catalysts

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Review

# Recent Advancements in Stereoselective Olefin Metathesis Using Ruthenium Catalysts

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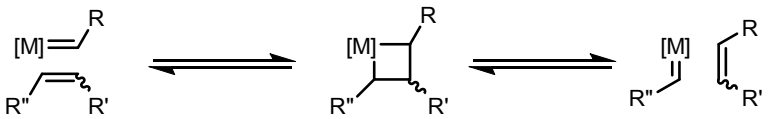
**Abstract:** Olefin metathesis is a prevailing method for the construction of organic molecules. Recent advancements in olefin metathesis have focused on stereoselective transformations. Ruthenium olefin metathesis catalysts have had a particularly pronounced impact in the area of stereoselective olefin metathesis. The development of three categories of *Z*-selective olefin metathesis catalysts has made *Z*-olefins easily accessible to both laboratory and industrial chemists. Further design enhancements to asymmetric olefin metathesis catalysts have streamlined the construction of complex molecules. The understanding gained in these areas has extended to the employment of ruthenium catalysts to stereoretentive olefin metathesis, the first example of a kinetically *E*-selective process. These advancements, as well as synthetic applications of the newly developed catalysts, are discussed.

**Keywords:** ruthenium; catalysts; stereoselective; asymmetric; *Z*-selective; olefin; metathesis

## 1. Introduction

Organic molecules, by definition, are composed of carbon–carbon bonds; thus, their construction is central to strategies aimed at the formation of useful, complex products. One method that has found wide application in this endeavor is olefin metathesis (OM) [1–8]. Initially viewed as a strange olefin rearrangement reaction [9,10], the utility of OM now ranges from synthetic organic chemistry [11,12] to materials chemistry [13,14]. Studies on OM have further enhanced the understanding of this process, promoting the development of interesting and useful metathesis catalysts. The generally accepted mechanism was originally proposed by Chauvin and Hérisson (Scheme 1) [15]. Upon generation of a metal-carbene, an olefin can chelate to the metal species. [2+2] cycloaddition can occur, forming a metallacyclobutane, which can then cyclorevert, forming a new olefin and metal-carbene species.




**Scheme 1.** Generally accepted mechanism for olefin metathesis (OM) proceeding through a [2+2] cycloaddition followed by cycloreversion to generate a new olefin.

Traditional methods of control in OM have relied on the intrinsic reactivity of an olefin, as well as thermodynamic selectivities, but recent developments in OM catalysts have allowed for tailoring of the catalytic scaffold to impart some stereochemical control on the olefinic products. Early stereoselective OM research focused on the desymmetrization of achiral olefins to provide chiral molecules through the alteration of the ligand scaffold [11,16,17]. As understanding for the stereochemical arrangement

of the metallacycle intermediate progressed, further variations were made in continual pursuit of one of the unmet challenges in OM: kinetic *Z*-selectivity [18–20]. An incredible amount of effort has been devoted to these quests, which have opened the door to numerous discoveries. This review will present recent advancements (since 2010) in stereoselective OM employing ruthenium catalysts which directly convey stereochemical control on the products for synthetic applications. Also, much progress has recently been made in the use of stereoselective molybdenum and tungsten metathesis catalysts [16,17,21–23]; however, this review will focus on ruthenium-based metathesis catalysts.

## 2. *Z*-Selective Olefin Metathesis

### *2.1. General Introduction*

Metathesis has had a far reaching impact on organic chemistry, and many exciting developments have occurred. Until recently, one of the unmet challenges in ruthenium-catalyzed OM was a kinetically *Z*-selective process [18,20]. Because OM is reversible and secondary metathesis readily occurs, the ratio of *E*- and *Z*-olefins typically reflects the thermodynamic energy difference between the two isomers, which is about 9:1, *E*:*Z* [24]. This presents a synthetic problem, because many natural products and biologically active molecules contain *Z*-olefins. Furthermore, the activity of these compounds can require high stereopurity to obtain the desired effect. Nevertheless, methods for separating olefin isomers through purification exist, although these are difficult and time consuming. Indirect methods to deliver *Z*-olefins have been developed, such as alkyne metathesis and subsequent partial reduction of the alkyne [25,26]. There have also been substrate dependent methods for *Z*-selectivity [27–30], but a universal method for *Z*-selective OM remained elusive.

The demands for a kinetically *Z*-selective OM depend on the ruthenacyclobutane (Figure 1). If the ruthenacyclobutane forms with the substituents in an *anti*-arrangement, (**II**), (sterically favored), cycloreversion will generate an *E*-olefin. However, if the ruthenacyclobutane forms with substituents in a *syn*-arrangement, (**IV**), (sterically less favored), cycloreversion furnishes the *Z*-isomer. Two factors favor the *E*-isomer over the *Z*-isomer: kinetics from the ruthenacyclobutane stereochemistry and thermodynamics of the olefin formed. To develop a *Z*-selective catalyst, olefin coordination to the ruthenium-carbene would need to be limited to occur from one side, and the generated ruthenacycle, following [2+2] cycloaddition, would need to form in a way to generate an all *syn*-ruthenacyclobutane. Upon cycloreversion, a *Z*-olefin would be obtained.

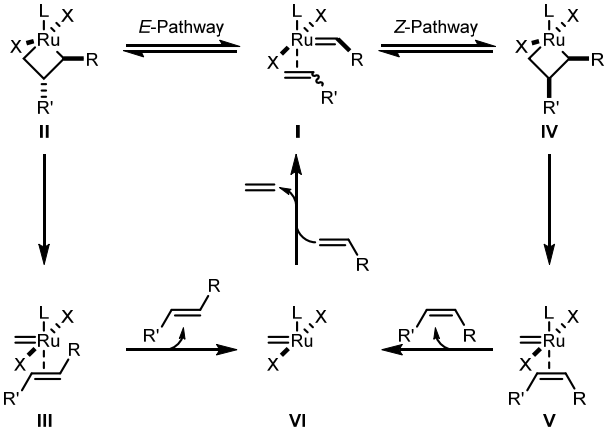



**Figure 1.** Catalytic cycle for olefin metathesis (OM) illustrating how stereochemical relationships in the ruthenacyclobutane affect the stereochemistry of the formed olefin.

## 2.2. Cyclometalated Catalysts

### 2.2.1. Cyclometalated Catalysts Development

Studies from Grubbs and coworkers aimed at generating a *Z*-selective ruthenium metathesis catalyst originally attempted to employ a large sulfonate or phosphonate in place of one of the chloride ligands on **1** [31]. Unfortunately the levels of *Z*-selectivity using this strategy were modest, and the catalysts evaluated were of low stability. Computational studies suggested that a pivalate group in place of one of the chlorides would enhance *Z*-selectivity. When attempts were made to generate **2**, it was discovered that C–H activation of an *ortho*-methyl in *N*-2,4,6-trimethylphenyl (Mes) occurred to generate a cyclometalated catalyst, **3** (Figure 2). Although cyclometalated ruthenium complexes have been reported as catalyst decomposition products [32,33], **3** performed the cross metathesis (CM) of allylbenzene and *cis*-1,4-diacetoxybutene in moderate conversion (58%) and the highest observed *Z*-selectivity for a ruthenium metathesis catalyst (at the time), 41% *Z* [34]. Following this result, it was proposed that a larger *N*-heterocyclic carbene (NHC) could enhance the steric demands of the catalyst, favoring an all *syn*-ruthenacycle, so one of the *N*-Mes groups was replaced with an *N*-adamantyl. Surprisingly, C–H activation occurred on the *N*-adamantyl group (**4**), which resulted in a more selective OM catalyst (88% *Z* in the CM of allylbenzene and *cis*-1,4-diacetoxy-2-butene) [34].

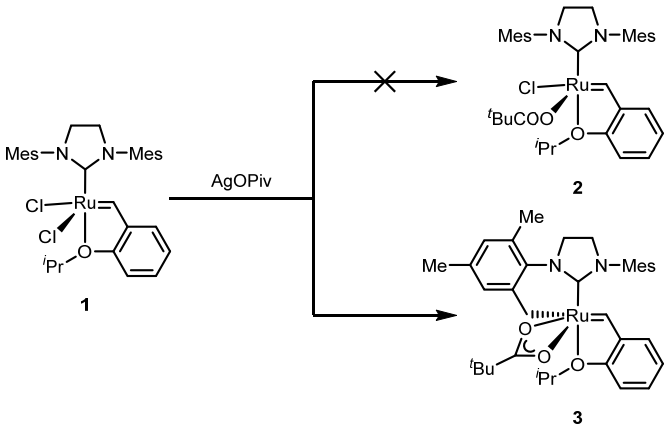



**Figure 2.** Surprising C–H activation leading to the initial cyclometalated ruthenium metathesis catalyst.

Computational and experimental studies were carried out to understand the *Z*-selectivity imparted by these cyclometalated catalysts [35,36]. The reaction is believed to proceed through a side-bound ruthenacyclobutane due to complex steric and electronic effects. Also, the cyclometalation locks the *N*-aryl group in place. Thus, it is postulated that the *N*-aryl group resides directly over the forming ruthenacylobutane, forcing all the substituents down in a *syn*-arrangement (Figure 3, **VII**). Cycloreversion furnishes a *Z*-olefin. For formation of the *E*-product, an *anti*-ruthenacycle (Figure 3, **VIII**) must form, which is sterically unfavored due to the *N*-aryl group blocking the top of the ruthenacycle.

Building on these discoveries, the catalytic scaffold was tuned to enhance stability, activity, and selectivity. Initial variations were made to the *X*-type ligands on the ruthenium center [37]. It was found that monodentate ligands were unreactive. When screening various bidentate *X*-type ligands, it was observed that replacing the pivalate with a nitrate (Figure 4a) enhanced both the activity and selectivity (58% conversion and 91% *Z* in the CM of allylbenzene and *cis*-1,4-diacetoxy-2-butene) [37]. Further efforts to improve the cyclometalated catalyst focused on the free *N*-aryl group. It was found that replacing the *N*-Mes group with a more bulky *N*-2,6-diisopropylphenyl (DIPP) (**9**) greatly improved the activity and selectivity (Figure 4b) [38]. Using **9**, the product of allylbenzene dimerization was obtained in >95% conversion and >95% *Z*.

