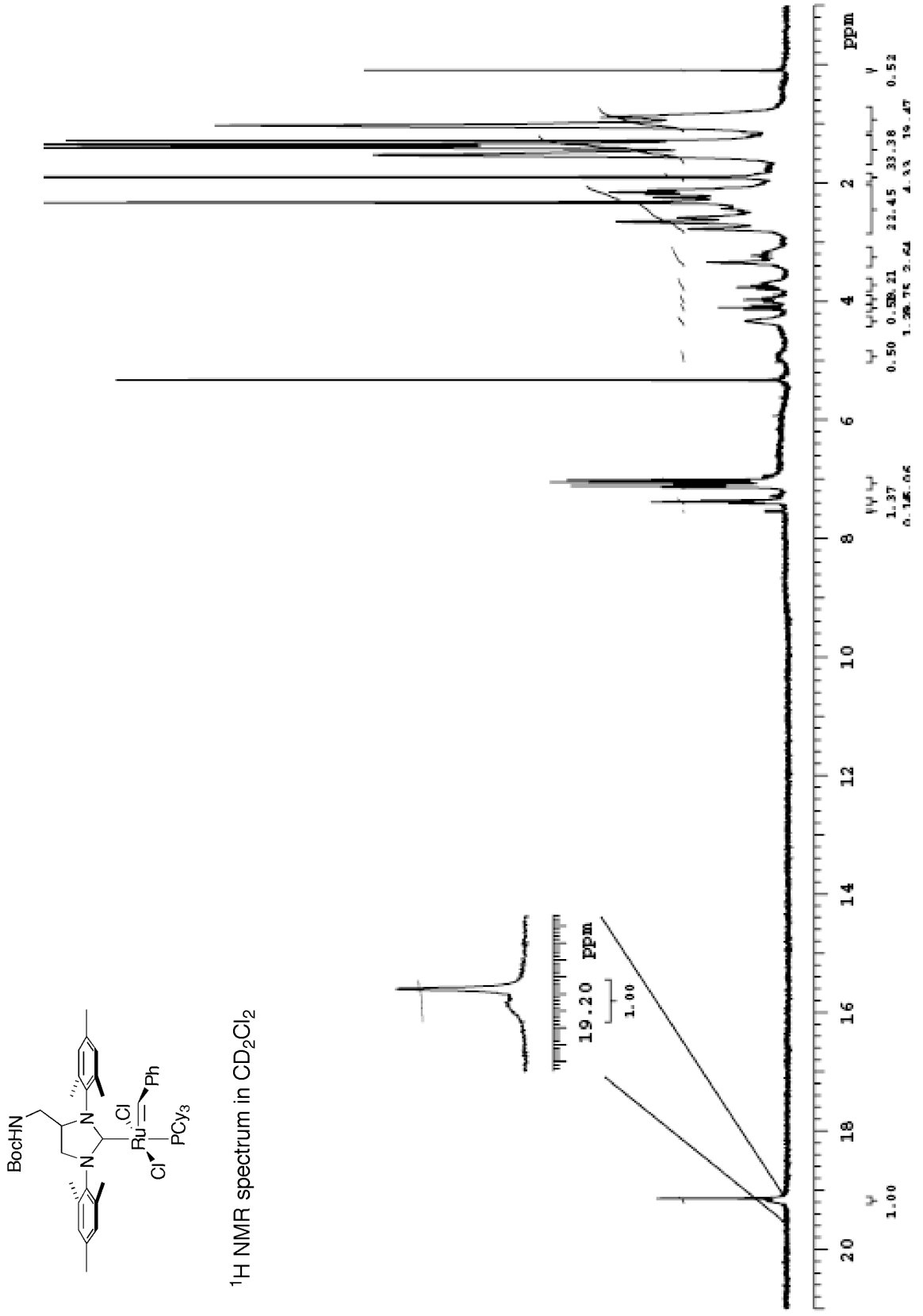
NMR Spectra for Selected Ruthenium Complexes


Li+
−O3SO
N
N
Ru
Cl
Cl
Ph
PCy3
1H NMR spectrum in CD2Cl2
ppm
1.00
0.93
6.34
1.01
4.67
39.94

