Olefin Cross Metathesis

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# *Z*-Selective Cross Metathesis with Ruthenium Catalysts: Synthetic Applications and Mechanistic Implications

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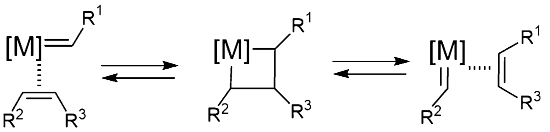
*Olefin cross metathesis is a particularly powerful transformation that has been exploited extensively for the formation of complex products. Until recently, however, constructing Z-olefins using this methodology was not possible. With the discovery and development of three families of ruthenium-based Z-selective catalysts, the formation of Z-olefins using metathesis is now not only possible but becoming increasingly prevalent in the literature. In particular, ruthenium complexes containing cyclometalated NHC architectures developed in our group have been shown to catalyze various cross metathesis reactions with high activity and, in most cases, near perfect selectivity for the Z-isomer. The types of cross metathesis reactions investigated thus far are presented here and explored in depth.*

## 1. Introduction

Olefin cross metathesis (CM) has been widely utilized for the formation of complex natural and nonnatural products, generally favoring formation of the more thermodynamically stable *E*- (or *trans*) carbon–carbon double bond isomer.[1] Olefin metathesis reactions proceed through a [2+2] cycloaddition reaction of an olefin with a metal alkylidene, generating a metallacyclobutane intermediate which can then undergo cycloreversion to produce a new olefin product (Scheme 1). Research into the structure and stability of substituted metallacyclobutanes has led to the development of catalysts capable of producing *Z*- (or *cis*) olefins with high stereoselectivity.[2] This was first realized by the groups of Schrock and Hoveyda, who synthesized monoaryloxide pyrrolide complexes of tungsten and molybdenum that could promote a variety of *Z*-selective metathesis reactions.[3]



**Scheme 1.** Mechanism of olefin metathesis.

More recently, a series of ruthenium catalysts with cyclometalated N-heterocyclic carbene (NHC) ligands capable of promoting *Z*-selective olefin metathesis has been reported. Catalysts **1–3** are three of the best-studied catalysts and are all derived from C–H activation of the *N*-adamantyl substituent contained on the NHC ligand (Figure 1).[5] Catalyst **1** features an *N*-mesityl (Mes) group as the nonchelated NHC substituent and is substituted with a pivalate X-type ligand. This catalyst promoted the homodimerization of terminal olefins with ca. 90% selectivity for the *Z*-olefin at as low as 1 mol% catalyst loading. Catalyst **2** was obtained by substitution of the pivalate ligand with a nitrate ligand, to produce a catalyst that showed a marked improvement in selectivity, exhibiting about 95% *Z*-selectivity across a broad range of homodimerization reactions. When the nonchelating *N*-aryl NHC substituent was changed to a bulkier *N*-DIPP (2,6-diisopropylphenyl) group, a further improvement in *Z*-selectivity was observed, as catalyst **3** exhibited >98% *Z*-selectivity in analogous homodimerization reactions. Catalysts **2** and **3** also

