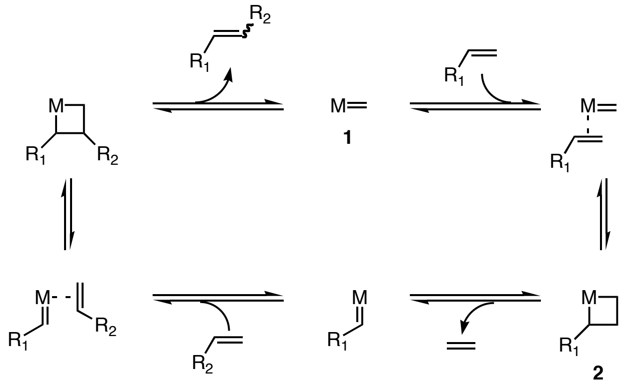
Chapter 1
Introduction

The olefin metathesis reaction is a powerful synthetic tool that scrambles the carbon atoms of carbon–carbon double bonds and creates new carbon–carbon double bonds. The mechanism of the reaction was proposed by Chauvin in 1971, and it is still accepted today (Scheme 1.1).[1] The key component to any olefin metathesis reaction is a transition metal species bearing a metal–carbon double bond (carbene or alkylidene). An alkene approaches the alkylidene (**1**) and undergoes a [2+2]-cycloaddition that generates a new carbon–carbon bond and affords a metallocyclobutane (**2**). A retro-[2+2], where different bonds break than were formed, generates a new olefin and a new metal alkylidene.



Scheme 1.1. Accepted olefin metathesis mechanism.

This simple transformation has been used in a wide variety of ways to synthesize simple organic molecules, complex natural products, supramolecules, and polymers.[2] Some of the common reactions are shown in Figure 1.1. Cross-metathesis (CM), ring-opening/cross metathesis (ROCM), and ring-closing metathesis are used in small molecule synthesis, and acyclic diene metathesis polymerization (ADMET) and ring-opening metathesis polymerization (ROMP) are processes that generate oligomers and polymers. These reactions are reversible, and in many cases the driving force for product formation is the release of gaseous by-products such as ethylene or the release of ring strain.

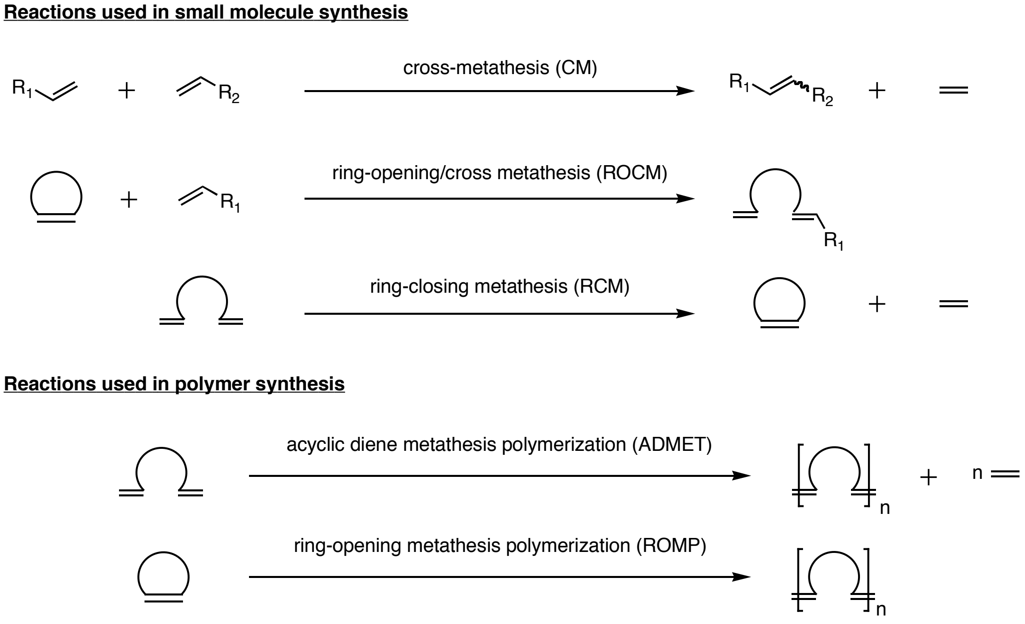
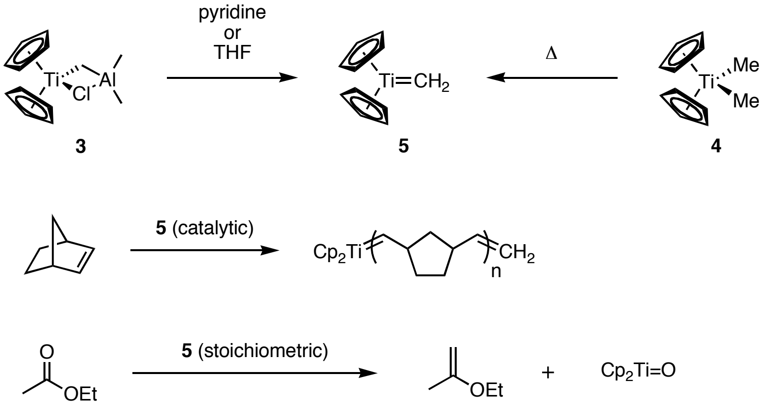


Figure 1.1. Common olefin metathesis reactions.