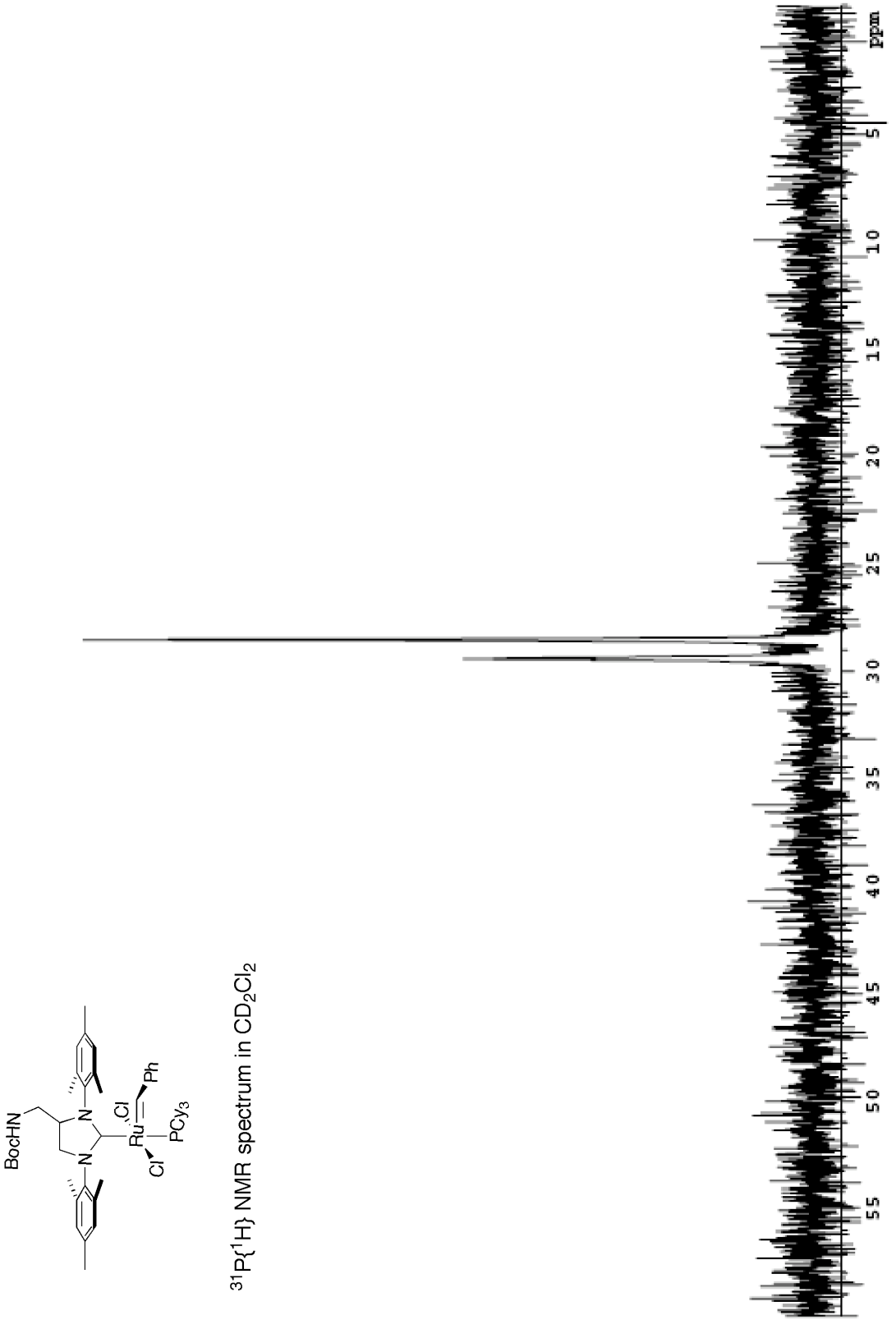


$^{31}P\{^{1}H\}$ NMR spectrum