Chapter 1

Introduction to *Z*-Selective Cyclometalated Ruthenium Metathesis Catalysts

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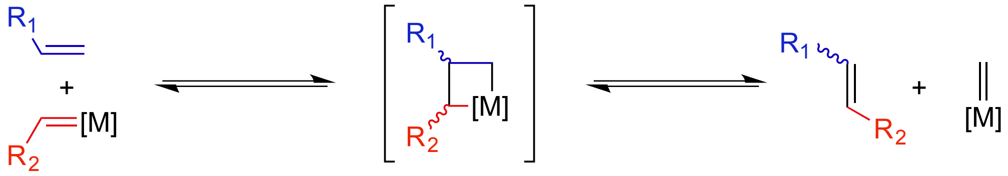
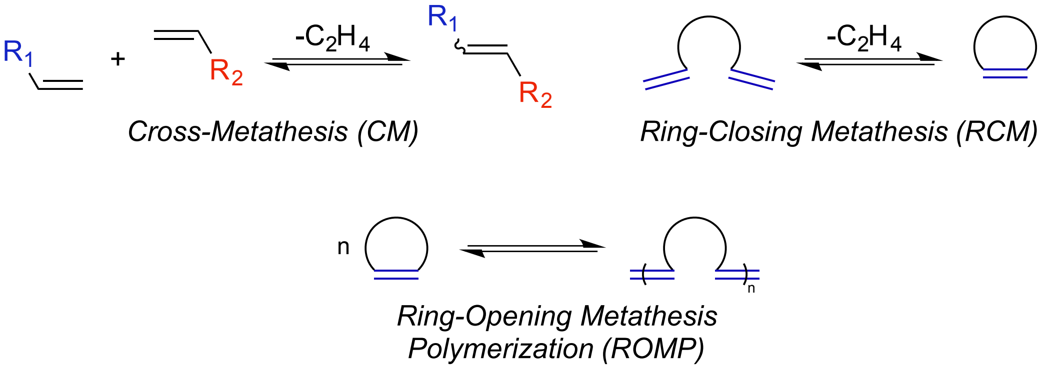
Introduction

Over the past half-century, olefin metathesis has emerged as an indispensable methodology for the construction of new carbon–carbon bonds.[1] The olefin metathesis reaction proceeds via the [2 + 2] addition of an alkene substrate to a metal alkylidene, forming a metallacyclobutane intermediate that can collapse in a productive fashion to afford a new olefinic product (Scheme 1.1). This reaction is incredibly versatile due to the wide variety of olefins that can be employed in or generated via metathesis; for example, two terminal olefins can undergo an intermolecular reaction to form a new internal alkene product in a process known as cross-metathesis (CM), while α,ω-dienes can react in an intramolecular fashion to yield cyclic olefins via ring-closing metathesis (RCM) (Scheme 1.2). Furthermore, polymeric olefins can be produced by the ring-opening metathesis polymerization (ROMP) of strained, mono- or polycyclic olefins. CM, RCM, and ROMP represent the three main classes of olefin metathesis reactions.



Scheme 1.1. Mechanism of olefin metathesis.



Scheme 1.2. General schemes for common metathesis reactions.

Seminal work in the 1970s identified early transition metal carbene complexes as proficient olefin metathesis catalysts.[2] This initial discovery led to the development of a number of well-defined systems that allowed for thorough mechanistic investigations, including elucidation of the factors affecting catalyst activity and selectivity. Capitalizing on these results, present-day olefin metathesis catalysts are straightforward to employ, air- and moisture-tolerant, and highly active across a broad range of olefin substrates. Furthermore, through judicious choice of metal and ligands, these catalysts can be readily tailored to specific applications or classes of substrates, and many of these systems are now either readily accessible or commercially available. As a result, olefin metathesis has been employed with great success in a number of fields, including biochemistry,[3] polymer and materials science,[4] and natural product synthesis.[5]

