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.

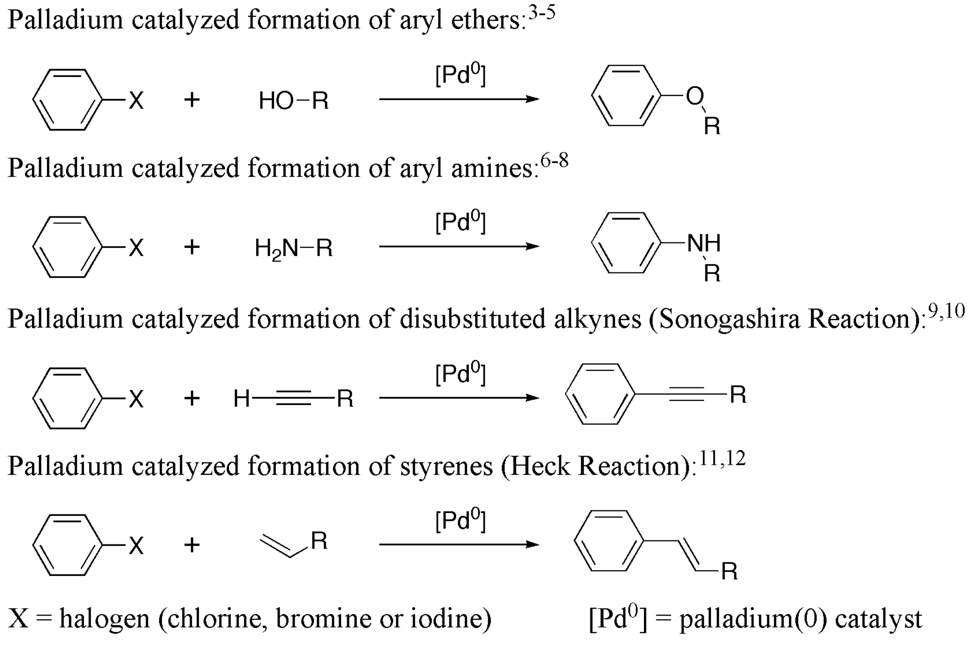


Figure 1.1. Palladium catalyzes the coupling of aryl halides with a variety of different partners. Just a few examples of the many palladium-mediated coupling reactions are shown.

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.

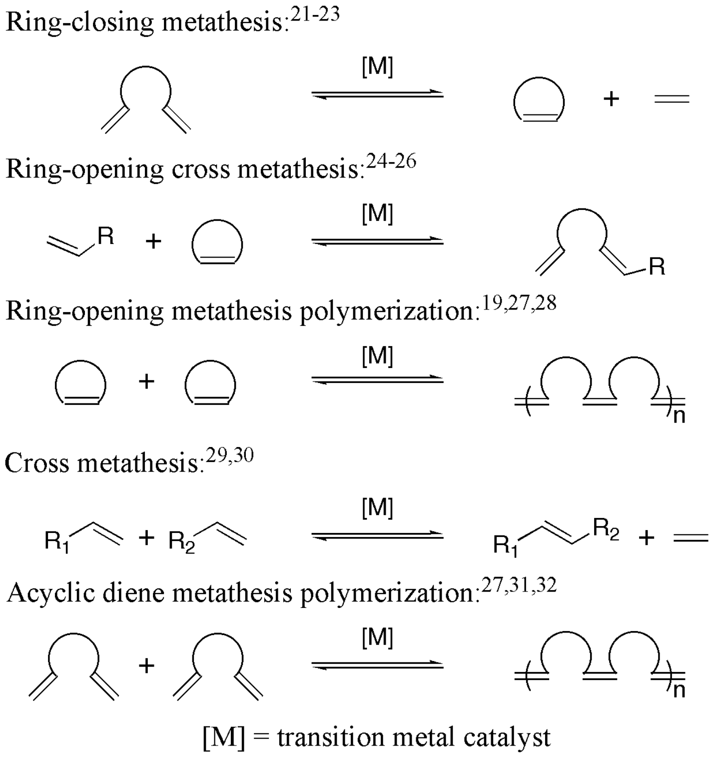
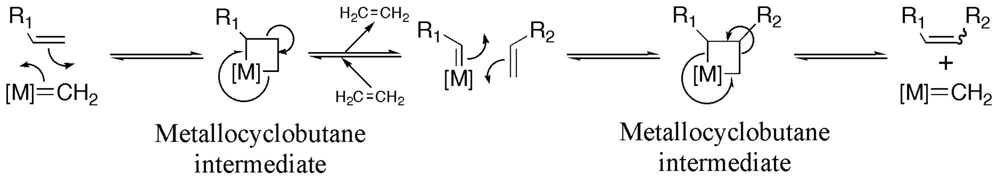