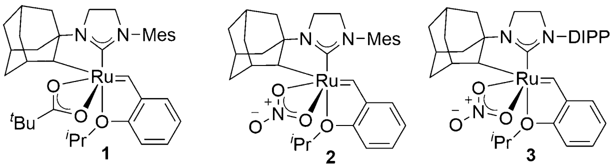


**Figure 1.** Cyclometalated ruthenium catalysts for *Z*-selective olefin metathesis.

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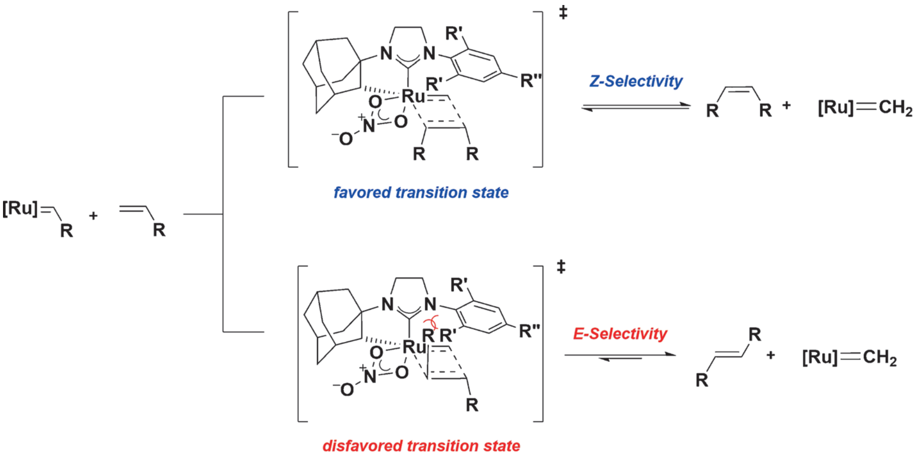
exhibited improved activity when compared to catalyst **1**, as the catalyst loadings could be lowered to as little as 0.01 mol%. These three cyclometalated catalysts have been evaluated in more complicated cross metathesis (CM), macrocyclic ring-closing metathesis (mRCM),[6] asymmetric ring-opening cross metathesis (AROCM),[7] and ring-opening metathesis polymerization (ROMP)[8] reactions and, as a result, have the potential to become widely used tools in chemical synthesis.

To understand the unprecedented *Z*-selectivity of these cyclometalated ruthenium catalysts **1**–**3**, experimental studies and density functional theory (DFT) calculations were performed.[9] It was discovered that metathesis reactions using these cyclometalated catalysts proceed through preferential formation of an unexpected side-bound ruthenacyclobutane intermediate, in which the metallacyclobutane is proximal to the NHC ligand (Scheme 2); this was attributed to a combination of intricate steric and electronic effects arising from the cyclometalated NHC architecture.[10] This effect causes the nonchelating *N*-aryl NHC substituent to be located directly over the forming ruthenacyclobutane. In the *anti*-metallacycle that leads to the formation of *E*-olefins, one substituent clashes with the *N*-aryl group and, hence, this intermediate is disfavored. In contrast, the *syn*-metallacycle avoids this unfavorable steric clash with both substituents pointing away from the *N*-aryl group. The resulting difference in energy leads to preferential formation of *Z*-olefin products.



***Scheme 2.*** Simplified model for the *Z*-selectivity exhibited by cyclometalated NHC catalysts. Adapted from Ref. [4e] with permission from The Royal Society of Chemistry.

The large improvement in *Z*-selectivity observed upon substitution of the *N*-Mes substituent with the bulkier *N*-DIPP group, as seen with catalyst **3**, can be easily rationalized based on this model.

After this family of cyclometalated catalysts was reported, two other families of *Z*-selective ruthenium metathesis catalysts were disclosed (Figure 2). The Jensen group reported catalysts **4** and **5**, bearing a single bulky thiophenolate X-type ligand, that exhibited generally high *Z*-selectivity (>85%) in terminal olefin homocoupling reactions with as little as 0.01 mol% catalyst loadings.[11] Notably, reactions using catalyst **5** could be performed under an air atmosphere and with unpurified substrates and solvents without a loss in activity or *Z*-selectivity. Subsequently, the Hoveyda group reported catalysts **6** and **7**, bearing chelating dithiolate X-type ligands.[12] These catalysts have proven to be highly active and *Z*-selective in AROCM, ROMP, and, more recently, CM reactions.[13] To showcase cyclometalated catalysts as powerful synthetic tools, complexes **1**–**3** have been used to synthesize a diverse set of products. This Minireview will discuss synthetic applications of *Z*-

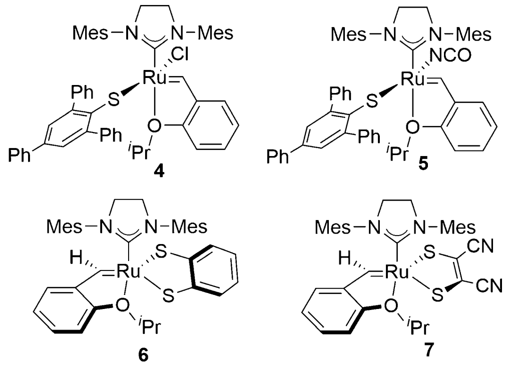


***Figure 2.*** Other reported *Z*-selective ruthenium metathesis catalysts.

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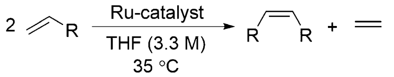
selective ruthenium-based catalysts that have been investigated thus far and the implications of observed reactivity on mechanism. Z-Selective molybdenum- and tungsten-based catalysts, although similarly powerful and efficient in complex CM transformations, will not be discussed here.[3]