in CD_2Cl_2

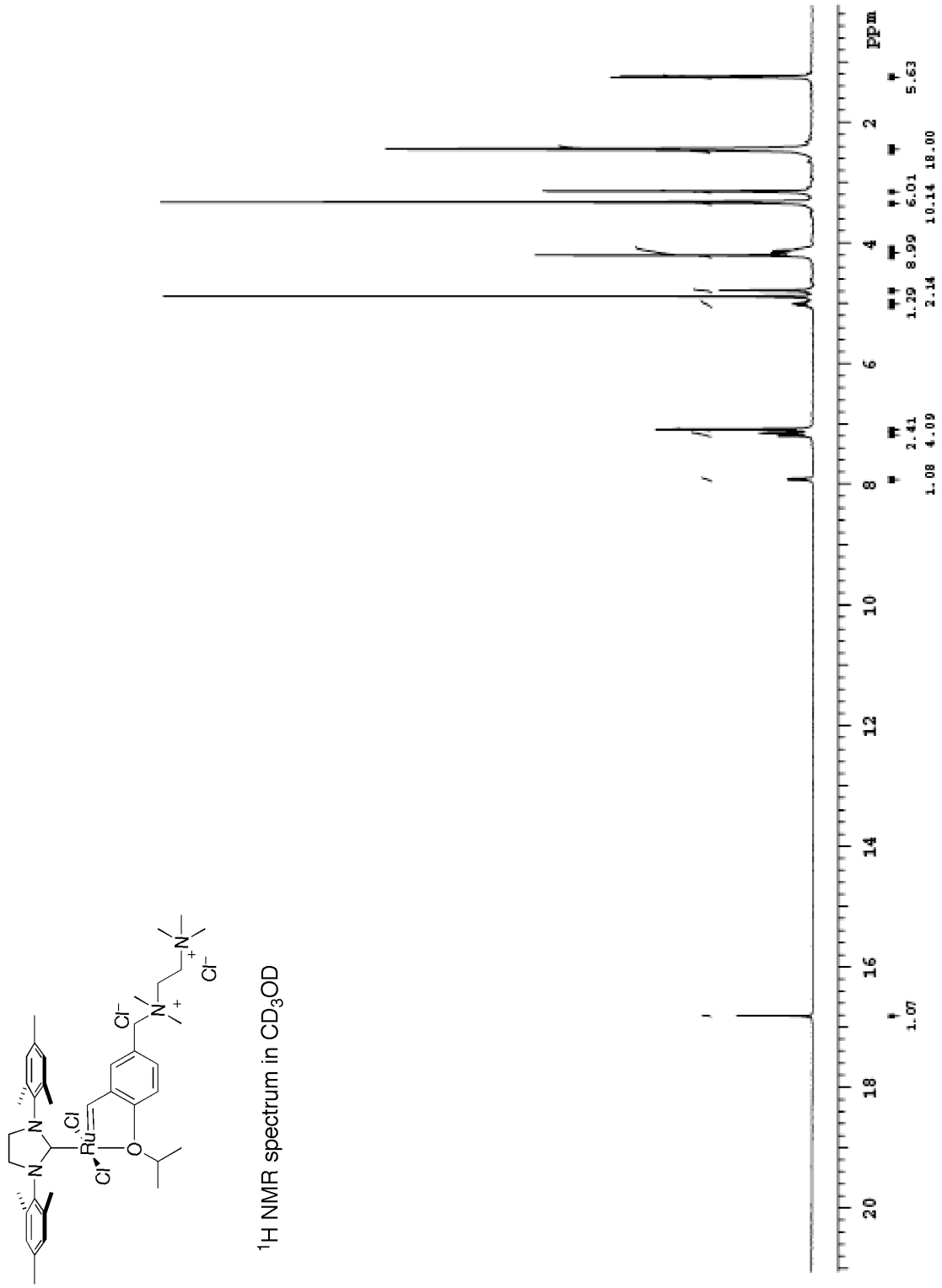