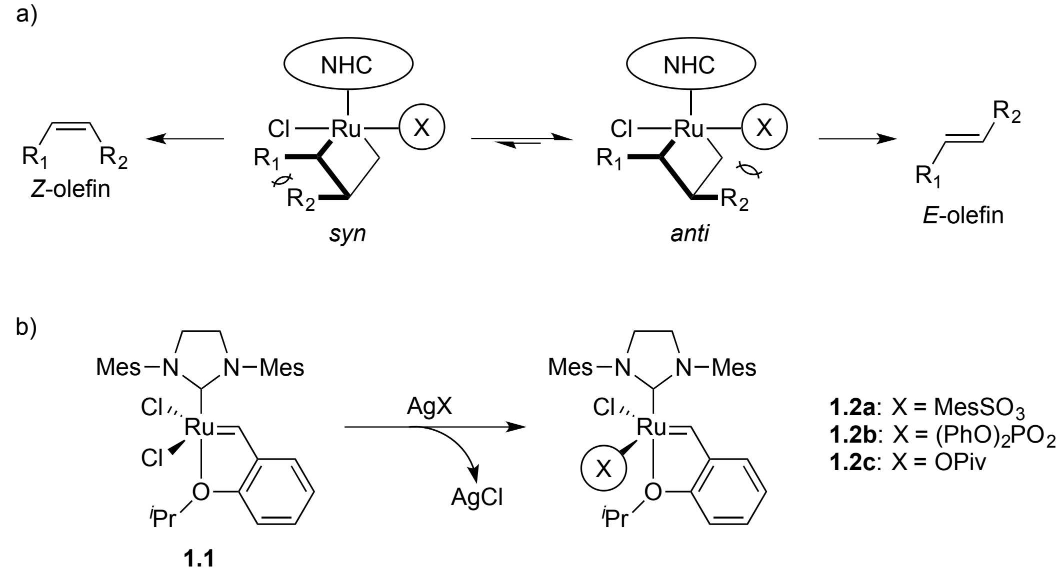
Due to the reversible nature of the olefin metathesis reaction, however, an ongoing challenge in the field has been the control of stereoselectivity.[6] At high conversions, the product distribution generally reflects the thermodynamic energy differences between olefin isomers, resulting in the predominant formation of *E*-olefins (ca. 80-90% *E*-selectivity). Many relevant natural products and pharmaceutical targets, on the other hand, contain functionality derived from *Z*-olefins. Moreover, the activity and properties of such molecules often depend heavily on the alkene geometry and can be adversely affected by even minute amounts of stereoisomeric impurities. While mixtures of *E*- and *Z*-isomers may be separated by chromatography or crystallizations, this often requires extensive optimization for each substrate and is not economical; additionally, purification is not possible in polymeric olefins containing both *E* and *Z* double bonds. Thus, it is highly desirable to develop catalyst systems that are not only kinetically selective for the formation of *Z*-olefins, but that are also capable of producing *stereopure* *Z*- or *E*-olefins. While indirect methods have been developed, including alkyne metathesis followed by highly *Z*-selective semireduction[7] and substrate-controlled macrocyclic-RCM of vinylsiloxanes followed by desilylation, the scope of these transformations is limited.[8]

Considerable effort has therefore been dedicated to the search for metathesis catalysts exhibiting kinetic selectivity for the formation of *Z*-olefins. Consequently, the Schrock and Hoveyda groups recently developed the first *Z*-selective metathesis catalysts using molybdenum and tungsten,[9] a groundbreaking development allowing for the effective synthesis essentially pure *Z*-olefins via metathesis for the first time. Efforts to develop comparable ruthenium-based systems have resulted in the discovery of a number of highly *Z*-selective catalysts,[10,11] including the class of cyclometalated ruthenium metathesis catalysts described in detail below. Many of these systems exhibit consistently high levels of activity and selectivity across a broad range of substrates and transformations, thus providing synthetic chemists with the ability to tackle a wide range of challenging and high-value targets derived from *Z*-olefins.

Development of *Z*-Selective Ruthenium Metathesis Catalysts

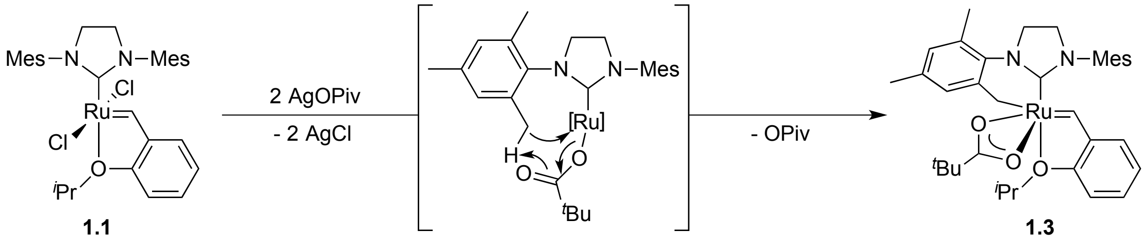
Original Strategy for the Design of Z*-Selective Ruthenium Alkylidenes*