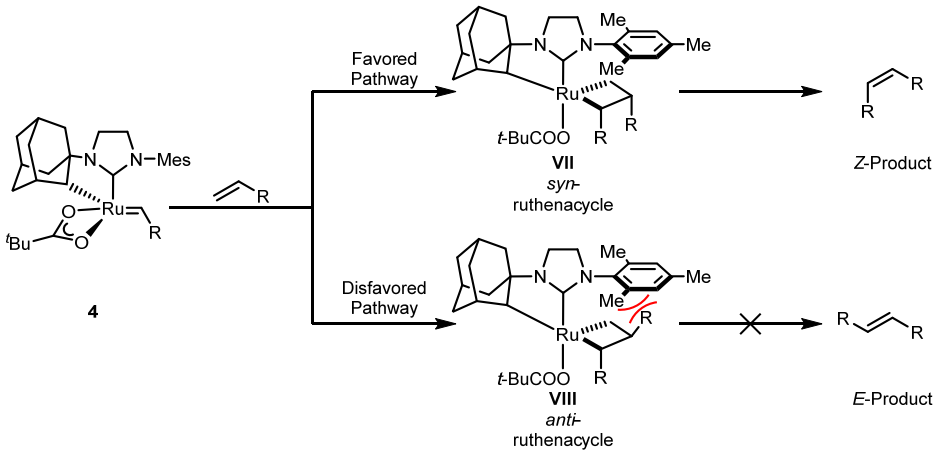



**Figure 3.** Depiction of the steric interactions leading to the favored *Z*-selective metathesis pathway using **4**.

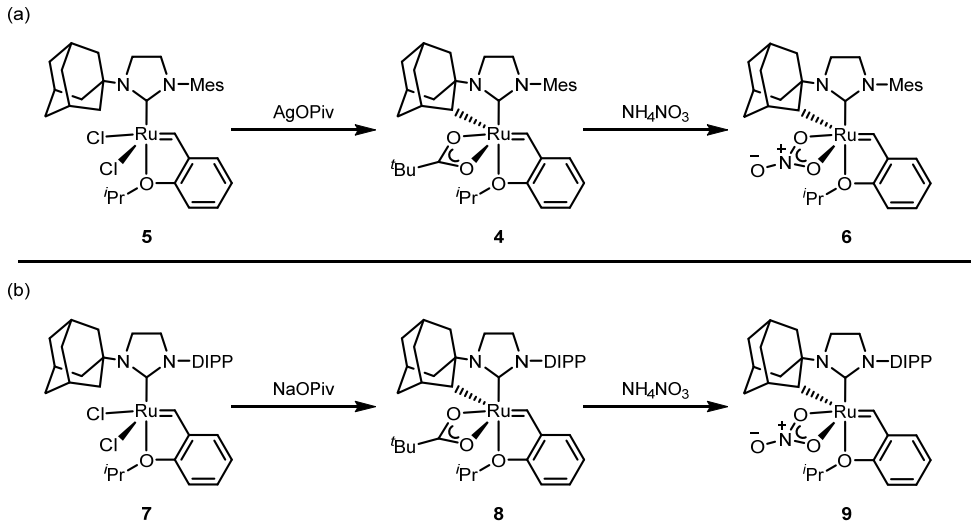



**Figure 4.** Modifications leading to improvements in cyclometalated catalysts. (**a**) Discovery of the nitrate ligand enhanced the performance of **6**; (**b**) Employing the *N*-2,6-diisopropylphenyl (DIPP) group further improved the reactivity and selectivity of the cyclometalated catalysts.

Efforts to improve the reactivity and selectivity of cyclometalated catalysts **6** and **9** have resulted in the preparation of novel cyclometalated complexes with varying carbene moieties including those with chelating *N*-substituents beyond *N*-1-adamantyl (Figure 5) [39–41]. The metathesis activity of these complexes was evaluated using standard terminal olefin homodimerization reactions of allylbenzene, 4-penten-1-ol, or methyl-10-undecenoate. Complex **10**, possessing a 6-membered NHC, was found to be inactive in the test reactions [40]. Complex **11** showed good activity and retained high *Z*-selectivity in the homodimerization of allylbenzene, but it generated the undesired β-methylstyrene through isomerization of the olefin in the starting material [40]. Catalyst **12** displayed low to poor activity and modest *Z*-selectivity [40]. Complexes **13** and **14** both displayed good selectivity, but **13** showed superior activity to **14** [41]. Catalyst **15**, bearing a four-membered chelate, showed little to no reactivity largely ascribed to catalyst instability [41]. Complex **16**, the DIPP variant of **3**, showed slightly higher selectivity and stability when compared to **3**, which is thought to be a product of the sterically larger *N*-aryl DIPP [39]. Complex **17**, containing a monodentate chloride ligand, was found to be *E*-selective [39]. It was postulated that the monodentate nature of the chloride ligand allows

metathesis to proceed through a bottom-bound ruthenacycle, thus favoring *E*-products. Complex **18** featuring a nitrite *X*-type ligand displayed slower initiation rates in comparison to **9** [42]. *Z*-Selectivity was retained at longer reaction times where the nitrite catalyst could achieve similar conversions.

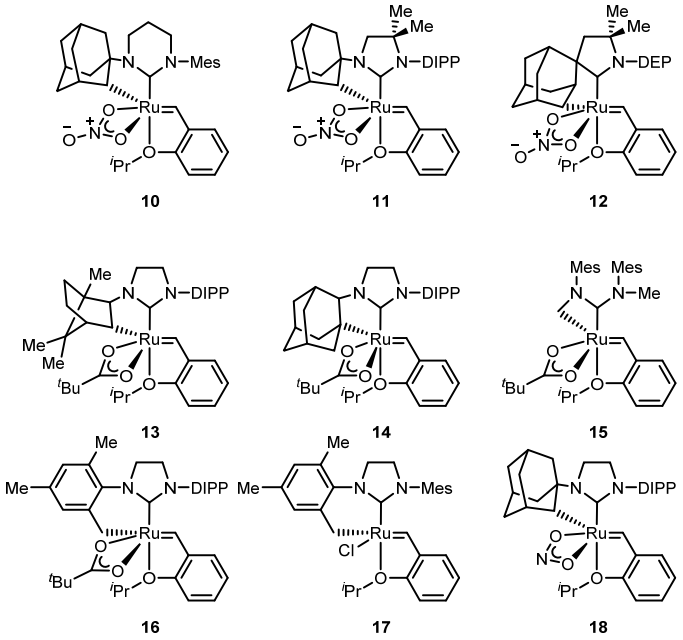
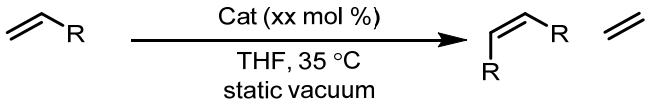



**Figure 5.** Various cyclometalated catalyst scaffolds evaluated.

A detailed discussion of the development of cyclometalated ruthenium OM catalysts can be found in a previous review from Grubbs and coworkers [24]. A more recent review of the synthetic applications of *Z*-selective cyclometalated ruthenium catalysts has also been revealed [43].

### 2.2.2. *Z*-Selective Homodimerization

**Table 1.** Homodimerization of terminal olefins using cyclometalated catalysts.




| Entry | *R* | Cat (xx mol %) | Yield (%) | *Z* (%) |
|---|---|---|---|---|
| 1 | $CH_2Ph$ | **4** (2) | 81 | 92 |
| 2 | $CH_2Ph$ | **6** (0.1) | 91 | 92 |
| 3 | $CH_2Ph$ | **9** (0.1) | >95 | >95 |
| 4 | $CH_2Ph$ | **9** (0.01) | 74 | >95 |
| 5 | $(CH_2)_8CO_2Me$ | **4** (2) | >95 | 73 |
| 6 | $(CH_2)_8CO_2Me$ | **6** (0.1) | 85 | 91 |
| 7 | $(CH_2)_8CO_2Me$ | **9** (0.1) | >95 | >95 |
| 8 | $(CH_2)_3OH$ | **6** (0.1) | 67 | 81 |
| 9 | $(CH_2)_3OH$ | **9** (0.1) | 77 | 95 |

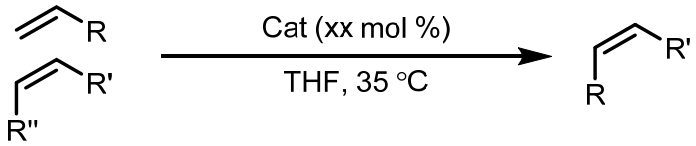
Initial investigations into the homodimerization of olefins utilized **4** (Table 1, entries 1 and 5) [44]. A wide substrate scope was tolerated such as alcohols, amines, esters, and ethers (selected examples to compare catalysts are found in Table 1). Surprisingly, optimal reaction temperature was determined to be 35 °C, even though the large adamantly group could inhibit catalyst initiation.

Furthermore, a high concentration of olefin was required for good reactivity, which could aid in catalyst initiation. These transformations were performed under static vacuum to promote removal of ethylene, driving the reaction forward. Problematic substrates in homodimerization included those with allylic substitution. As improvements were made to the catalyst, **6** and **9** were evaluated in the homodimerization of olefins (Table 1, entries 2–4 and 6–9) [37,38,41]. **9** showed exceptional reactivity and *Z*-selectivity, reaching 7400 turnover numbers while maintain selectivity >95% *Z* (Table 1, entry 4).

### 2.2.3. *Z*-Selective Cross Metathesis

The CM of two olefins is more difficult than the homodimerization because a CM can theoretically provide three different products: homodimerization of each olefin and the CM product. The understanding developed from previous generations of ruthenium metathesis catalysts [45] was applied to the new cyclometalated catalysts. Studies using 4 commenced by probing the reactivity and selectivity with a CM system that included allylbenzene and *cis*-1,4-diacetoxy-2-butene (Table 2, entry 1) [34]. The desired CM products were isolated in moderate yield, but high levels of *Z*-selectivity were observed. As modifications were made to the cyclometalated catalysts, new scaffolds were assessed (Table 2, entries 2–4), but 9 proved to be the best catalyst to date [37–40,42].

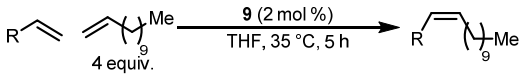
**Table 2.** Comparison of cyclometalated catalysts using cross metathesis (CM).

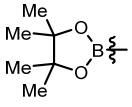



| Entry | *R* | *R′* | *R″* | Cat (xx mol %) | Yield (%) | *Z* (%) |
|---|---|---|---|---|---|---|
| 1* | $CH_2Ph$ | $CH_2OAc$ | $CH_2OAc$ | 4 (5) | 60 | 84 |
| 2 | $CH_2Ph$ | $CH_2OAc$ | $CH_2OAc$ | 6 (1) | 58 | 91 |
| 3 | $(CH_2)_3Me$ | $(CH_2)_7OAc$ | H | 6 (0.5) | 70 | 91 |
| 4 | $(CH_2)_3Me$ | $(CH_2)_7OAc$ | H | 9 (0.5) | 71 | >95 |

* Entry 1 was carried out in refluxing THF.