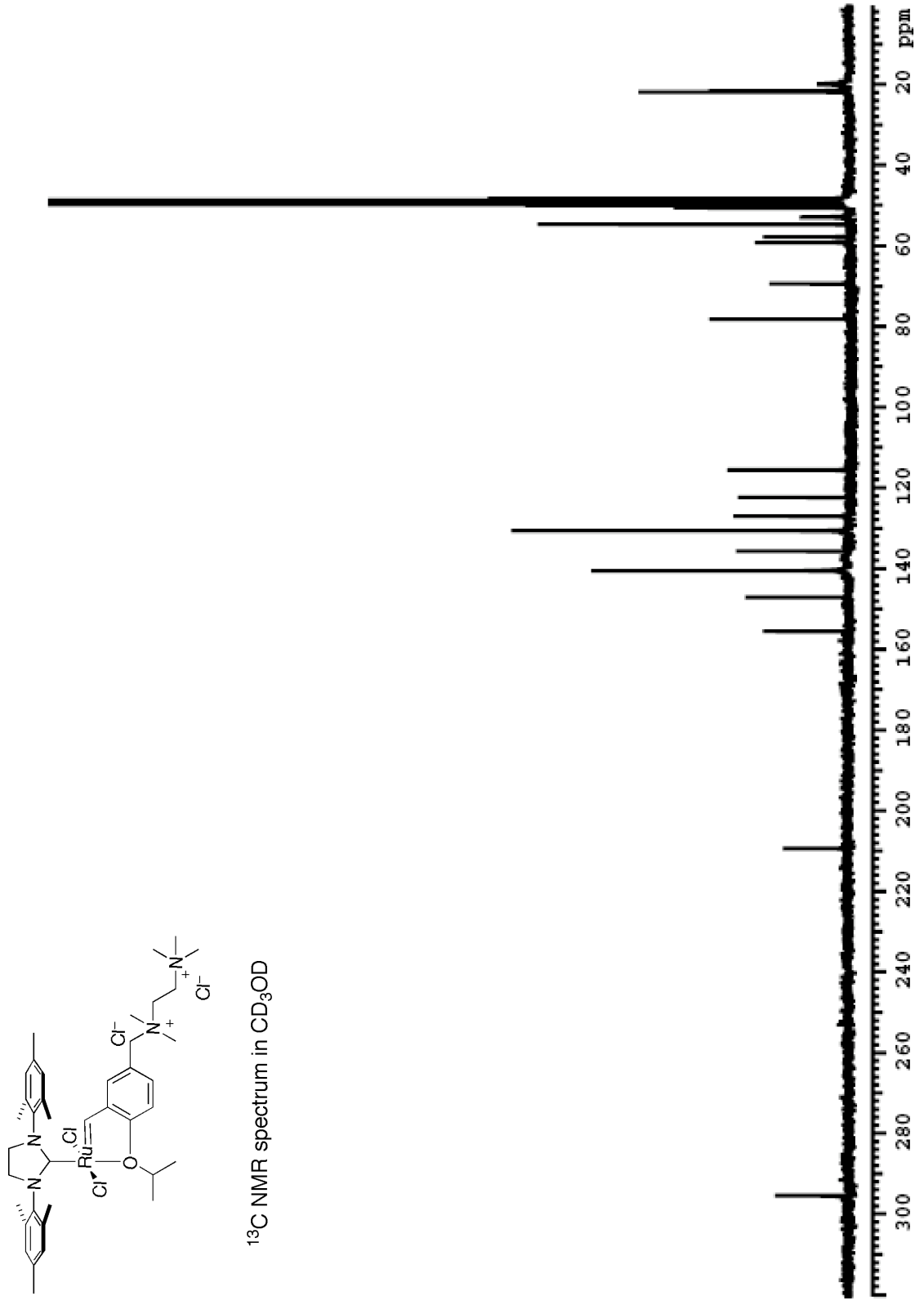
^{1}H NMR spectrum in CD_2Cl_2