Kinetic selectivity for *Z*-olefins results from the preferential formation of *syn*-metallacyclobutanes, in which the olefin substituents are on the same side of the metallacycle, following olefin binding (*anti*-metallacycles are those in which the substituents are positioned on *opposite* sides of the metallacycle). Cycloreversion of a *syn*-metallacycle produces *Z*-olefins; *anti*-metallacycles generate *E*-olefins. Importantly, for many ruthenacyclobutanes, such as those formed by prior generation *N*-heterocyclic carbene (NHC)-substituted metathesis catalyst **1.1** (Scheme 1.3b), the metallacycle is "bottom-bound," meaning that it is positioned opposite the NHC ligand in the equatorial plane, while the chloride ligands are located in apical positions (Scheme 1.3a).[12] As a result, initial attempts at synthesizing a *Z*-selective Ru-based catalyst focused on replacing one chloride ligand of **1.1** with a bulkier sulfonate (**1.2a**), phosphonate (**1.2b**), or carboxylate ligand (**1.2c**), anionic ligands which could be expected to experience significant steric interactions with *anti*-metallacycles (Scheme 1.3b).[13] This could, in turn, potentially increase preference for the formation of *syn*-metallacycles and thus *Z*-olefins (Scheme 1.3a).



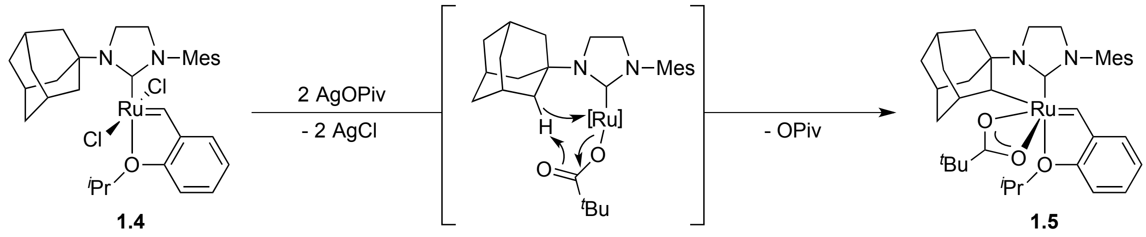
Scheme 1.3. (a) Proposed steric interactions for bottom-bound ruthenacycles. (b) Preparation of *Z*-selective ruthenium metathesis catalysts **1.2a–1.2c** with large X-type ligands. Mes = 2,4,6-trimethylphenyl.

Complexes **1.2a** and **1.2b** did exhibit slightly increased *Z*-selectivity relative to **1.1** but were still overall selective for the formation of *E*-olefins. (It was eventually discovered, however, that employing a sterically hindered 2,4,6-triphenyl-thiophenol ligand in place of one chloride ligand yielded a moderately *Z*-selective catalyst).[11a] Computational models predicted that the use of an anionic pivalate ligand, such as in **1.2c**, might dramatically increase *Z*-selectivity. Attempts to synthesize catalyst **1.2c** from **1.1** using silver pivalate (AgOPiv), however, did not lead to the formation of the desired mono-substituted product; instead, di-substitution of the chlorides by pivalate ligands followed by a carboxylate-assisted C–H bond insertion generated cyclometalated complex **1.3** (Scheme 1.4).[14] Notably, this marked the first time a cyclometalated ruthenium-based complex was isolated in which the ruthenium alkylidene remained intact (previously reported examples of cyclometalated complexes were the result of decomposition processes and were found to be metathesis inactive).[15]



Scheme 1.4. Mechanism of carboxylate-driven C–H bond insertion to form catalyst **1.3**. Mes = 2,4,6-trimethylphenyl.