**Table 3.** CM of allylically substituted olefins using **9**.




| Entry | *R* | Yield (%) | *Z* (%) |
|---|---|---|---|
| 1 |  | 82 | >95 |
| 2 |  | 70 | >95 |
| 3 |  | 44 | 94 |
| 4 |  | 81 | 92 |
| 5 |  | 40 | >95 |

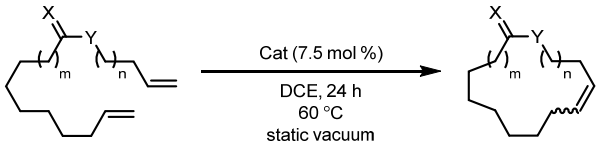
As previously mentioned, allylic substitution proved to be a problem in homodimerization and CM. Investigations using 9 met this challenge. Vinyl acetals were shown to be excellent coupling partners with 1-dodecene when employing 9, affording the desired CM products in good yields and

excellent selectivities (Table 3, entries 1–2) [46]. In addition to vinyl acetals, excellent selectivities were observed with a cyclic alkane, vinylboronic acid pinacol ester and 2-vinyl oxirane (Table 3, entries 3–5), though the products were afforded in moderate yield. Interestingly, under conditions similar to Table 3, entry 1, 1 affords excellent yields of product highly enriched in the thermodynamic stereoisomer (92% yield, 95% *E*). Functionalities in the terminal olefin were also tolerated; esters, alcohols, and halides all afforded good yields and excellent selectivities.

### 2.2.4. *Z*-Selective Macrocyclic Ring-Closing Metathesis

Macrocycles are important moieties in natural products and other valuable molecules [47]. Recently, the fragrance industry has become interested in molecules termed macrocyclic musks, which are less hazardous than some of the traditionally used fragrance compounds [48]. Unfortunately, macrocyclic ring-closing metathesis (mRCM) suffers from some drawbacks not seen in ring-closing metathesis (RCM) of smaller ring systems. Oligomerization can occur more readily, so high dilutions and catalyst loadings are necessary. Moreover, former methods used to form macrocycles *via* RCM suffered from generating the desired products in unpredictable ratios of *Z*- and *E*- isomers. Catalyst **6** was employed in the synthesis of *Z*-macrocycles through mRCM [49]. A number of different ring sizes were constructed in good yield and good *Z*-selectivities (Table 4). Some limitations still persist, such as the need for high dilution and static vacuum to promote mRCM. The authors noted that macrocycles containing alcohols and ketones displayed increased *Z*-degradation over time (as low as 50% *Z* after 24 h), but no reasoning was provided. As improvements were made to the cyclometalated catalyst scaffold, 9 was also evaluated in various mRCM, delivering exceptional levels of *Z*-selectivity (Table 4) [38].

**Table 4.** *Z*-Selective macrocyclic ring-closing metathesis (mRCM) employing **6** and **9**.



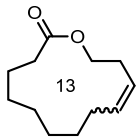
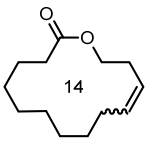
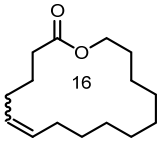
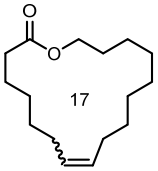
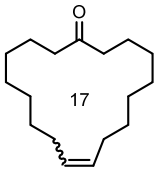
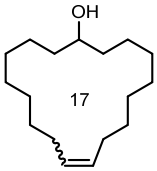

| Entry | Product | Cat | Yield (%) | *Z* (%) |
|---|---|---|---|---|
| 1 |  | **6** | 40 | 86 |
| 2 |  | **6** | 58 | 85 |
| 3 |  | **6** | 72 | 84 |
| 4 |  | **6**<br>**9** | 71<br>64 | 89<br>>95 |

**Table 4.** *Cont.*

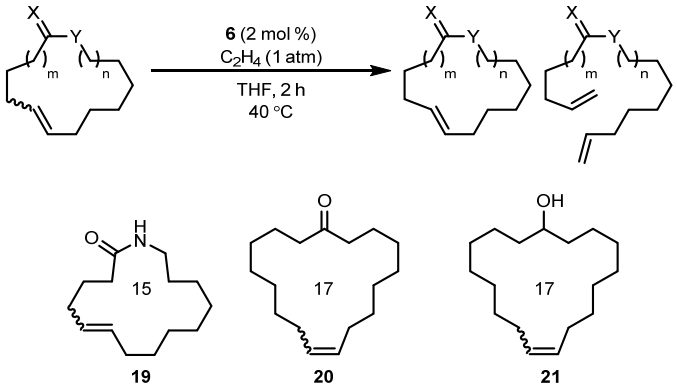
| Entry | Product | Cat | Yield (%) | *Z* (%) |
|---|---|---|---|---|
| 5 |  | **6**<br>**9** | 50<br>36 | 68<br>>95 |
| 6 |  | **6**<br>**9** | 56<br>45 | 65<br>>95 |

### 2.2.5. *Z*-Selective Ethenolysis

The aforementioned cyclometalated ruthenium catalyst, **6**, is known to perform kinetically *Z*-selective homodimeriztions and CM, generating a disubstituted olefin and ethylene gas (Tables 1 and 2). However, any CM is in equilibrium with the back reaction, ethenolysis, which is the cleavage of an internal olefin to generate two terminal olefins. Furthermore, ethenolysis of internal olefins has received attention as a method to access materials and fuels from renewable sources such as seed oil derivatives [50–55]. It was postulated that **6** could be employed in a *Z*-selective ethenolysis as a method to purify *E*-olefins. Unfortunately, no protocol to generate *E*-olefins kinetically was available when employing a ruthenium catalyst [56]. This is an issue when extremely pure quantities of a specific olefin isomer are required, such as in medicinal chemistry.

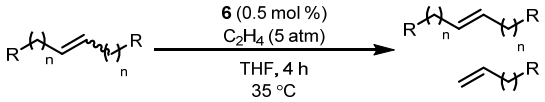
Cyclometalated complex **6** was found to promote ethenolysis of internal *Z*-olefins as a method to purify an *E*/*Z*-mixture of variously sized and functionalized macrocycles (Table 5) delivering the *E*-macrocycles in high purity [49]. Additional studies found that linear internal olefinic mixtures could be purified using this technique, providing *E*-olefins almost exclusively (Table 6) [57]. Complex **6** was found to tolerate a wide variety of functional groups such as free alcohols (Table 6, entry 3), esters (Table 6, entries 2 and 4), amines (Table 6, entry 5), and ketones (Table 6, entry 6). Additionally, low to moderate ethylene pressures were operable.

**Table 5.** *Z*-Selective ethenolysis furnishing *E*-isomer enriched macrocycles.




| Entry | Substrate | Initial *E* (%) | Final *E* (%) |
|---|---|---|---|
| 1 | **19** | 55 | >95 |
| 2 | **20** | 80 | >95 |
| 3 | **21** | 80 | >95 |

**Table 6.** *Z*-Selective ethenolysis of symmetric internal olefins providing *E*-isomer enrichment.



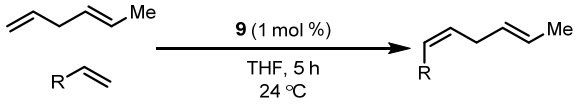

| Entry | *R* | *n* | Initial *E* (%) | Final *E* (%) |
|---|---|---|---|---|
| 1 | Me | 3 | 52 | 90 |
| 2 | OAc | 7 | 78 | >95 |
| 3 | OH | 4 | 68 | 90 |
| 4 | $CO_2Me$ | 6 | 80 | >95 |
| 5 | NHPh | 3 | 80 | >95 |
| 6 | C(O)Me | 2 | 72 | >95 |

The study of **6** in ethenolysis also provided a better mechanistic understanding for CM and mRCM. It was observed that the CM of two internal *Z*-olefins cannot directly occur, but each olefin must first be ethenolyzed to the terminal olefins, which can subsequently participate in metathesis to generate a new internal *Z*-olefin [57]. *E*-olefins will not participate in this process; therefore, this is a promising method to separate *Z*- and *E*-isomers.

### 2.2.6. Chemoselectivity in Z-Selective Olefin Metathesis

The ability of **6** to selectively react with terminal or *Z*-olefins, as was seen in the ethenolysis methodology, offered a platform to perform chemoselective OM on substrates containing multiple olefins. It was reported by Grubbs and coworkers that **9** was able to differentiate between terminal olefins and internal *E*-olefins with great discretion, providing 1,4-diene CM products in good yields with excellent selectivities (Table 7) [58]. Carbonyl and amine functionality was also tolerated (Table 7, entries 2–7). They also found that internal *Z*-olefins reacted preferentially to *E*-olefins and chemoselective RCM formed macrocyclic dienes.

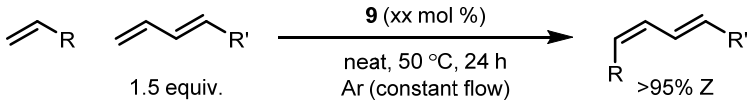
**Table 7.** Chemoselective CM with *trans*-1,4-hexadiene using **9**.




| Entry | *R* | Yield (%) | *Z* (%) |
|---|---|---|---|
| 1 | $CH_2Ph$ | 63 | >95 |
| 2 | $(CH_2)_8CHO$ | 70 | >95 |
| 3 | $(CH_2)_2COMe$ | 49 | >95 |
| 4 | $(CH_2)_7CO_2Me$ | 82 | >95 |
| 5 | $CH_2NHPh$ | 68 | >95 |
| 6 | $CH_2NHBoc$ | 54 | >95 |
| 7 | $CH_2OCO_2Me$ | 79 | >95 |
| 8 | $CH_2BPin$ | 65 | >95 |

Stereoselective coupling of terminal olefins with 3*E*-1,3-dienes was demonstrated with **9**, affording functionally diverse *E*, *Z* conjugated dienes in excellent selectivity [59]. The transformation was conducted in neat substrate, and good yields were obtained for substrates bearing alcohols, allylic ethers, and esters while halides, amides, ketones, carbonates and aldehydes afforded moderate yields (Table 8). Nitriles and dienes in conjugation with aromatic rings resulted in poor yields (Table 8, entries 11, 13–14).

**Table 8.** *Z*-Selective CM of 3*E*-1,3-dienes with terminal olefins.




| Entry | *R* | *R′* | **9** (xx mol %) | Yield (%) |
|---|---|---|---|---|
| 1 | $(CH_2)_7OH$ | $(CH_2)_9Me$ | 2 | 84 |
| 2 | $CH_2OCH_2CCPh$ | $(CH_2)_9Me$ | 3 | 82 |
| 3 | $CH_2NHBoc$ | $(CH_2)_9Me$ | 4 | 60 |
| 4 | $(CH_2)_8CHO$ | $(CH_2)_9Me$ | 4 | 59 |
| 5 | $CH_2BPin$ | $(CH_2)_9Me$ | 4 | 60 |
| 6 | $(CH_2)_4OAc$ | $(CH_2)_9Me$ | 4 | 69 |
| 7 | $CH_2CH_2COMe$ | $(CH_2)_9Me$ | 4 | 41 |
| 8 | $CH_2OCO_2Me$ | $(CH_2)_9Me$ | 4 | 42 |
| 9 | $(CH_2)_6Br$ | $(CH_2)_9Me$ | 4 | 34 |
| 10 | $(CH_2)_2CN$ | $(CH_2)_9Me$ | 4 | 12 |
| 11 | $(CH_2)_7OH$ | $(CH_2)_4OAc$ | 4 | 75 |
| 12 | $(CH_2)_7OH$ | Ph | 4 | 15 |
| 13 | $(CH_2)_7OH$ | 4-MeOPh | 4 | 25 |

Homodimerization of 3*E*-1,3-dienes afforded *E*,*Z*,*E*-trienes in moderate yields. ROCM was conducted with dienes and norbornene or cyclobutene derivatives, providing the ring-opened products in excellent yield (>89%) and *Z*-selectivity (>20:1).