Although the olefin metathesis reaction has been known since the 1960s,[3] it was not until the development of well-defined, homogeneous catalysts that it found applications in organic synthesis. There are many transition metal alkylidenes that catalyze olefin metathesis reactions to some degree, but complexes based on titanium, molybdenum, and ruthenium receive the most use.[4] The different metals impart different reactivities to the alkylidenes, and, even within a family of complexes derived from one metal, small adjustments in the ligand environment cause large changes in catalyst behavior. Generally, early transition metal alkylidenes are more oxophilic than late metals complexes, and this property has a large impact on the chemoselectivity of the catalyst.

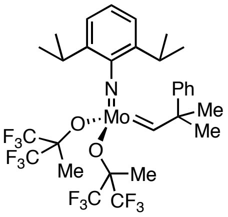
The most commonly used titanium alkylidenes are generated in situ from either Tebbe's reagent (**3**)[5] or dimethyltitanocene (**4**)[6] (Scheme 1.2). These compounds form a titanium methylidene, which can catalyze the ROMP of strained olefins. Other alkenes can react with titanium methylidenes to afford titanacyclobutanes, but an efficient catalytic cycle does not typically occur. The low reactivity of titanium alkylidenes allowed them to act as model systems and provide valuable insight into the olefin metathesis reaction.[7] Due to their high oxophilicity and the stability of the Ti–O bond, these complexes will react stoichiometrically with aldehydes, ketones, esters, lactones, and amides to afford methylenated products.[8] Although these complexes are not typically used as olefin metathesis catalysts, they have found a place in organic synthesis as carbonyl methylenating agents.



Scheme 1.2. Reactions of titanium methylidenes.

Many different molybdenum and tungsten alkylidenes have been synthesized,[9] and the catalyst that is used most often is **6**.[10] It is much more active that the titanium catalysts in performing olefin metathesis, and it has been applied to organic and polymer synthesis. The main disadvantage of the molybdenum-based catalysts is their air and moisture sensitivity as well as their reactivity with oxygen-containing functional groups.

Carboxylic acids, primary amines, aldehydes, most alcohols, and some ketones react with them and remove them from the olefin metathesis catalytic cycle. These functional groups are found in many organic compounds, limiting the use of the molybdenum catalysts.



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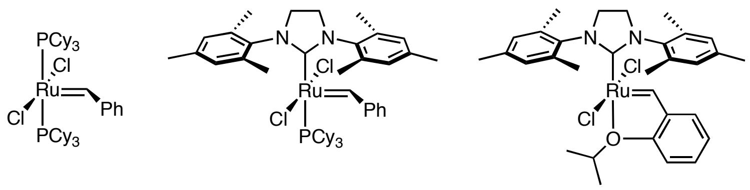
The main disadvantage of the early transition metal catalysts presented above is a lack of selectivity for olefins over other functional groups, and selectivity is a crucial part of any synthetic methodology. Some of the most successful reactions used in organic chemistry are those that reliably react with a certain functional group in a certain way and do not disturb the rest of the molecule. It was the development of ruthenium olefin metathesis catalysts that bridged the gap between olefin metathesis and organic synthesis.[11] Due to the functional group tolerance of ruthenium catalysts, olefin metathesis has become a selective reaction that has found widespread use among organic and polymer chemists. Just as in the case of molybdenum, many different metathesis-active ruthenium catalysts are known. A few of the most common catalysts are shown in Figure 1.2.[12] All three alkylidenes are stable to air and moisture, and complexes **8**[12b] and **9**[12c] exhibit catalytic activities similar to those of the highly active molybdenum systems.



7 **8** **9**

Figure 1.2. Selected ruthenium olefin metathesis catalysts.

This brief introduction has not done justice to all of the time and effort that has been dedicated to understanding olefin metathesis and developing it into a reliable, practical reaction. However, it has illustrated the importance of selectivity. Unlike the early transition metal-based alkylidenes, the ruthenium catalysts react preferentially with alkenes over many common functional groups, so they are the catalysts of choice in synthetic organic chemistry. But another question remains: could these ruthenium catalysts (or derivatives thereof) react selectively with one alkene in the presence of more than one? The exploration of chemo- and stereoselective olefin metathesis and its application in the synthesis of important organic compounds is presented in the following chapters of this dissertation.

As described in chapter 2, the synthesis of trisubstituted vinyl boronates using catalyst **8** was moderately successful. The lack of reactivity of catalyst **8** toward 1,1-disubstituted alkenes discovered during the work in chapter 2 afforded insight into how to develop a chemoselective olefin metathesis reaction. The research presented in chapter 3 focuses on the chemoselective CM of substituted conjugated dienes. This reaction generates compounds that are known to be versatile synthetic intermediates and are found in natural products. Chapter 4 contains the results from a study on asymmetric ring-closing metathesis (ARCM) that used chiral derivatives of **8**. All of the substrates were achiral trienes, and the extent to which a catalyst reacted with one alkene over another was determined by the enantiomeric excess of the chiral products. The application of ARCM in the enantioselective total synthesis of (+)-5-*epi*-citreoviral is presented in chapter 5. Finally, comments on the formation of tetrasubstituted olefins using unhindered ruthenium catalysts are presented in appendix 1, and the results from research directed toward the generation of a cis-selective olefin metathesis catalyst bearing a bidentate ligand are described in appendix 2.

References

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