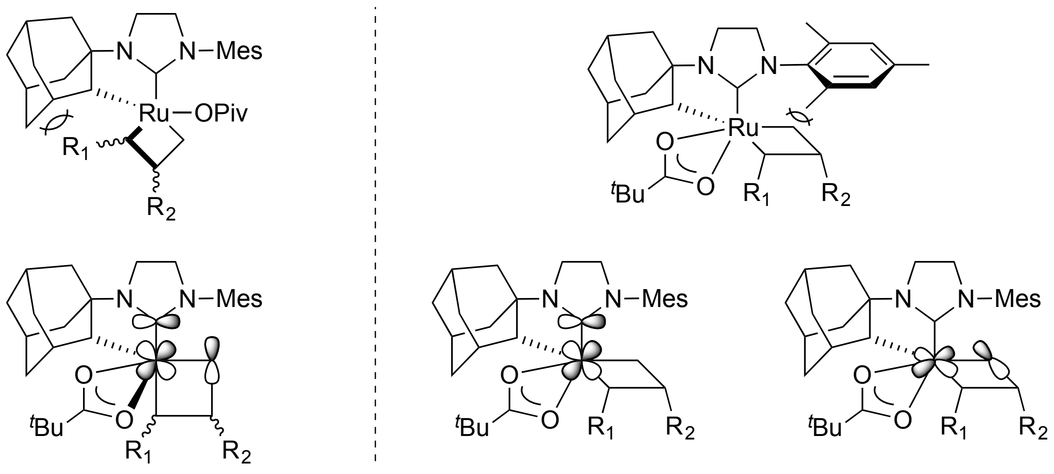
Initial studies with catalyst **1.3** revealed unprecedented *Z*-selectivity (41% *Z*) in the standard CM reaction of allylbenzene and *cis*-1,4-diacetoxybutene.[14] It was proposed that increasing the steric bulk of the non-cyclometalated substituent on the NHC might result in a more *Z*-selective catalyst; accordingly, activation of **1.4** containing a bulky *N*-adamantyl group was attempted using AgOPiv (Scheme 1.5). In the resulting cyclometalated catalyst **1.5**, however, the C–H activated substituent was not the *N*-mesityl group as anticipated but rather the *N*-adamantyl group. While this result was initially unexpected, it could be explained by the relatively short distance (2.80 Å) between the C12 carbon of the adamantyl group and Ru, which resulted in rapid C–H activation to form the adamantyl chelate. Unlike the air- and moisture-stable, dark green complex **1.1**, catalyst **1.5** was isolated as an air-sensitive, bright purple solid. Remarkably, the new cyclometalated catalyst **1.5** was found to be highly *Z*-selective (91% *Z*) in the CM of allylbenzene and *cis*-1,4-diacetoxybutene. Despite its promising selectivity, however, catalyst **1.5** exhibited a maximum of only 50 turnovers.



Scheme 1.5. Preparation of cyclometalated ruthenium catalyst **1.5**. Mes = 2,4,6-trimethylphenyl.

Model for Z-Selectivity in Cyclometalated Ruthenium Complexes

To better understand the mechanism and origins of *Z*-selectivity in cyclometalated ruthenium systems, catalysts **1.3** and **1.5** were studied using computational methods.[16] In contrast to the bottom-bound metallacycles (**1.6**) observed with catalyst **1.1** and prior generations of ruthenium metathesis catalysts, computational studies suggest that **1.3** and **1.5** adopt "side-bound" ruthenacycles (**1.7**) (Figure 1.1). This is thought to be the result of two factors: (1) a side-bound conformation avoids significant steric interactions that are present between the *N*-adamantyl group and a bottom-bound metallacycle, and (2) the side-bound conformation is electronically stabilized relative to the bottom-bound conformation. Namely, while the bottom-bound conformation requires back-donation from the same ruthenium d-orbital that back-donates into the NHC, a separate metal d-orbital is available for back-donation into the side-bound metallacycle.[16a]