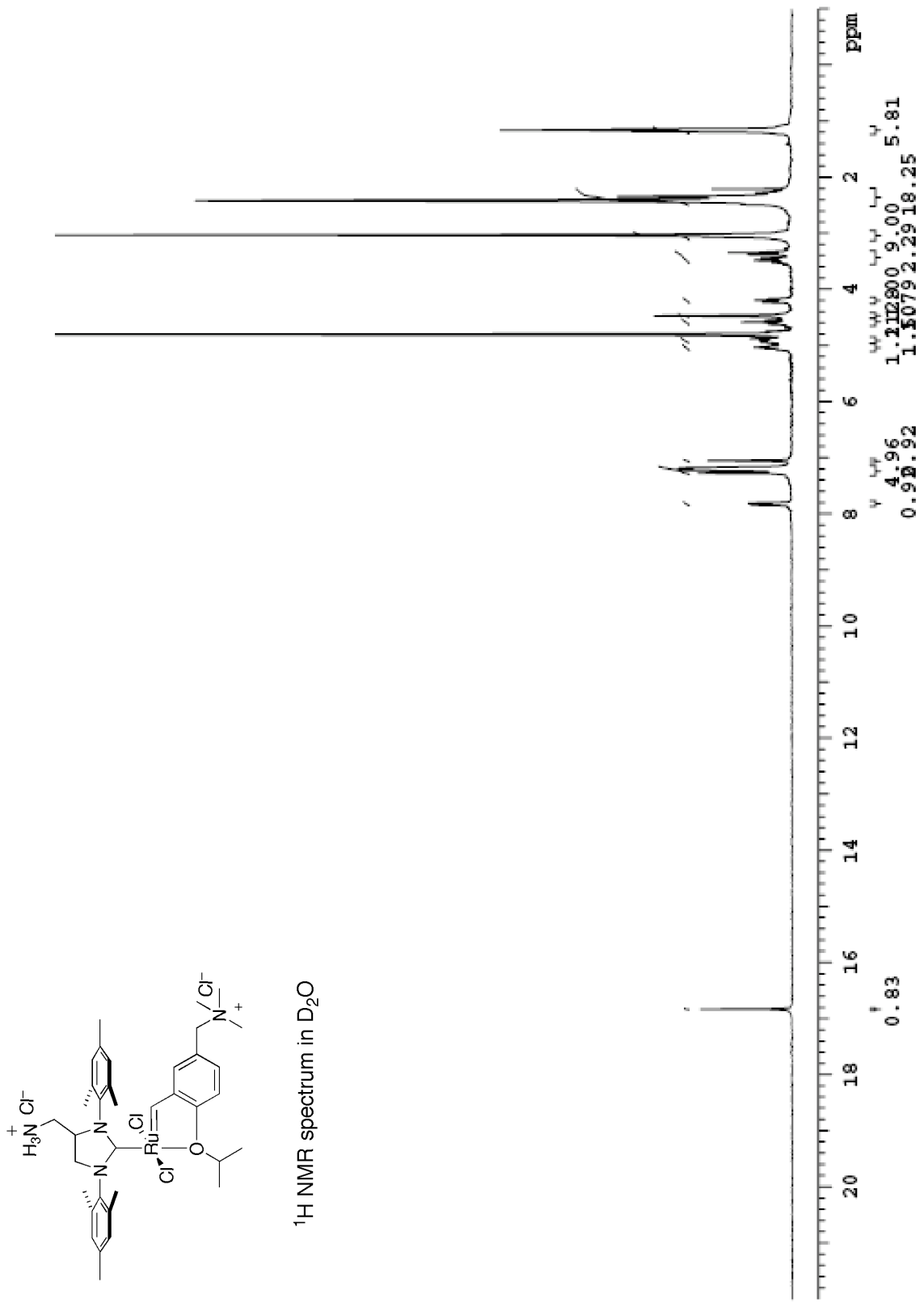
$^{31}P\{^{1}H\}$ NMR spectrum in CD_2Cl_2