Figure 1.2. In olefin metathesis, a transition metal mediates the exchange of two olefins' substituents. This process enables the shown reactions.

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.



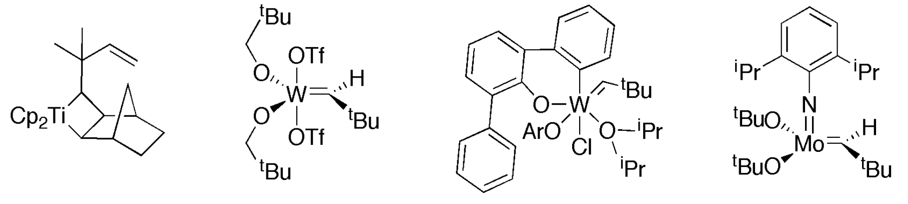
[M] = transition metal complex

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]

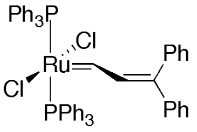


R. H. Grubbs[35] J. A. Osborn[36] J.-M. Basset[39] R. R. Schrock[40]

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]



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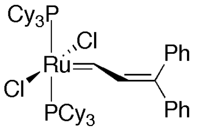

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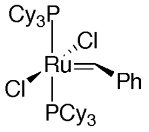

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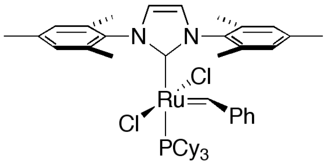
Table 1.1 illustrates the functional-group tolerance of a metathesis catalyst as a function of the identity of the catalyst's transition-metal center.[43] As reflected in this table, ruthenium catalyst **3** tolerates a greater range of organic functionality than its early-metal counterparts. This tolerance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

↑ Increasing Reactivity

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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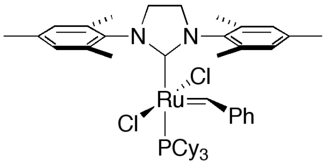

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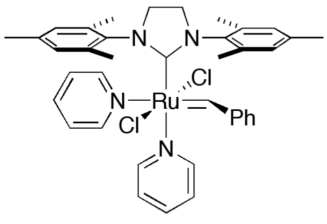

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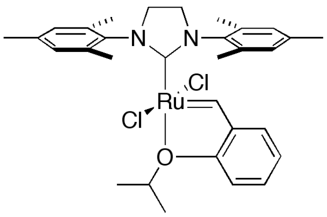