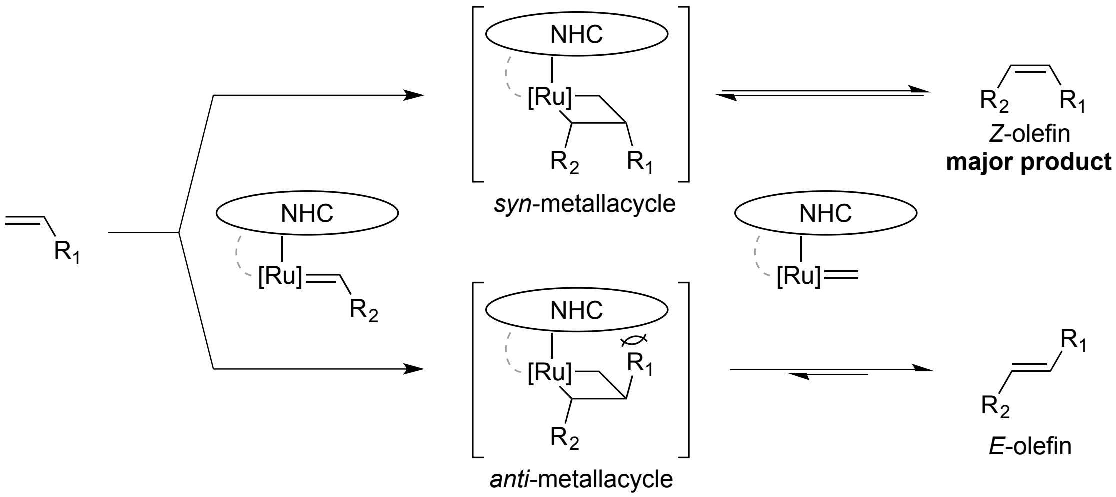


bottom-bound ruthenacycle (**1.6**)
= ***disfavored***

side-bound ruthenacycle (**1.7**)
= ***favored***

Figure 1.1. Comparison of the proposed steric and electronic interactions for side- and bottom-bound ruthenacycles. Mes = 2,4,6-trimethylphenyl.

Significantly, the adoption of the side-bound conformation **1.7** in catalysts **1.3** and **1.5** places the metallacycle directly below the *N*-aryl substituent of the NHC. As a result, it is proposed that *syn*-metallacycles (leading to the formation of *Z*-olefins) would form in preference to *anti*-metallacycles (leading to the formation of *E*-olefins), as the latter would presumably experience substantial steric interactions with the *N*-aryl substituent (Scheme 1.6). Indeed, *anti*-metallacycles derived from catalyst **1.5** have been computed to be much higher in energy than their *syn* counterparts.[16,17] Moreover, the congested steric environment about the alkylidene further discourages the formation of trisubstituted metallacycles, which in turn is hypothesized to slow the rate of *Z*-degradation caused by secondary metathesis events in cyclometalated systems. This property, combined with the inherent kinetic selectivity for *Z*-olefins in catalysts **1.3** and **1.5**, ensures that *Z*-selectivity remains high even at high conversions.[17]

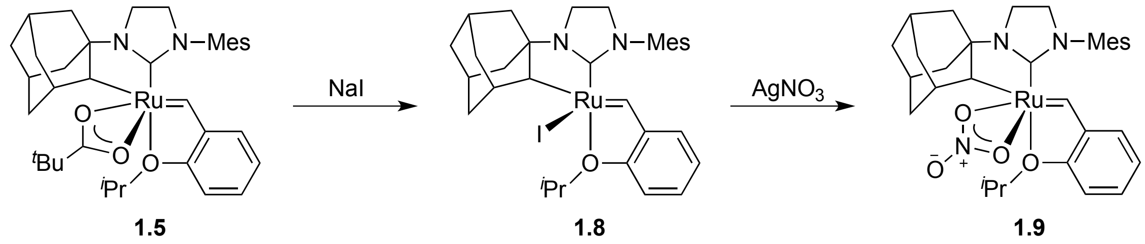


Scheme 1.6. Origins of *Z*-selectivity in cyclometalated ruthenium metathesis catalysts.

Evolution of Cyclometalated Ruthenium Complexes

Encouraged by the promising *Z*-selectivity observed with catalyst **1.5** in preliminary metathesis assays,[14,18] the syntheses of a variety of new cyclometalated complexes were attempted. Efforts focused specifically on the design of more active and *Z*-selective catalysts through the variation of three key structural elements of the catalyst: the X-type ligand, the chelate, and the *N*-aryl group.

It was determined that the most straightforward way to synthesize and assay a large number of new cyclometalated catalysts would be through variation of the X-type ligand.[19] Unfortunately, only carboxylate-type ligands were shown to be capable of inducing C–H activation. As a workaround, catalysts with monodentate (κ^1) ligands such as iodo-complex **1.8** were prepared by the treatment of catalyst **1.5** with sodium or potassium salts (Scheme 1.7). Catalyst **1.8** could in turn undergo transmetallation with a variety of silver (I) salts to give stable chelated species with new anionic, bidentate (κ^2) ligands, such as nitrato-complex **1.9**. Other new cyclometalated systems containing mono- or bidentate ligands (catalysts **1.10–1.12**) are shown in Figure 1.2.



Scheme 1.7. Preparation of mono- and bidentate cyclometalated catalysts. Mes = 2,4,6-trimethylphenyl.