### *2.3. Monothiolate Catalyst*

Monothiolate Catalyst Development and Applications

Early examples for *Z*-selective OM catalysts were based on Mo and W modified by monoalkoxide–pyrrolide ligands [60–63]. These catalytic designs built on the previously used scaffolds of the nonselective Mo and W catalysts. Grubbs and coworkers briefly looked at a catalytic system that employed a similar design to the nonselective ruthenium catalysts by replacing one of the chloride ligands with a sulfonate or phosphonate [31]. Because these catalysts were plagued by modest selectivities and showed low stability, this idea was shelved when the cyclometalated catalysts were discovered. Jensen and coworkers continued to build on the idea that a *Z*-selective scaffold could be similar to the traditional ruthenium metathesis catalysts. They performed a substitution on **1** to displace one of the chlorides with 2,4,6-triphenylbenzenethiol, forming **22** [64]. This very large *X*-type ligand can act as a barrier to one side of the catalyst, forcing all the substituents of the metallacycle to reside in a *syn*-arrangement, generating *Z*-olefins upon cycloreverison (Figure 6, **IX**). When assaying **22** in the dimerization of terminal olefins, it was found to deliver high *Z*-content at low conversion (Table 9). Unfortunately, isomerization problems persisted (Table 9, entry 1).

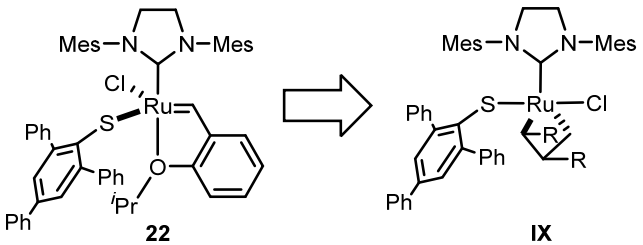
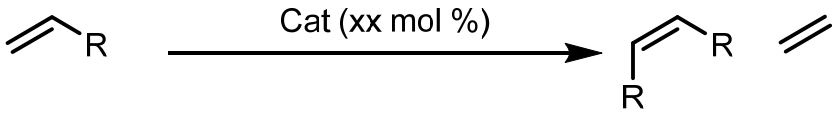


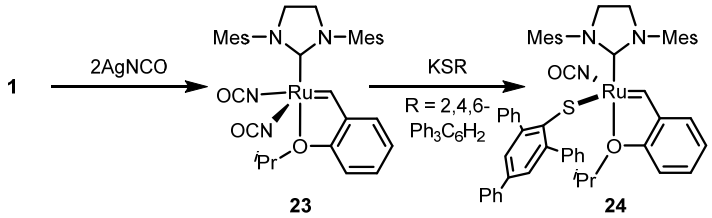

**Figure 6.** Model of **22**'s mode of selectivity by shielding one side of the ruthenacycle.

**Table 9.** Homodimerization of olefins employing **22** and **24**.




| Entry | *R* | Cat (xx mol %) | Solvent | *T* (°C) | Time (h) | Yield (%) | *Z* (%) |
|---|---|---|---|---|---|---|---|
| 1 | $CH_2Ph$ | 22 (0.25) | THF | 40 | 0.5 | 12 | 80 |
| | | | | | 2 | 14 | 39 |
| 2 | $CH_2Ph$ | 24 (0.25) | THF | 40 | 0.5 | 6 | 88 |
| | | | | | 2 | 10 | 56 |
| 3 | $CH_2SiMe_3$ | 22 (0.25) | THF | 60 | 18 | 12 | 95 |
| 4 | $CH_2SiMe_3$ | 24 (0.25) | THF | 60 | 16 | 9 | 96 |
| 5 | $(CH_2)_5Me$ | 22 (0.01) | neat | 60 | 2 | 20 | 86 |
| 6 | $(CH_2)_5Me$ | 24 (0.01) | neat | 60 | 1.5 | 13 | 88 |

Expanding on early catalyst architecture which led to promising *Z*-selectivities at low conversion, the Jensen group replaced the remaining anionic chloride ligand with an isocyanate, affording **24** (Scheme 2) [65]. Initial head-to-head comparisons with the parent catalyst showed improved *Z*-selectivity at the expense of reactivity (Table 9, entries 2, 4, and 6). Interestingly, this new catalyst was found to be quite robust and, unlike **22**, can be purified using standard chromatographic conditions (silica gel and unpurified solvents). Spurred by this finding, reactions conducted with **24** under air or in the presence of an acid under argon were shown to reduce the amount of isomerization observed in the starting material (chain-walking) and product (*Z*:*E*). Additional studies were aimed at understanding the effect of changing the identity of the donor ligand (NHC in **22** and **24**). Phosphine supported, or first-generation, analogues of **22** (Figure 7) were prepared, characterized crystallographically, and studied computationally but generally demonstrated lower activities and *Z*-selectivities [66].




**Scheme 2.** Formation of **24**.

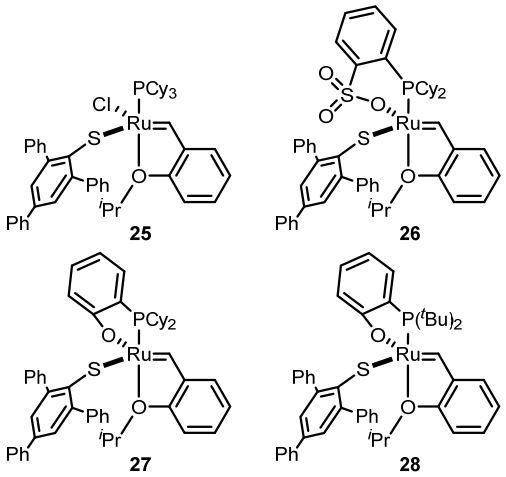



**Figure 7.** Phosphine and bidentate monothiolate catalysts evaluated.

### *2.4. Dithiolate Catalysts*

#### 2.4.1. Catalyst Development

Expanding on their own work in conjunction with Schrock and coworkers developing molybdenum and tungsten *Z*-selective OM catalysts [60–63], the Hoveyda group sought to utilize this large versus small ligand scaffold idea in ruthenium-catalyzed *Z*-selective OM (Figure 8). They believed if a side-bound ruthenacycle was operative, the large axial ligand could force an all *syn* ruthenacyclobutane (Figure 8a). As has been previously discussed, traditional metathesis catalysts are believed to proceed through a bottom-bound ruthenacyclobutane due to unfavorable steric and electronic factors in the side-bound isomer (Figure 8b). Thus Hoveyda and coworkers considered using a bidentate dianionic species to promote a side-bound ruthenacycle, providing the desired catalytic scaffold to achieve a *Z*-selective OM (Figure 8c). Replacing the chlorides with catecholate or catechothiolate (**29**), furnished catalysts with the anticipated ligand arrangement, which performed ring-opening metathesis polymerization (ROMP) and ring-opening cross metathesis (ROCM) with high efficiency and *Z*-selectivity [29,67,68].

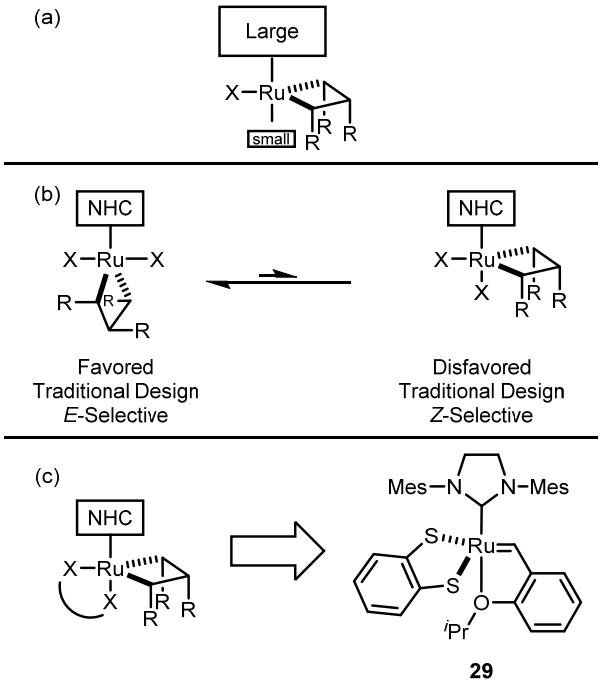



**Figure 8.** Design process for **29**. (**a**) Mimicking the design of the Mo and W *Z*-selective catalyst; (**b**) Observations showing the bottom-bound ruthenacycle is favored; (**c**) Employing a bidentate chelate that would induce a side-bound ruthenacyclobutane.

The application of **29** to the more demanding CM of terminal with internal olefins necessitated catalyst improvements for enhanced stability. Catalyst decomposition was proposed to occur via migratory insertion of the propagating carbene into the ruthenium-sulfur bond *trans* to the NHC [69]. Incorporation of electron-withdrawing halogen substituents into the backbone of the dithiolate moiety theoretically and experimentally resulted in improved catalyst efficiency. Though reactivities and selectivities for catalysts **30**–**34** were similar (Figure 9), **30** has the practical advantage of being readily prepared from commercially available 3,6-dichloro-1,2-benzenedithiol. Complex **30** was subsequently demonstrated to catalyze the CM of *cis*-2-butene-1,4-diol with both a variety of terminal olefins bearing a wide range of functionalities and internal *cis*-olefin bearing substrates, oleyl alcohol and oleic acid.