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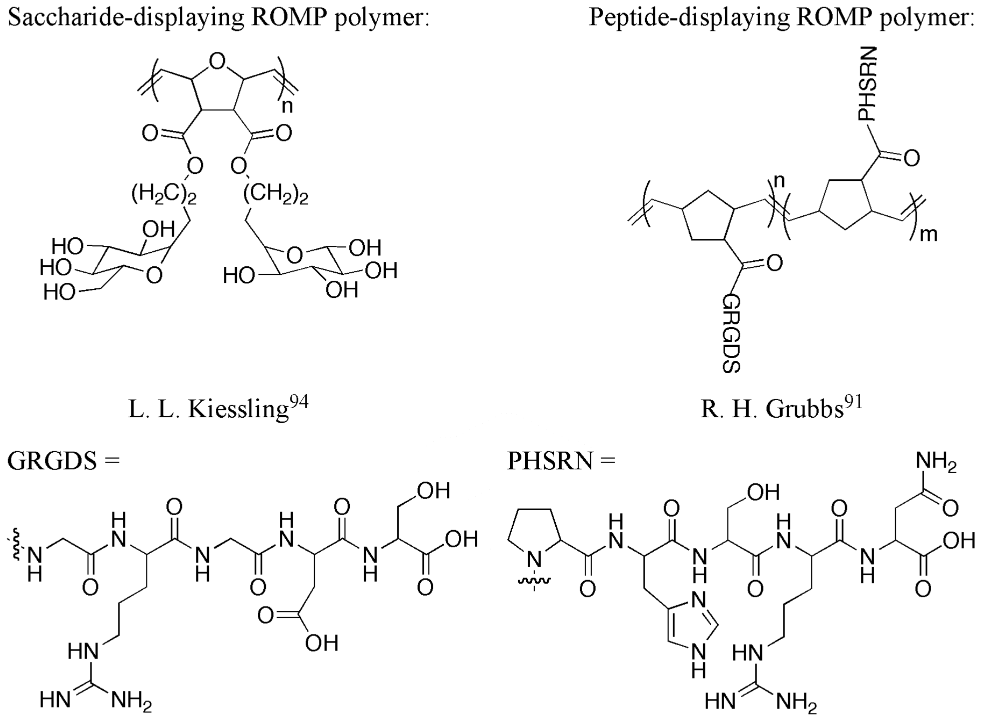
Due to its success, the effects of altering the ligand sphere of catalyst **5** have been widely researched.[65-86] A variety of NHC ligands have been examined.[64-76] These ligands include enantiopure, chiral NHC ligands for the production of stereoselective ruthenium metathesis catalysts.[65-68] Moreoever, 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]



Saccharide-displaying ROMP polymer:

Peptide-displaying ROMP polymer:

L. L. Kiessling[94]

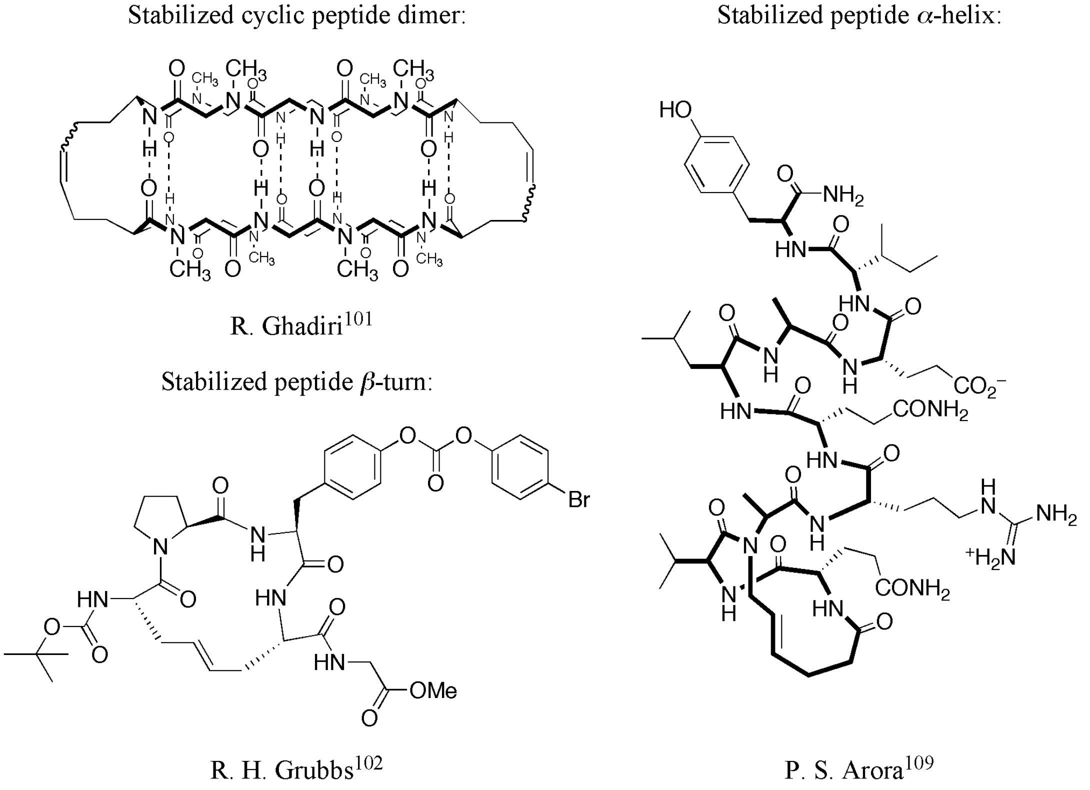
R. H. Grubbs[91]