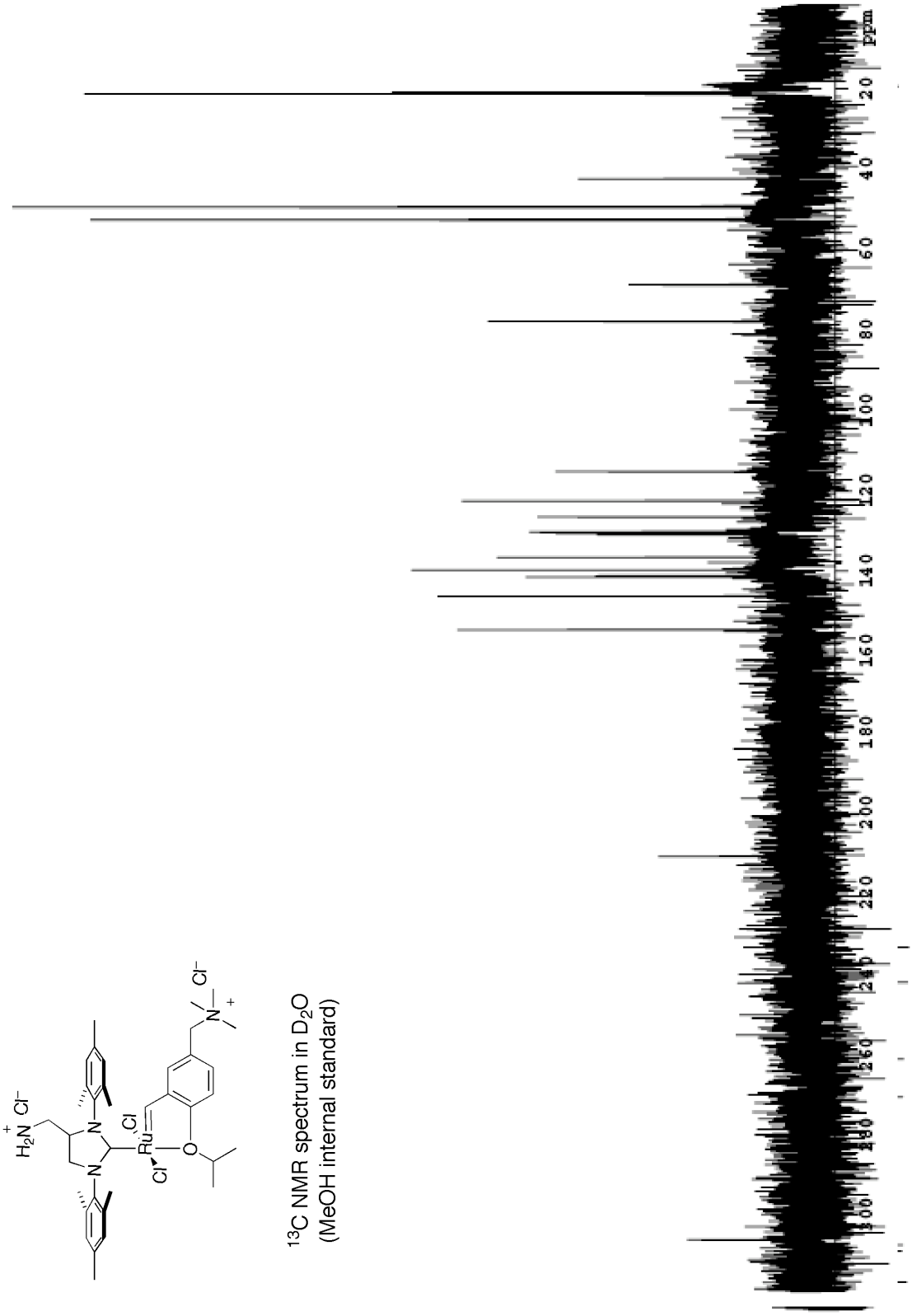
^{1}H NMR spectrum in CD_3OD



^{13}C NMR spectrum in CD_3OD



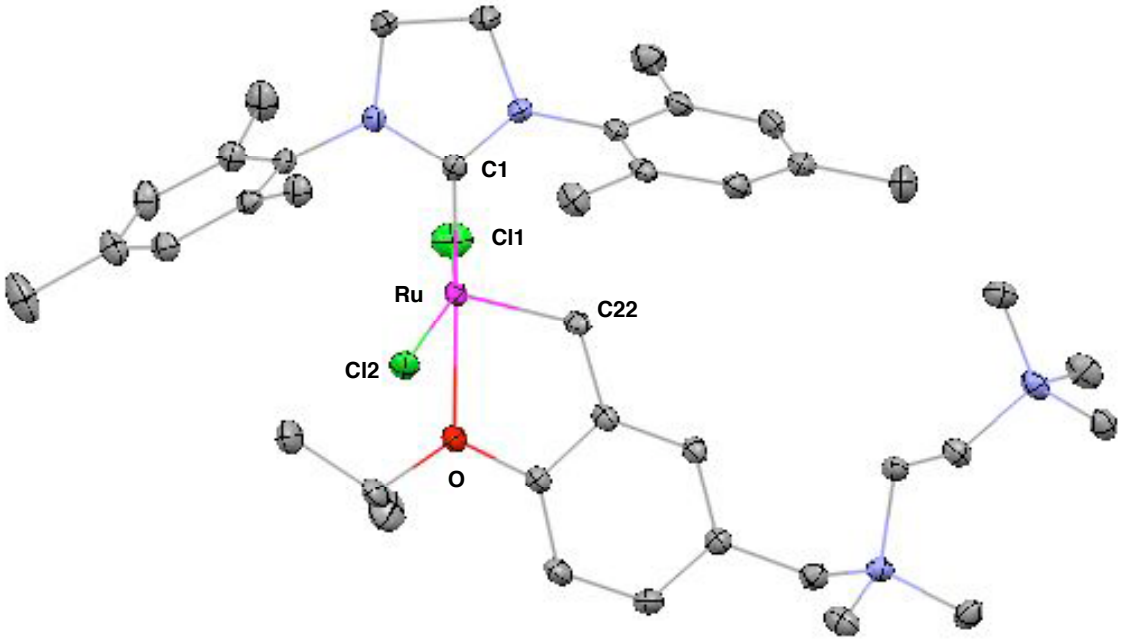
^{1}H NMR spectrum in D_2O



^{13}C NMR spectrum in D_2O
(MeOH internal standard)