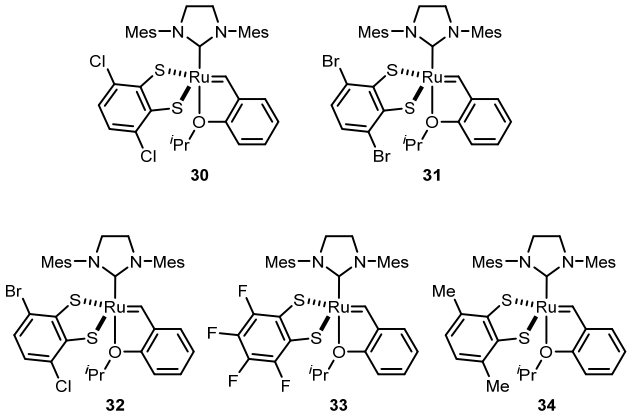
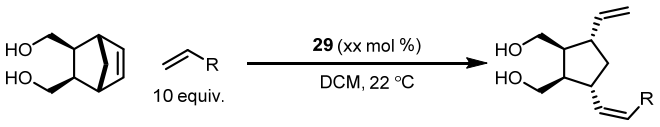


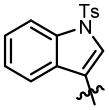
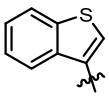
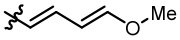
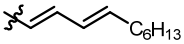

**Figure 9.** Various dithiolate catalysts synthesized by Hoveyda and coworkers.

### 2.4.2. *Z*-Selective Ring-Opening Cross Metathesis

Until recently the only ruthenium-catalyzed *Z*-selective ring-opening/cross metathesis (ROCM) was substrate dependent and relied on complex catalytic design [70]. The dithiolate-based catalyst saw initial success in this relatively uncharted area [29,67,68]. Hoveyda and coworkers provided the first examples of ROCM involving styrenes (Table 10, entries 1 and 2). They continued pursuing the scope of this transformation to expand it to a variety of useful olefins including heteroaryl olefins (Table 10, entries 6 and 7) and dienes (Table 10, entries 8 and 9) as well as employing free alcohols on the norbornene (Table 10). It was noted that allyl ethers performed much poorer than the free alcohols as coupling partners in ROCM. It is proposed that there is a significant *trans* influence conveyed from the NHC to the axial thiolate, thus some electronic charge builds up on the thiolate. When employing a free alcohol as the coupling partner, hydrogen bonding can occur to dissipate the electron repulsion experienced by placing the oxygen and sulfur in proximity (Figure 10, **X**). If an allyl ether is used, no hydrogen bonding can occur, so the two heteroatoms experience repulsion and destabilize the ruthenacycle intermediate (Figure 10, **XI**).

**Table 10.** Ring-opening/cross metathesis (ROCM) of norbornene diols with terminal olefins.




| Entry | *R* | 29 (xx mol %) | Time (h) | Yield (%) | *Z* (%) |
|---|---|---|---|---|---|
| 1 | Ph | 1 | 1 | 92 | 97 |
| 2 | *m*-$FC_6H_4$ | 1 | 1 | 93 | 96 |
| 3 | $(CH_2)_2$OTBS | 5 | 8 | 68 | >98 |
| 4 | $(CH_2)_2$C(O)NHPh | 5 | 8 | 65 | >98 |
| 5 | $(CH_2)_7$Me | 5 | 8 | 58 | >98 |
| 6 |  | 5 | 2 | 93 | 93 |
| 7 |  | 5 | 2 | 97 | >98 |
| 8 |  | 2 | 2 | 84 | 91 |
| 9 |  | 5 | 2 | 80 | >98 |
| 10 | O$^n$Bu | 2 | 2 | 95 | >98 |
| 11 | SEt | 5 | 12 | 80 | 92 |

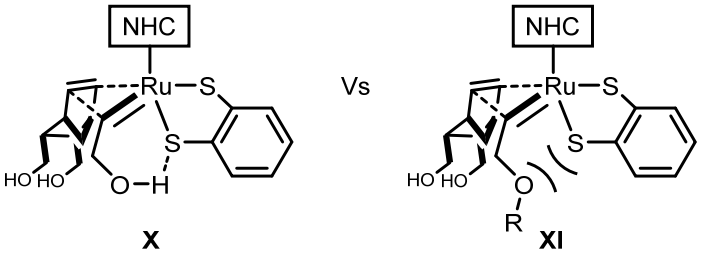
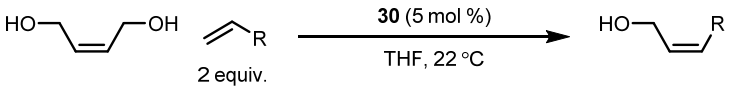


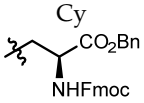
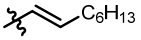
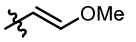
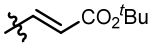
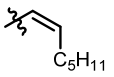

**Figure 10.** Different reactivity observed between allylic alcohols and allylic ethers believed to be a product of electron density buildup on the sulfur atom *trans* to the ***N*-heterocyclic carbene** (NHC).

### 2.4.3. *Z*-Selective Cross Metathesis

Many advances were made in the field of *Z*-selective CM using ruthenium catalysts, but some unmet challenges existed: CM to afford allyl alcohols and use of sterically hindered olefins. Hoveyda and coworkers were able to employ dithiolate catalyst **30** to address this issue [69]. They found that *cis*-2-butene-1,4-diol participated in CM with sterically hindered partners (Table 11), but elevated catalyst loadings are required. Additionally, functionality such as aldehydes (Table 11, entry 7) and free carboxylic acids (Table 11, entry 8) partook in CM. Allyl ether was also tolerated (Table 11, entry 4), which is somewhat surprising considering the issue with these substrates in ROCM previously discussed. Modifications were made to the dithiolate catalyst to make the dithiolate less electron rich to exhibit higher stability. Using computational studies, it was proposed that reducing the electron density on the dithiolate by adding the chlorides in **30** would also weaken the *trans* influence, thus stabilizing the interaction between two heteroatoms seen in Figure 10. Complex **30** also displayed great utility in the CM of disubstituted olefin feedstocks, such as oleic acid, with *cis*-2-butene-1,4-diol to generate high-value *Z*-olefin products.

**Table 11.** CM scope of *cis*-1,4-butene diol with terminal olefins.




| Entry | *R* | Time (h) | Yield (%) | *Z* (%) |
|---|---|---|---|---|
| 1 | $(CH_2)_9Me$ | 4 | 72 | 96 |
| 2 | $(CH_2)_2OTBS$ | 4 | 65 | 93 |
| 3 | $(CH_2)_2OPNP$ | 4 | 74 | 96 |
| 4 | $CH_2O^nBu$ | 12 | 57 | 91 |
| 5 | $(CH_2)_2CO_2Bn$ | 4 | 80 | 98 |
| 6 | $(CH_2)_4Phth$ | 4 | 64 | 98 |
| 7 | $(CH_2)_8CHO$ | 4 | 80 | 94 |
| 8 | $(CH_2)_3CO_2H$ | 4 | 70 | 96 |
| 9* | Ph | 4 | 53 | 94 |
| 10 | Cy | 4 | 59 | 98 |
| 11 |  | 4 | 73 | 98 |
| 12 |  | 8 | 66 | 95 |
| 13 |  | 8 | 63 | 92 |
| 14 |  | 8 | 56 | 96 |
| 15 |  | 8 | 54 | 87 |

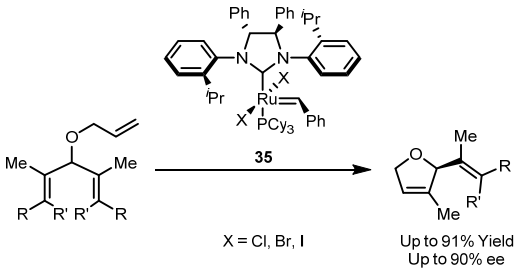
* Entry 9 was carried out using Catalyst 32.

## 3. Asymmetric Olefin Metathesis

### *3.1. General Introduction*

Asymmetric catalysis represents an important area in synthetic organic chemistry. Many asymmetric catalysts find their origins in achiral transformations, but through structural manipulations of the catalyst, the transformation is rendered asymmetric. OM is no exception. Early work employed non-selective molybdenum-, ruthenium-, and tungsten-based catalysts to perform metathesis [1,2,4,5]. Recently, catalytic scaffolds have been modified to create a synthetic pathway to asymmetric structures through metathesis [11,16,17]. Although OM promotes the formation of carbon–carbon double bonds, asymmetric structures can be made indirectly through the desymmetrization of *meso*-compounds.

The first example of asymmetric OM using a ruthenium catalyst employed a chiral NHC ligand [71]. This catalyst performed a desymmetrization of achiral trienes through asymmetric ring-closing metathesis (ARCM), furnishing the cyclic products in high enantioselectivities (Scheme 3). Since this seminal work from Grubbs and coworkers, many studies have commenced with the goal of developing a more selective and efficient ruthenium metathesis catalyst for asymmetric OM [11,17,21]. There have been a variety of catalyst designs to address this issue (Figure 11). Subsequent reports from Grubbs and coworkers continued to use the gearing-effect of the NHC backbone to tailor the steric environment around the ruthenium catalyst (Figure 11a) [72,73]. The Hoveyda group employed $C_1$-symmetric bidentate NHC's that induced chirality at the ruthenium center to control orientation of olefin complexation (Figure 11b) [74–76]. Monodentate $C_1$-symmetric ligands have also been studied in these processes (Figure 11c) [77,78]. The following sections on various asymmetric metatheses will focus on advancements made since 2010.




**Scheme 3.** Seminal example of asymmetric OM employing a $C_2$-symmetric, chiral *N*-heterocyclic carbene (NHC) ligand.

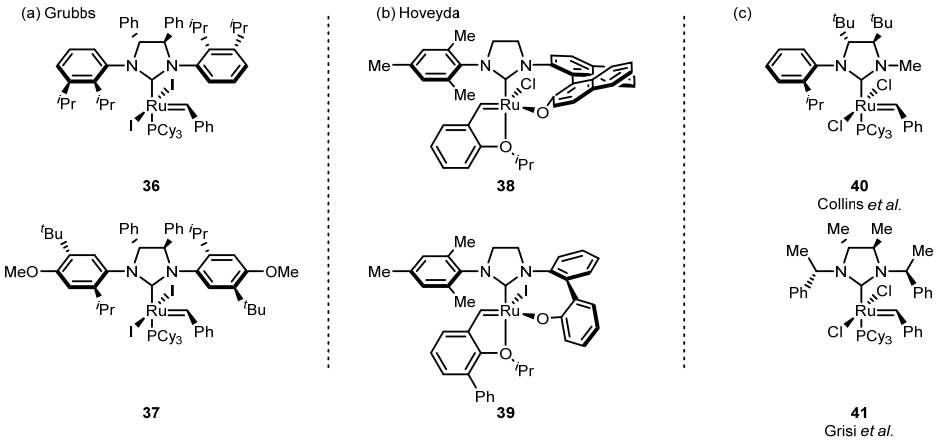
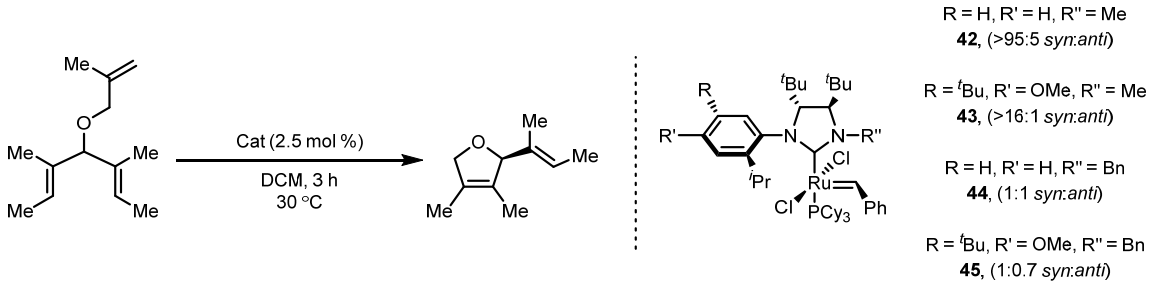



**Figure 11.** Various catalyst designs used to achieve asymmetric OM. (**a**) $C_2$-symmetric NHC ligands employed by Grubbs and coworkers; (**b**) Bidentate NHC ligands employed by Hoveyda and coworkers; (**c**) Geared NHC ligands employed by the Collins and Grisi groups.