GRGDS =

PHSRN =

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:

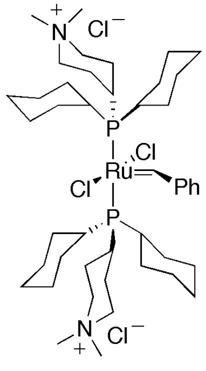
P. S. Arora[109]

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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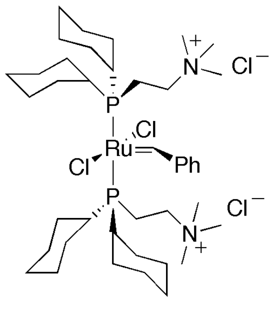
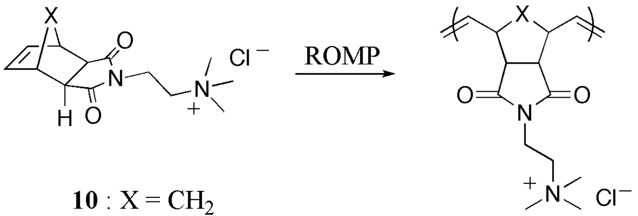


9

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]

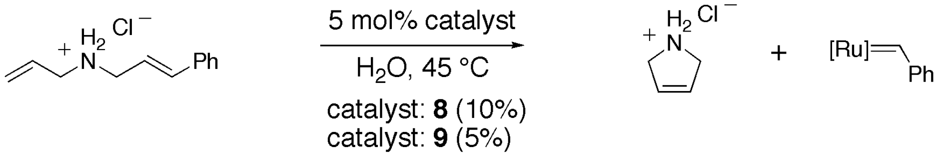


10 : X = CH_2
11 : X = O

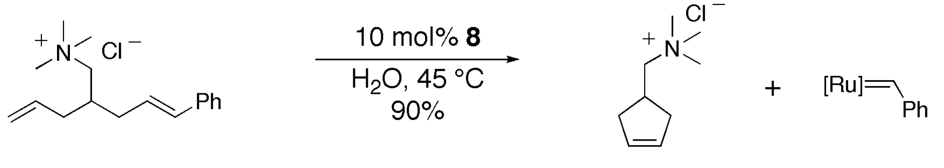
Figure 1.6. Catalysts **8** and **9** can mediate the ROMP of monomers **10** and **11** in a living manner.