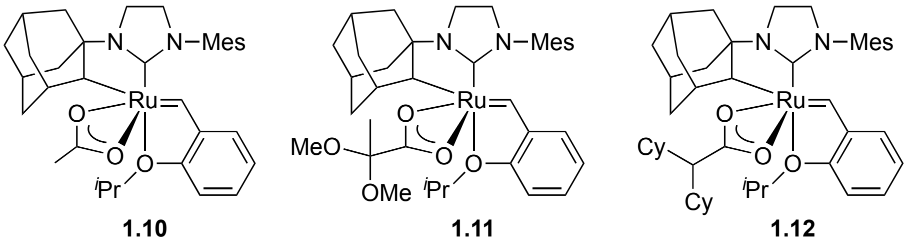
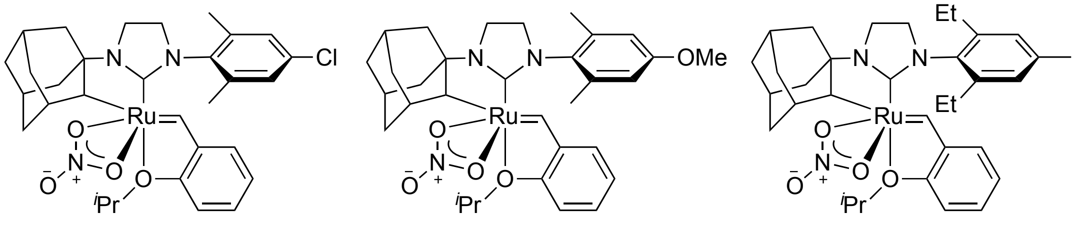


Figure 1.2. Cyclometalated ruthenium metathesis catalysts **1.10–1.12**. Mes = 2,4,6-trimethylphenyl.

Of the newly synthesized derivatives, nitrate-substituted catalyst **1.9** was found to be the highest performing, catalyzing a variety of CM reactions with near 1000 turnovers and ca. 90% *Z*-selectivity across the board.[19] Additionally, **1.9** produced highly *cis* polynorbornenes and norbornadienes (up to >95% *cis*);[20] however, the polymers were not highly tactic, a result in line with prior generation Ru-based metathesis catalysts. In contrast to pivalate-substituted catalyst **1.5** that decomposed in solution within 2 h upon exposure to air, complex **1.9** exhibited significantly improved stability, remaining active in solution for up to 12 h. Furthermore, **1.9** was found to be air- and moisture-stable in the solid-state for a minimum of 10 days.[19]

Following the discovery of the superior stability and activity afforded by the nitrate ligand, a number of derivatives of **1.9** containing different *N*-aryl groups were targeted.[19] Alterations to the *para*-substituent of the *N*-aryl group were found to have a limited effect on activity and selectivity: catalysts **1.13** and **1.14**, containing a *p*-chloro and *p*-methoxy group, respectively, displayed similar metathesis activity to catalyst **1.9** (Figure 1.3). Similarly, installation of an *N*-2,6-diethylphenyl group (**1.15**) resulted in minimal change in reactivity relative to catalyst **1.9**.



1.13 **1.14** **1.15**

Figure 1.3. Cyclometalated ruthenium metathesis catalysts **1.13–1.15**.

Computational data suggested that further increasing the bulk of the *ortho*-substituents on the *N*-aryl group might result in enhanced *Z*-selectivity. Unfortunately, however, it appeared that only subtle steric and electronic modifications of the *N*-aryl group were possible when using AgOPiv, as attempts to C–H activate a precursor complex bearing an *N*-2,6-diisopropylphenyl (DIPP) group resulted in the formation and eventual decomposition of a metastable complex.[21] Similar results were observed when significant modifications to the cyclometalated group were attempted. As such, an alternative method to access new cyclometalated *Z*-selective catalysts was highly desired.

In this dissertation, a milder method to effect the salt metathesis and C–H activation of cyclometalated ruthenium metathesis catalysts using sodium carboxylates in place of silver (I) carboxylates is presented. As a result of this advance, a variety of new catalyst architectures were synthesized and studied. *Chapter 2* describes the development of this new approach and its application to the synthesis of the most active, *Z*-selective cyclometalated ruthenium complexes to date, including the previously inaccessible *N*-DIPP-*N*-adamantyl complex described above. *Chapter 3* is composed of two sections: the first details the synthesis of a series of cyclometalated initiators displaying unprecedented activity and selectivity in ROMP, and the second comprises a detailed mechanistic study of these new complexes and prior cyclometalated systems in stereoselective ROMP. Work in this chapter was performed in conjunction with the Houk group at UCLA, who performed computational studies that were essential to the development of a complete mechanistic picture.

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