### 3.2. Asymmetric Ring-Closing Metathesis

Much progress has been made employing chiral ruthenium catalysts in ARCM to obtain cyclized products in good enantioselectivities and high conversions [71,72,75,77,78]. A persisting challenge in ARCM is the formation of tetrasubstituted olefins. Collins and coworkers revealed ruthenium catalysts bearing a $C_1$-symmetric NHC ligand that performed ARCM to desymmetrize *meso*-trienes, furnishing tetrasubstituted olefinic products (Table 12) [79]. All the catalysts bearing $C_1$-symmetric NHC ligands were isolated as mixtures of both the *syn*- and *anti*-isomers due to difficult separations (*syn* refers to the alkyl group on the NHC ligand residing on the same side as the ruthenium-carbene). Interestingly, slight separation of **45** could be obtained furnishing a mixture of 1:8 *syn*:*anti* (**45** *anti*). Upon assessing the performance of these catalysts in the ARCM to generate a tetrasubstituted olefin moderate to high yields were obtained (Table 12). Unfortunately, modest enantioselectivities were observed, with the highest levels of asymmetry obtained using **45** *anti* (Table 12, entry 5). Six-membered ring formation was also operable when employing **45** *anti*.

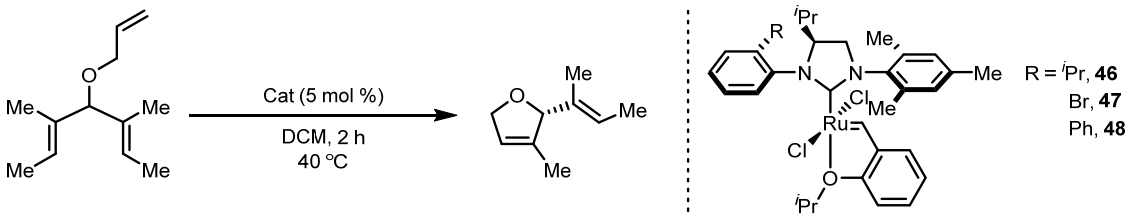
**Table 12.** Asymmetric ring-closing metathesis (ARCM) to form tetrasubstituted olefins using unsymmetrical *N*-heterocyclic carbene (NHC) ligands.




| Entry | Cat | Conversion (%) | ee (%) |
|---|---|---|---|
| 1 | **42** | 95 | 8 |
| 2 | **43** | 95 | 38 |
| 3 | **44** | 90 | 52 |
| 4 | **45** | 86 | 50 |
| 5 | **45** ***anti*** | 46 | 59 |

Many of the catalysts employed in asymmetric metathesis employ a disubstituted NHC backbone, but the Blechert group has explored mono-substituted NHC backbones with two different *N*-substituents (**46**–**48**) [80]. The idea behind this design was to induce significant perturbation on one of the *N*-substituents to enhance the chiral pocket of the catalyst. Moderate levels of enantioselectivity were observed in the ARCM of trienes (Table 13).

**Table 13.** Employment of unsymmetrical NHC ligands in ARCM by Blechert and coworkers.

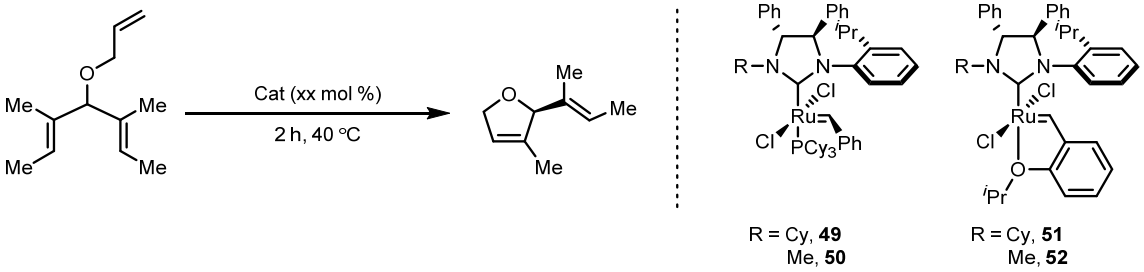



| Entry | Cat | Conversion (%) | ee (%) |
|---|---|---|---|
| 1 | **46** | >98 | 59 |
| 2 | **47** | 58 | 50 |
| 3 | **48** | 87 | 66 |

Ruthenium catalysts employed in ARCM typically use an imidazoline ring system as the NHC-backbone, but Grela and coworkers synthesized a 1,2,4-triazole backbone to assess in ARCM [81]. Unfortunately, the ruthenium catalyst modified by this interesting NHC-scaffold failed to provide any improvement when compared to known catalysts for ARCM and asymmetric ring-opening/cross metathesis (AROCM).

The Grisi group investigated unsymmetrical NHC ligands containing an *N*-alkyl group as well as phenyl groups on the backbone (**49**–**52**) (Table 14) [82,83]. As previously seen, the NHC backbone substitution proved effective in enhancing the stereochemical properties of the catalysts, providing the ring-closed product in moderate enantioselectivity. However, differences in *N*-substitution on enantioselectivity proved to be negligible. It was also observed that the addition of NaI increased the selectivity of the ARCM (Table 14, entries 2, 4, 6, and 8).

**Table 14.** Effects of the *N*-alkyl groups on the enantioselectivity of ARCM using unsymmetric NHC ligands are negligible.



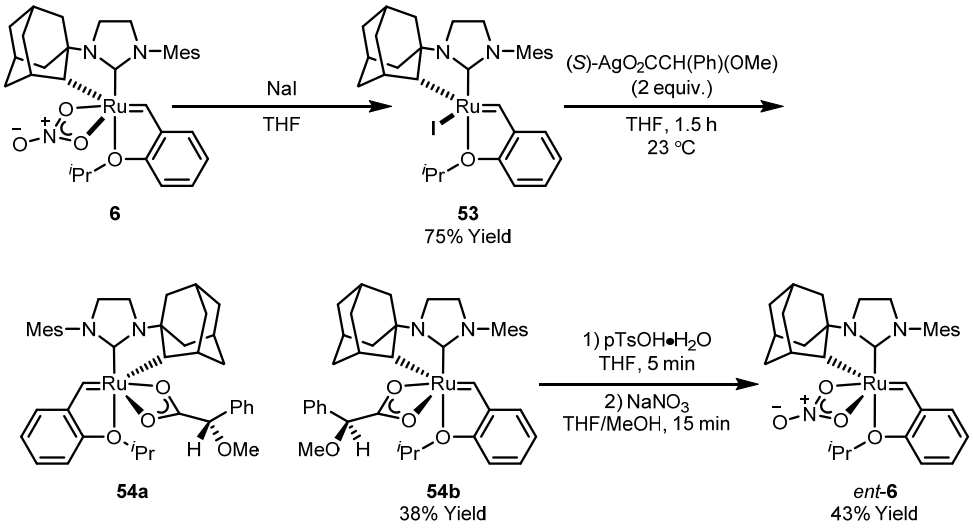

R = Cy, **49**
Me, **50**

R = Cy, **51**
Me, **52**

| Entry | Cat (xx mol %) | Solvent | Additive | Conversion (%) | ee (%) |
|---|---|---|---|---|---|
| 1 | 49 (2.5) | DCM | - | >98 | 18 |
| 2 | 49 (4.0) | THF | NaI | >95 | 53 |
| 3 | 50 (2.5) | DCM | - | >98 | 33 |
| 4 | 50 (4.0) | THF | NaI | >98 | 50 |
| 5 | 51 (2.5) | DCM | - | >98 | 19 |
| 6 | 51 (4.0) | THF | NaI | >95 | 52 |
| 7 | 52 (2.5) | DCM | - | >98 | 33 |
| 8 | 52 (4.0) | THF | NaI | >98 | 47 |

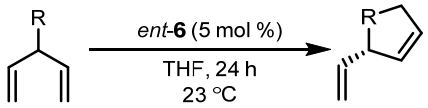
The cyclometalated *Z*-selective ruthenium catalysts presented an interesting opportunity for a chiral-at-ruthenium approach to ARCM [84]. Initially, catalyst **6** was resolved so that a single enantiomer of the catalyst could be used (Scheme 4). This was accomplished through ligand exchange of **6** nitrate for iodide, which was further exchanged for a chiral silver-carboxylate to form **54a** and **54b**. Complex **54b** was then separated from the other diastereomer using trituration techniques. Lastly, treatment of ruthenium-carboxylate **54b** with sodium nitrate furnished *ent*-**6**. When choosing a substrate for ARCM, many methods use substituted olefins because additional substituents can aid in the differentiation of enantiotopic faces of olefins; however, this extra substitution can limit the synthetic utility of the ARCM products. Hence, terminal olefins were chosen as substrates for *ent*-**6**. Additionally, **6** is known to be sensitive to steric bulk at the allylic position, so it was postulated that formation of the alkylidene on the allyl fragment would be favored over carbene formation on one of the enantiotopic olefins. Terminal trienes containing silyl ethers and amides were assessed in the ARCM, generating the ring-closed products in modest to high yields and good enantioselectivities (Table 15). It was also found that when forming less stable rings, ethylene removal played an important role in limiting the reversibility of the reaction, thus enhancing the enantioenrichment of the isolated product (Figure 12). As was observed in the formation of seven-membered rings, when performing the transformation in a closed system, a racemic product is isolated, but when allowing the generated ethylene to escape, modest levels of enantioselectivty are detected (Figure 12a). Ethylene-induced reversibility is not an issue when forming a stable ring system such as five-membered rings (Figure 12b).

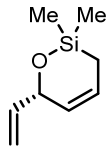
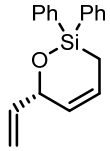
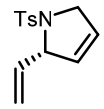
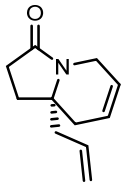
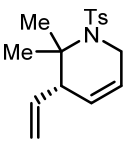
Cyclometalated complexes employing achiral and enantiopure carboxylate ligands (similar to **54b**) were also assessed in this transformation but provided inferior results compared to *ent*-**6**.