## 2. Synthetic Applications

### 2.1. Z-Selective Terminal Olefin Homocoupling

Cyclometalated catalyst **1** was initially evaluated in simple homodimerization reactions of terminal olefin substrates (Scheme 3).[4a] Optimal conditions were found to involve high concentrations of substrate (3.3 M) in THF at 35 °C with 2 mol % of **1**. These reactions were performed in open vials in a glovebox to facilitate the removal of ethylene which drives the reaction. Under these mild conditions, a wide variety of functional groups were tolerated, including alcohols, amines, esters, and ethers, and the products were formed with generally high Z-content (66–95 %). Notably, substrates containing allylic substituents (e.g., 3-methyl-1-hexene) and those containing a pendant carboxylic acid (e.g., 4-pentenoic acid) could not be homodimerized. In addition, substrates with allylic functionality (e.g., allyl aniline and allyl acetate) led to lower yields but were tolerated nonetheless. Although THF was selected as optimal, a variety of other solvents could be used, including alcohols and polar aprotic solvents.



***Scheme 3.*** Z-selective homodimerization reaction.

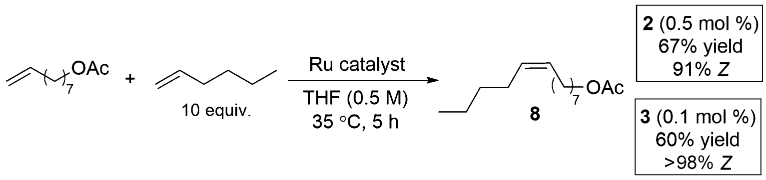
Subsequently, catalysts **2** and **3** were evaluated and proved to be significantly more active and selective in homodimerization reactions. Catalyst **2** exhibited improved yields and ca. 95 % Z-selectivity with 0.1 mol % catalyst loadings. Catalyst **3** exhibited even higher Z-selectivity (> 98 %) and experiments with 0.01 mol % catalyst loading at higher concentrations demonstrated up to 7400 turnovers. Thiophenolate-substituted catalysts **4** and **5** were evaluated in homocoupling reactions with similar terminal olefin substrates. Although high activity and good Z-selectivity was observed for all substrates tested, optimal conditions tended to be substrate-specific. In a number of cases, undesired olefin isomerization reactions were competitive with productive product formation. This is in contrast to homocoupling reactions catalyzed by **2** and **3**, in which a single set of reaction conditions led to high turnovers and Z-selectivity across a range of substrates.

### 2.2. Z-Selective Olefin Cross Metathesis

Compared to olefin homocoupling, the CM of two different terminal olefins is a more challenging transformation as it leads to the formation of a statistical mixture of the three possible different internal olefin products: the homodimers of both substrates in addition to the desired cross product. As demonstrated with previous generations of ruthenium catalysts, there are situations in which high yields of cross products can be obtained with a near stoichiometric balance of reactants;[14] therefore, similar rules should apply to these cyclometalated catalysts. To favor formation of the desired product in cases where the electronic and steric environment of the olefins are similar, one olefin starting material must be used in excess and the catalyst loading must be slightly higher than with homodimerization reactions. Catalyst **1** was evaluated in the standard CM reaction of allyl benzene and *cis*-1,4-diacetoxybutene. Using 5 mol % of **1**, reactions performed in THF (0.5 M) at 35 °C led to the formation of the desired cross product with 50 % conversion and 86 % Z-selectivity. When catalyst **2** was tested under these conditions, it was found that the catalyst loading could be lowered to 1 mol % with slightly higher conversion and Z-selectivity. A recent report has demonstrated that dithiolate catalyst **6** and a related analogue could catalyze the CM of a terminal olefin with a symmetrical internal olefin to produce an intermediate in the synthesis of the natural product (+)-neopeltolide with high yields (55–70 %) and Z-selectivity (97–98 %).[13] This reaction was performed at room temperature and at 10 mol % catalyst loading.