APPENDIX 2

Crystal Structure Data for Chapter 5



Selected bond lengths [Å] and angles [°] for JPJ02 (CCDC 623282)

Ru(1)-C(22)	1.8266(16)	C(22)-Ru(1)-C(1)	101.68(7)
Ru(1)-C(1)	1.9683(17)	C(22)-Ru(1)-O(1)	79.64(6)
Ru(1)-O(1)	2.2601(12)	C(1)-Ru(1)-O(1)	178.65(5)
Ru(1)-Cl(2)	2.3378(4)	C(22)-Ru(1)-Cl(2)	97.14(5)
Ru(1)-Cl(1)	2.3459(5)	C(1)-Ru(1)-Cl(2)	96.62(5)
		O(1)-Ru(1)-Cl(2)	82.94(3)
		C(22)-Ru(1)-Cl(1)	101.01(5)
		C(1)-Ru(1)-Cl(1)	91.65(5)
		O(1)-Ru(1)-Cl(1)	88.32(3)
		Cl(2)-Ru(1)-Cl(1)	158.086(18)

Crystal Data and Structure Refinement for JPJ02 (CCDC 623282)

Empirical Formula	$[C_{39}H_{62}N_4OCl_2Ru]^{+2}\ 2Cl^{-} \bullet 2(CH_4O) \bullet 0.14O$
Formula Weight	908.06
Crystallization Solvent	Methanol/diethylether
Crystal Habit	Blade
Crystal Size	0.41 x 0.22 x 0.14 mm^3
Crystal Color	Green

Data Collection

Type of diffractometer	Bruker SMART 1000
Wavelength	0.71073 Å MoKα
Data Collection Temperature	100(2) K
θ range for 25368 reflections used in lattice determination	2.24 to 37.53°
Unit cell dimensions	a = 27.8035(9) Å b = 12.0719(4) Å β = 104.1250(10)° c = 14.2362(4) Å
Volume	4633.8(3) $Å^3$
Z	4
Crystal system	Monoclinic
Space group	P2/c
Density (calculated)	1.302 Mg/m^3
F(000)	1908.4
θ range for data collection	1.69° to 38.47°
Completeness to θ = 38.47°	87.9%
Index ranges	$-47 \le h \le 48, -17 \le k \le 19, -24 \le l \le 24$
Data collection scan type	ω scans at 5 ϕ settings
Reflections collected	83777
Independent reflections	22903 [R_{int}= 0.0907]
Absorption coefficient	0.608 mm^{-1}
Absorption correction	None
Max. and min. transmission	0.9197 and 0.7885

Structure Solution and Refinement

Structure solution program	Bruker XS v6.12
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Geometric positions
Structure refinement program	Bruker XL v6.12
Refinement method	Full matrix least-squares on F^2
Data/restraints/parameters	22903/0/501
Treatment of hydrogen atoms	Riding
Goodness-of-fit on F^2	1.219
Final R indices [I>2σ(I), 14094 reflections]	R1 = 0.0476, *w*R2 = 0.0816
R indices (all data)	R1 = 0.0914, *w*R2 = 0.0871
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.004
Average shift/error	0.000
Largest diff. peak and hole	1.995 and -1.110 e.Å^{-3}

Special Refinement Details

The Ru complex co-crystallizes with two molecules of methanol. The difference electron density Fourier contains a large peak on the 2-fold axis with no other nearby peaks. This peak was incorporated in the model as a site partially occupied by the oxygen of a water molecule. Least-squares refinement suggests 0.14 H_2O at this site forming a hydrogen bond to Cl4 at a distance of 3.1 Å.

Refinement of F^2 against ALL reflections. The weighted R-factor (*w*R) and goodness of fit (S) are based on F^2, conventional R-factors (R) are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.