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]

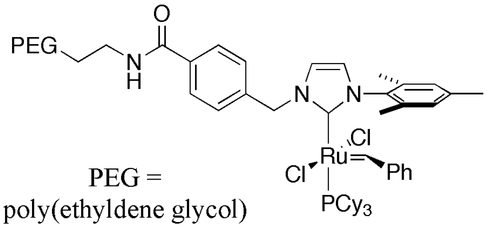
Analysis of catalysts **8** and **9** in deuterium oxide and methanol-d_4 reveal a novel reactivity of the alkylidene protons of the two catalysts in polar protic solvents.[123] When dissolved in deuterated methanol and water, the alkylidene protons of **8** and **9** participate in nondestructive exchange 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.

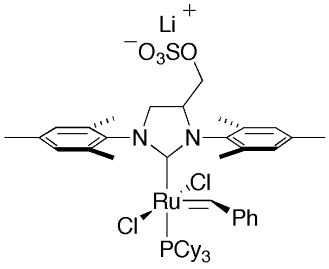
The increased stability and activity of NHC-containing olefin metathesis catalysts over their bis(phosphine) analogs inspires the production of water-soluble catalysts like **12** (Chapter 2).[56,124,125] The hypothesis is that the benefits that NHC ligands provide ruthenium-based olefin metathesis catalysts 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.



PEG =
poly(ethyldene glycol)

12



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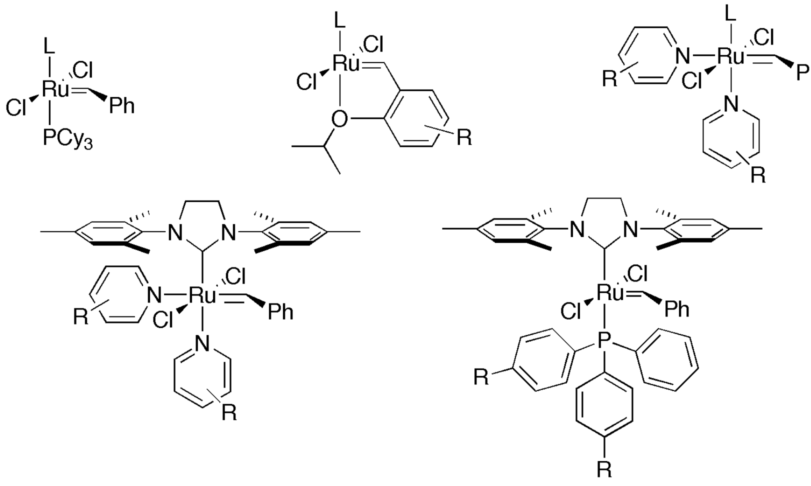
A consideration of the structure and activity of catalyst **12** prompts various strategies to generate water-soluble metathesis catalysts with improved stabilities and activities (Figure 1.7). Chapter 3 describes early attempts to synthesize complexes resembling those shown in Figure 1.7. These efforts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



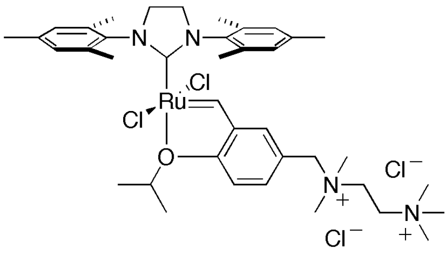
R = H or water-soluble group

L = water-soluble *N*-heterocyclic carbene 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]



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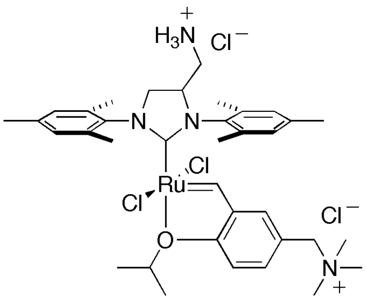

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The synthesis and activity of catalysts **14** and **15** is discussed in Chapter 5.[128,129] These catalysts both show increased ROMP activity over water-soluble catalysts **9** and **12**. More importantly, catalysts **14** and **15** both competently 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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