One application of olefin CM that has been previously explored is the formation of Lepidopteran insect pheromones for pest control applications.[1b] Catalyst **2** was employed in the synthesis of nine Z-insect pheromone cross products approved by the EPA as pest control agents.[15] It was found that low catalyst loadings (1 mol %) led to moderate to good yield (40–77 %) and high Z-content (76–88 %) of the desired products at room temperature.

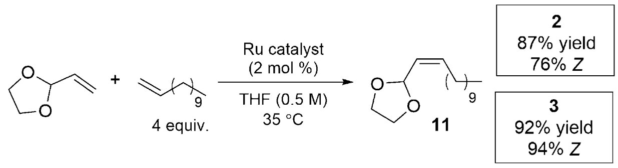
Catalyst **3** was subsequently compared to **2** in the CM reaction of 1-hexene and 8-nonenyl acetate to form the insect pheromone derivative **8** (Scheme 4). Using catalyst **2**, compound **8** was formed in 67 % yield and 91 % Z-selectivity at 0.5 mol % catalyst loadings. With catalyst **3** bearing the bulkier N-DIPP group, however, the same species could be formed at lower catalyst loadings (0.1 mol %) with only slightly diminished yield (60 %) and with perfect selectivity for the Z-olefin isomer (> 98 %). More recently, catalysts **2** and **3** had been employed for the synthesis of Z-olefins containing pendant amino acids and peptides.[16] As expected, catalyst **3** provided higher Z-selectivity compared to **2**; however, both were active in forming complex and biologically relevant compounds. These results highlight the potential for further application of catalyst **3** in the synthesis of complex cross products with high Z-selectivity.



***Scheme 4.*** CM reaction for the formation of pheromone **8** by catalysts **2** and **3**.

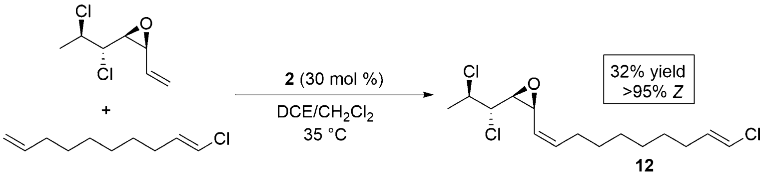
### 2.3. Z-Selective Cross Metathesis of Allyl-Substituted Olefins

As previously mentioned, the allyl-substituted terminal olefin 3-methyl-1-hexene showed no appreciable reactivity in homodimerization reactions using cyclometalated catalyst **1**. These types of substrates have typically exhibited enhanced *E*-selectivity (up to 95% *E*) with previous generations of ruthenium catalysts.[14] Recently, however, it was shown that a variety of other allyl-substituted terminal olefins could undergo CM with unhindered terminal olefins to form cross products, like compound **11**, with high *Z*-selectivity (91 to >95%) using catalyst **3** (Scheme 5);[17] use of catalyst **2** resulted in reduced *Z*-selectivity (ca. 76%) as expected. The fact that catalyst **3** can overcome the substrate-dependent preference for *E*-olefin formation and catalyze the transformation with high *Z*-selectivity represents a significant improvement in CM chemistry.



**Scheme 5.** CM reaction of allylic substituted olefins using catalysts **2** and **3**.

In a separate publication, the Vanderwal group was able to synthesize intermediate **12** en route to the chlorosulfolipid natural product mytilipin A using high catalyst loadings (30 mol%) of **2** (Scheme 6).[18] This reaction involved the CM of a substituted vinyl epoxide with a terminal olefin, and proceeded in 32% yield with >95% *Z*-selectivity. This result further showcases the ability of these cyclometalated catalysts to react with more complex allyl-substituted olefins.