**Scheme 4.** Synthesis of *ent*-**6** was carried out through separation of the two diastereomeric salts formed by metalation of (*S*)-methoxyphenylacetate followed by nitration.

**Table 15.** Scope of *ent*-**6** in the ARCM.




| Entry | Product | Yield (%) | ee (%) |
|---|---|---|---|
| 1 |  | 65 | 69 |
| 2 |  | 29 | 67 |
| 3 |  | 95 | 54 |
| 4 |  | 72 | 47 |
| 5 |  | 90 | 57 |

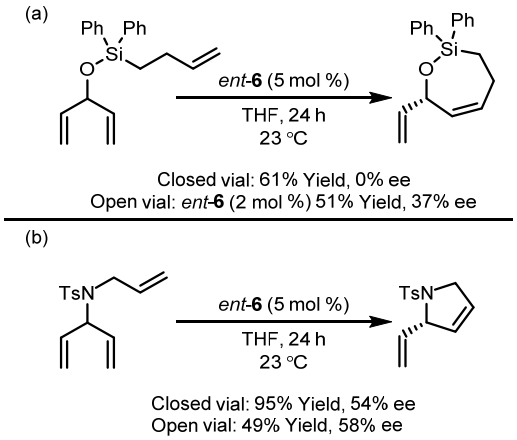
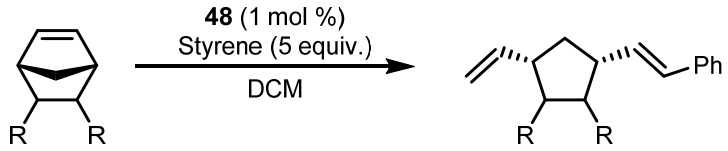


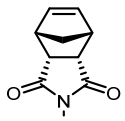
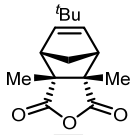
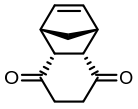
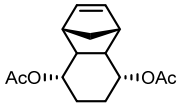

**Figure 12.** Effects of ethylene removal on asymmetric ring-closing metathesis (ARCM). (**a**) Effect of ethylene in ARCM to form seven-membered rings; (**b**) Effect of ethylene in ARCM to form five-membered rings.

### *3.3. Asymmetric Ring-Opening/Cross Metathesis*

Ruthenium-catalyzed AROCM has received much attention over the last few years [73–76]. It seems this method of asymmetric metathesis is more easily controlled because of the inherent facial selectivity for the norbornene substrates which complex through the *exo* face of the olefin [85]. Thus, only the propagating species and its orientation must be controlled. AROCM has become a powerful method for the formation of enantioenriched dienes, which contain differentiated olefins poised for chemoselective derivations [11,86].

**Table 16.** Asymmetric ring-opening/cross metathesis (AROCM) of various substrates with styrene.

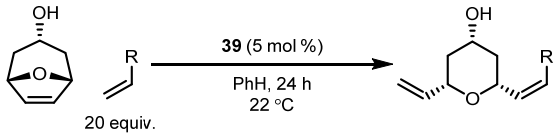



| Entry | Substrate | *T* (°C) | *E*:*Z* | Conversion (%) | ee (%) |
|---|---|---|---|---|---|
| 1 |  | 25<br>−10 | 24:1<br>13:1 | >98<br>>98 | 82<br>92 |
| 2 |  | 25<br>−10 | 21:1<br>23:1 | >98<br>>98 | 82<br>90 |
| 3 |  | 25 | 19:1 | 61 | 86 |
| 4 |  | 25 | >30:1 | >98 | 76 |
| 5 |  | −10 | 21:1 | >98 | 70 |

Blechert and coworkers employed **48** in the AROCM of norbornene derivatives with styrene (Table 16) [80]. It was found that this catalyst provided the desired diene products in good enantioselectivity with a major preference for the *E*-isomer. They found that cooling the reaction increased enantioselectivity (Table 16, entries 1 and 2). Later the Blechert group investigated a quinoline-based ligand scaffold [87]. This quinoline-based system restricted rotation of one *N*-aryl group, anchoring it in position, thus enhancing the chiral pocket for the formation of the ruthenacyclobutane, providing the desired diene in good enantioselectivity (up to 99% conversion and 98% ee).

Hoveyda and coworkers have investigated bidentate NHC ligands with an aryloxy bridge, which provide a stereogenic-at-ruthenium catalyst for AROCM [70,88]. Interestingly, these catalysts furnish the tetrahydropyran products of AROCM, favoring the *Z*-isomer of the disubstituted olefin when using an enol ether or thiol ether as the coupling partner (Table 17). It is believed that a Curtin-Hammett scenario is in effect (Figure 13). The *exo*- (**39a**) and *endo*-intermediates (**39b**) are in equilibrium. If the reaction proceeds through the *exo*-intermediate (**39a**), which is more stable due to the ether group pointing away from the chelating group, the resulting ruthenium-carbene, **39a III**, is less stable because of steric clash between the generated tetrahydropyranyl carbene and the chelating group (Figure 13a). In addition to creating a more sterically unstable intermediate, the stability imparted by the Fischer carbene is lost to the generation of a C-substituted carbene. If the reaction proceeds through the *endo*-intermediate (**39b**), which is the least stable intermediate due to steric interactions between the vinyl ether and the chelating group, the resulting ruthenium-carbene species, **39b III**, is more stable because of a lack of steric interaction between the tetrahydropyranyl carbene and the chelating group (Figure 13b). Even though resonance stabilization of the Fischer carbene is lost, a sterically more stable intermediate is formed (**39b III**), and there is also the driving force from eliminating ring-strain due to the ring-opening event. When using a carbon-substituted coupling partner instead of an enol ether, this Curtin-Hammett effect is not observed [74–76,89].

**Table 17.** AROCM with enol and thiol ethers using a bidentate ruthenium aryloxide.




| Entry | *R* | Yield (%) | *Z*:*E* | ee (%) |
|---|---|---|---|---|
| 1 | $O^nBu$ | 80 | 95:5 | 96 |
| 2 | OCy | 64 | 98:2 | 96 |
| 3 | OPMP | 67 | 95:5 | 94 |
| 4 | $OCH_2CF_3$ | 65 | 94:6 | 92 |
| 5 | $O(CH_2)_2Cl$ | 63 | 95:5 | 96 |
| 6 | SPh | 67 | 91:9 | 92 |

Building on the previously discussed work from the Hoveyda group which used heteroatom-substituted terminal olefins as cross partners in AROCM to furnish the *Z*-isomeric products, Grubbs and coworkers employed *ent*-**6** in the AROCM of norbornene and cyclobutene derivatives with terminal olefins to furnish enantioenriched dienes containing a *Z*-olefin [84,90,91]. When performing AROCM on norbornene substrates, they found good tolerance for ether containing norbornenes (Table 18, entries 1, 4–5). A rigid norbornene derivative also participated in the AROCM (Table 18, entry 3). Interestingly, it was observed that both the *Z*- and *E*-products were formed with identical enantioselectivity. This offered a glimpse into the mechanism (Figure 14a). It was proposed that the enantiodetermining step most likely precedes the olefin geometry-determining step. The enantioselectivity is governed by the approach of the methylidene to the *exo*-face of the norbornene. Also, the *N*-Mes group forces all the bulk in the down direction due to steric effects. Conversely, the enantioselectivity of AROCM of cyclobutenes is different for both the *Z*- and *E*-isomers. In the case

of cyclobutenes, it is believed both the enantio- and diastereodetermining step occur simultaneously (Figure 14b). This could occur if the cyclobutene substrates participate in AROCM with an alkylidene (norbornene only reacts with methylidenes because of steric demands). Since, cyclobutenes are more strained and possess less steric bulk than norbornene species, cyclobutanes are able to react directly with an alkylidene.

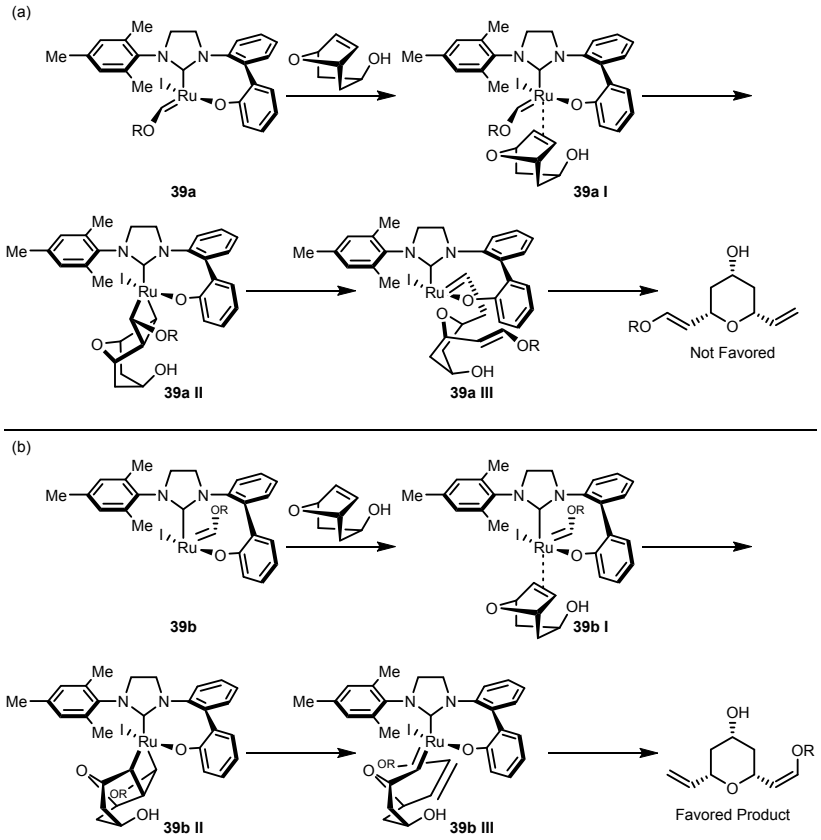
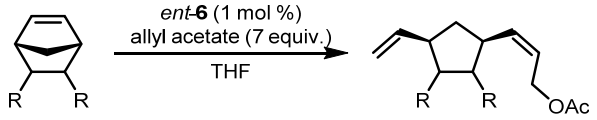



**Figure 13.** Curtin-Hammett effect of Fischer carbene in asymmetric ring-opening/cross metathesis (AROCM). (**a**) AROCM proceeding through an *exo*-intermediate; (**b**) AROCM proceeding through an *endo*-intermediate.