**Scheme 6.** Synthesis of intermediate **12** en route to mytilipin A.

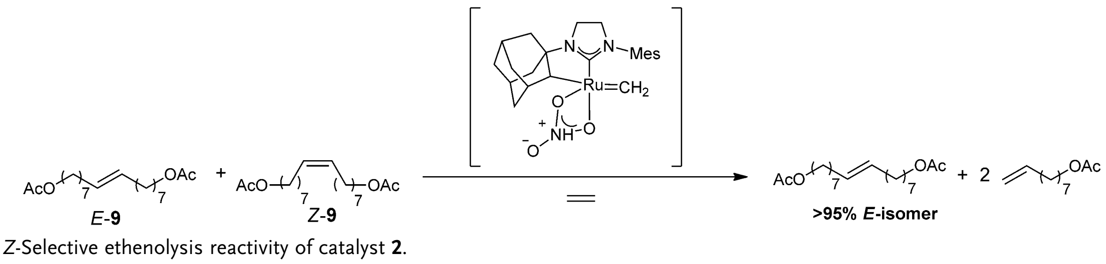
### 2.4. Z-Selective Ethenolysis

In CM reactions catalyzed by this series of cyclometalated catalysts, two terminal olefins are reacted to produce a *Z*-internal olefin and ethylene (Scheme 3). Since high *Z*-selectivity is exhibited in these reactions, it was envisioned that high *Z*-selectivity could also be observed in the reverse reaction, ethenolysis (Scheme 7). This is a process in which an internal olefin reacts with ethylene to produce two terminal olefins through a metal methylidene intermediate.[3f] Since CM and ethenolysis are complementary reactions, they proceed through the same metallacyclobutane intermediates, thus the explanation for *Z*-selectivity presented in the introduction for productive CM reactions applies to the selectivity observed in ethenolysis reactions (Scheme 2). When we tested catalyst **2** for the selective ethenolysis of a mixture of *Z*- and *E*-olefins, we were pleased to find that it exhibited both high ethenolysis activity and high *Z*-selectivity, as *Z*-olefins were selectively converted to terminal olefins whereas *E*-olefins remained intact.[6,19]

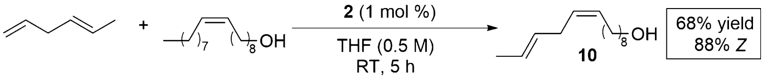
The *Z*-selective ethenolysis activity of cyclometalated catalyst **2** was evaluated in reactions with stereoisomeric mixtures of various *Z*- and *E*-olefins, and ethylene (Scheme 7). It was discovered that exposure of 0.5 mol% of catalyst **2** to the diacetate-substituted internal olefin **9** (80% *E*) under 5 atm of ethylene at 35 °C led to enrichment of the *E*-isomer to >95%. The enriched *E*-isomer and the ethenolyzed *Z*-isomer product, 8-nonenyl acetate, could then be recovered in quantitative yield by flash column chromatography. Subsequent experiments showed that when stereoisomeric mixtures of internal olefin substrates (generally ca. 80% *E*) bearing alcohol, ester, amine, and ketone functional groups were tested under the conditions outlined above, the desired *E*-enriched products could be formed with high selectivity (>95% *E*-isomer). Accordingly, this could emerge as a powerful, functional-group-tolerant method to form purely *E*-olefin-containing products. The *Z*-selective ethenolysis reactivity of catalyst **3** has not yet been evaluated but it is envisioned that, as with its CM reactivity, it will exhibit increased activity and *Z*-selectivity.

### 2.5. Chemoselective Olefin Metathesis

Considering that internal *E*-olefins were shown to be unreactive with this family of cyclometalated catalysts under ethenolysis conditions, it was proposed that internal *E*-olefins would be similarly inert under CM conditions. Indeed, the



**Scheme 7.** *Z*-Selective ethenolysis reactivity of catalyst **2**.



*Scheme 8.* Chemoselective CM reaction for the direct formation of nonconjugated *E*,*Z* diene **10**.

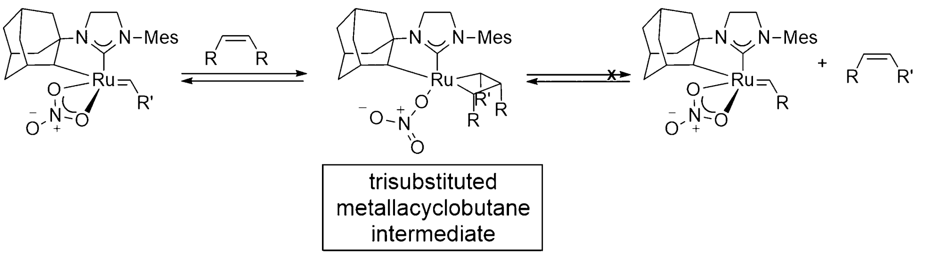
direct synthesis of compound **10** containing an *E*,*Z* nonconjugated diene from *E*-1,4-hexadiene was successfully carried out with 68% yield and 88% *Z*-selectivity using catalyst **2** (Scheme 8).[15] Notably, no products derived from reaction with the *E*-internal olefin were observed. This represents one of the first examples of diene-selective metathesis and was found to be generally applicable for the construction of a variety of polyenes in a subsequent report from our group.[20] It was shown that catalyst **3** could promote highly *Z*-selective CM reactions to produce a diverse set of products that also contained *E*-internal olefins, 1,1-disubstituted terminal olefins, or even *Z*-α,β-unsaturated esters.

## 3. Mechanistic Studies

### 3.1. Influence of Metallacyclobutane Structure on Activity and Selectivity

All of the aforementioned cyclometalated catalysts are unable to catalyze CM reactions of two internal olefins, a phenomenon that is possible with most metathesis catalysts.[14] For internal–internal CM to occur, substituted alkylidenes must be reacted with internal olefins to form trisubstituted metallacyclobutane intermediates (Scheme 9). Since no such reactivity was observed with cyclometalated catalysts **1–3**, it was proposed that trisubstituted metallacyclobutane intermediates of these catalysts were very high in energy and thus could not react productively; DFT calculations provided evidence for this supposition.[20]

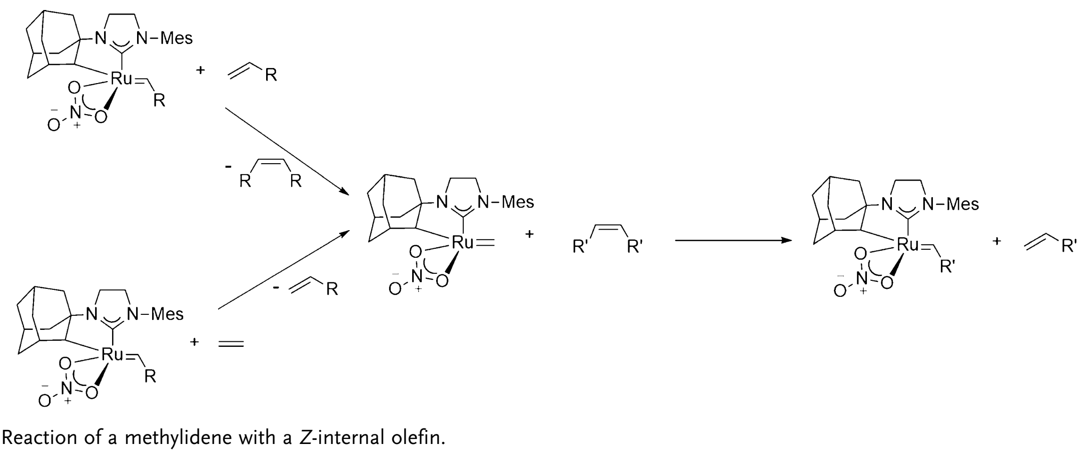
Subsequent experiments revealed that CM reactions of two internal olefins could proceed but only in the presence of added ethylene gas and if the *Z*-internal olefin isomer was used. With the corresponding *E*-olefin isomer, none of the desired cross product was observed even when ethylene was added. This supports a mechanism in which a methylidene species must be formed before productive CM can occur; methylidenes can be formed after a productive CM reaction or by addition of ethylene gas (Scheme 10). After its formation, an internal olefin can then react with this methylidene to concurrently generate a substituted alkylidene and a terminal olefin. Productive product formation can finally occur by reaction of the substituted alkylidene and a terminal olefin which proceeds through a 1,2-disubstituted metallacycle. Based on the results presented here, synthetic chemists intending to use these catalysts for the synthesis of complex products should avoid using *E*-internal olefins as starting materials and instead try to use terminal olefins whenever possible. Based on these studies, it seems that the ethenolysis activity and selectivity of these cyclometalated catalysts have direct relations to their unique metathesis mechanism.



*Scheme 9.* Highly unfavorable cycloaddition of internal olefin with substituted alkylidene to form trisubstituted metallacycle.

### 3.2. Z-Content Degradation

When CM reactions catalyzed by **1–3** are monitored over time, there is an evident decrease in *Z*-selectivity at higher conversions. The rate of *Z*-content degradation is catalyst-dependent, with catalyst **3** exhibiting generally slower degradation than **2** which, in turn, is slower than **1**. The presence of



*Scheme 10.* Reaction of a methylidene with a *Z*-internal olefin.

ethylene seems to accelerate *Z*/*E* isomerization processes and, as such, one mode of *Z*-content degradation may be related to the *Z*-selective ethenolysis reactivity of these catalysts in subsequent turn overs of the internal olefin products. While *Z*-degradation is general for all substrates, species with certain functional groups, such as alcohols, tend to degrade *Z*-content at a faster rate and thus other pathways for *Z*-content degradation are expected and envisioned. The precise mechanistic pathways contributing to the observed degradation are not yet understood and studies are currently being carried out to elucidate what pathways are contributing. A better understanding of these processes may provide insight into improved reaction conditions which maintain near-perfect *Z*-selectivity at high conversions. Based on previously reported data, shorter reaction times can lead to only minor reductions in yield and significantly less *Z*-content degradation.

## 4. Summary and Outlook

The discovery and development of ruthenium catalysts **1**–**7** has enabled the formation of a diverse array of *Z*-olefin cross products, including insect pheromones and more complex natural products. Investigating the mechanism of reactivity with this family of cyclometalated catalysts has revealed key differences in the accessibility of important metallacyclobutane intermediates unique to these catalysts. These mechanistic insights have suggested unprecedented ways to exploit the selectivity of these catalyst systems, highlighting their potential as powerful synthetic tools. *Z*-selective CM has proven to be an effective method to form *Z*-olefins, and *Z*-selective ethenolysis is emerging as a powerful method to selectively isolate *E*-olefins from stereoisomeric mixtures. Now, using olefin metathesis, purely *Z*-internal olefins can be formed directly and purely *E*-olefins can be formed in two steps using *Z*-selective ethenolysis. The development of new and improved catalysts capable of carrying out transformations not possible with the current catalysts will be necessary for the expansion of this methodology. For example, the *Z*-selective CM of two internal olefins and the formation of highly *Z* trisubstituted olefins using ruthenium metathesis catalyst are not currently possible, but have been reported for *Z*-selective molybdenum and tungsten catalysts.[3a,g] In presenting some key aspects of the reactivity observed so far with these ruthenium catalysts, we hope to have highlighted their broad synthetic potential for the formation of diverse *Z*-olefin products in the presence of various functional groups.

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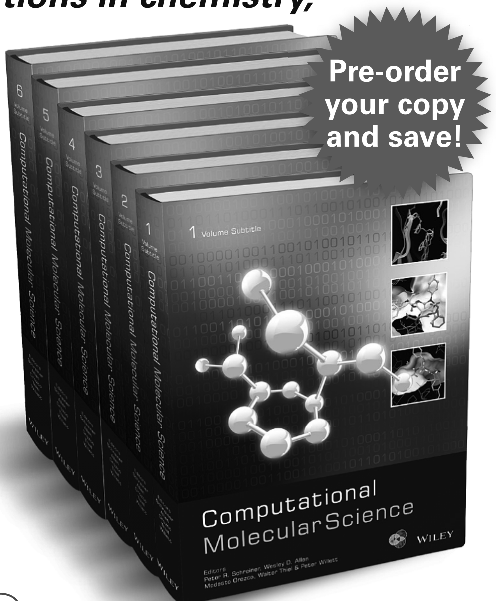

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