**Table 18.** *Z*-Selective AROCM of norbornenes using the *ent*-**6**.



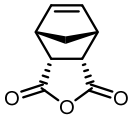

| Entry | Substrate | Yield (%) | *Z*:*E* | ee (%) |
|---|---|---|---|---|
| 1 |  | 64 | 95:5 | 93 |
| 2 |  | 58 | 98:2 | 75 |

**Table 18.** *Cont.*

| Entry | Substrate | Yield (%) | *Z*:*E* | ee (%) |
|---|---|---|---|---|
| 3 |  | 55 | 76:24 | >98 |
| 4 |  OBn | 56 | 15:85 | 94 |
| 5 |  O(*p*-$CF_3$)Ph | 40 | 70:30 | 95 |

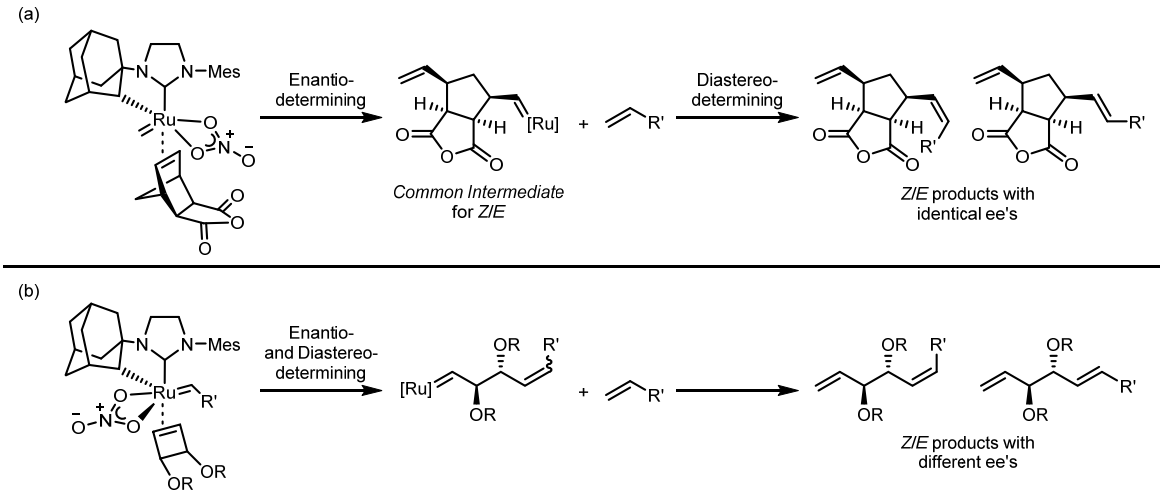
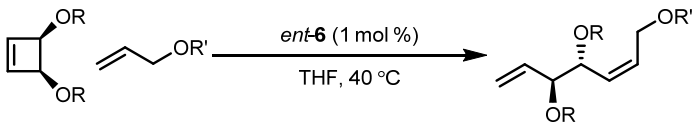



**Figure 14.** Proposed mechanistic differences for AROCM of norbornenes and cyclobutenes with terminal olefins. (**a**) Enantiodetermining step occurs before the diastereodetermining step; (**b**) Enantio- and diastereodetermining events occur in the same step.

Further evaluating the scope of cyclobutenes led to the formation of various 1,2-*anti*-diols (Table 19), which can be derivatized to useful monosaccharides.

**Table 19.** *Z*-Selective AROCM of cyclobutenes using *ent*-**6**.



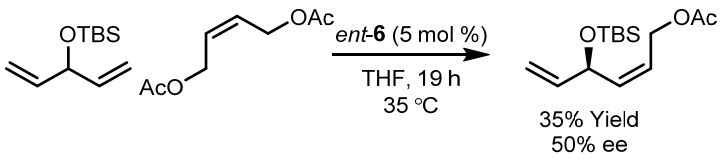

| Entry | *R* | *R′* | Yield (%) | *Z*:*E* | ee *Z* (ee *E*) (%) |
|---|---|---|---|---|---|
| 1 | H | Bz | 67 | 75:25 | 91 (67) |
| 2 | Bz | H | 69 | 75:25 | 96 (82) |
| 3 | Bn | Ac | 79 | 85:15 | 95 |
| 4 | Bn | $CH_2C(O)Me$ | 65 | 90:10 | 92 (84) |

The Grisi group evaluated the previously discussed unsymmetrical NHC ligands (Table 14) in AROCM of *cis*-5-norbornene-*endo*-2,3-dicarboxlic anhydride and styrene [83]. It was found that the catalyst with the more sterically demanding *N*-cyclohexyl rings (**49** and **51**) furnished the diene products in higher enantioselectivities than the catalyst with the *N*-methyl groups (**50** and **52**).

The larger cyclohexyl rings are thought to create a more defined chiral pocket, thus imparting a higher degree of asymmetry on the approach of the carbene species to the norbornene species.

### *3.4. Asymmetric Cross Metathesis*

Asymmetric cross metathesis (ACM) seems to be the most difficult of the asymmetric metathesis transformations due to the requirement of the catalyst to control the stereochemistry of the propagating species and the enantiotopic facial selectivity of the olefin. Since the first example of ACM was published by Grubbs and coworkers [73], progress in the field of ACM has been slower than both ARCM and AROCM. Grubbs and coworkers demonstrated the power of cyclometalated **6** through ACM [84]. By using the previously discussed chiral resolution techniques, they were able to perform ACM with *ent*-**6**, employing this catalyst in the desymmetrization of a *meso*-diene. Complex *ent*-**6** delivered modest levels of enantioselectivity (Scheme 5) and furnished the *Z*-isomer of the product, which is complementary to previous methods which provide the *E*-isomer [73].




**Scheme 5.** Asymmetric cross metathesis (ACM) of *meso*-silyl ether using *ent*-**6**.

## 4. Stereoretentive Olefin Metathesis

As have been previously discussed, *E*-olefins are usually the thermodynamically preferred products of OM. Recent studies have aimed at the development of a kinetically *Z*-selective metathesis catalyst, but unfortunately a catalyst that kinetically selects for *E*-olefins remained elusive [56]. Methods for generating *E*-olefins, such as *Z*-selective ethenolysis, require additional manipulations. One idea for a kinetically *E*-selective catalyst is to create an environment that promotes stereoretention. A number of tungsten-based OM catalysts have shown stereoretention in the self-metathesis of olefinic hydrocarbons [92–94]. Upon further investigation, **30** was found to promote the self-metathesis of both *Z*- and *E*-olefins, affording products that retained the stereochemistry of the starting material in high fidelity [95]. It is believed that the large N-aryl groups on the NHC force the substituents at the 2- and 4-positions of the ruthenacyclobutane down (Figure 15). Thus when using *Z*-olefins, all the substituents on the ruthenacyclobutane are *syn*, in the down orientation, and deliver *Z*-olefinic products. When *E*-olefins are employed, the 2- and 4-positions of the ruthenacyclobutane are still forced down, but there is a space between the large *N*-aryl groups of the NHC that allow the 3-position to adopt an up orientation (Figure 15). This gives rise to an *anti*-ruthenacyclobutane, favoring the formation of *E*-olefins, and delivering a stereoretentive OM of *E*-olefins. The proposed stereochemical model explaining the observed stereoretention was supported by evaluating catalysts with NHC ligands of varied steric encumbrance. It was discovered that as the size of the *ortho*-substituents on the *N*-aryl group began to decrease ($^{i}$Pr > Me > F), the reactivity of the catalyst with *E*-olefins increased. Thus, smaller *ortho*-substituents lead to a larger open space for the substituent at the 3-position to point up, *syn* to the NHC ligand, furnishing *E*-olefins. This effect is observed in the CM of *trans*-4-octene and *trans*-1,4-diacetoxy-2-butene (Table 20). Stereoretention of *Z*-olefins follows the same stereochemical model invoked in *Z*-selective OM [67–69].

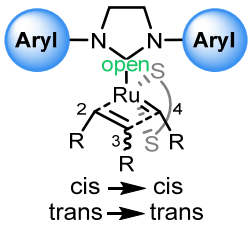
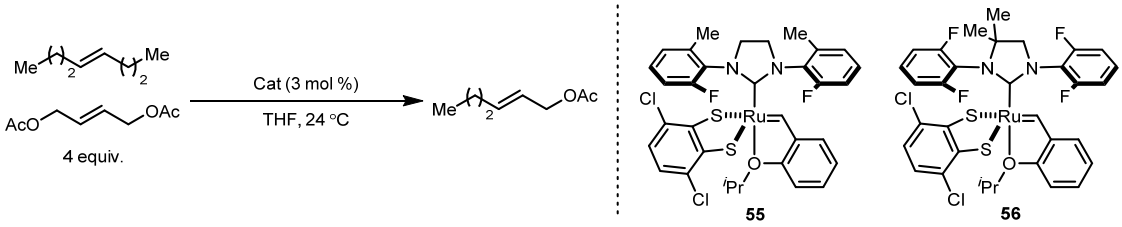



**Figure 15.** Stereochemical model illustrating the steric environment governing stereoretentive OM.

**Table 20.** Effects of *N*-aryl *ortho*-substituents on the reactivity of stereoretentive olefin methathesis (OM).




| Entry | Cat | Time (h) | Yield (%) | *Z*:*E* |
|---|---|---|---|---|
| 1 | **30** | 1 | 0 | <1:99 |
| 2 | **30** | 2 | 2 | <1:99 |
| 3 | **30** | 4 | 4 | <1:99 |
| 4 | **30** | 72 | 13 | <1:99 |
| 5 | **55** | 1 | 2 | <1:99 |
| 6 | **55** | 2 | 5 | <1:99 |
| 7 | **55** | 4 | 11 | <1:99 |
| 8 | **55** | 72 | 24 | <1:99 |
| 9 | **56** | 1 | 4 | <1:99 |
| 10 | **56** | 2 | 7 | <1:99 |
| 11 | **56** | 4 | 14 | <1:99 |
| 12 | **56** | 72 | 28 | <1:99 |

## 5. Stereoselective Olefin Metathesis in Synthetic Applications

Recently, great advancements in stereoselective OM have been achieved. As many of the methods are developed through tedious study of the reaction details, the real impact of these new technologies can be viewed through the lens of synthesis. Incredible progress has been made in applying OM to the formation of materials and complex molecules [5,86,96,97]. The synthetic applications in this section will only discuss recent examples of catalysts which directly impart some stereoselectivity in a transformation and their applications to organic synthesis.

Insect pheromones have received much attention as an alternative pest control method to toxic pesticides [98–100]. Typically, female insect sex pheromones are dispersed in an attempt to disrupt the mating cycle of a species of insect, thus rendering the match-making process more difficult by overloading the male sensory organs and preventing the males from efficiently finding a mate. Seemingly cruel to the insects targeted, this method is much less toxic to other species, which can be affected by the use of pesticides. Grubbs and coworkers have utilized **6** to aid in the synthesis of nine pheromones from the lepidopteran order of insects [101]. Many of the pheromones from this order of insects contain or can utilize a *Z*-olefin in the synthesis [102], thus making **6** a good candidate to streamline the synthesis of these desired compounds. Figure 16 shows these pheromones with the bonds formed using **6** highlighted. The number of steps from commercially available material is also provided.

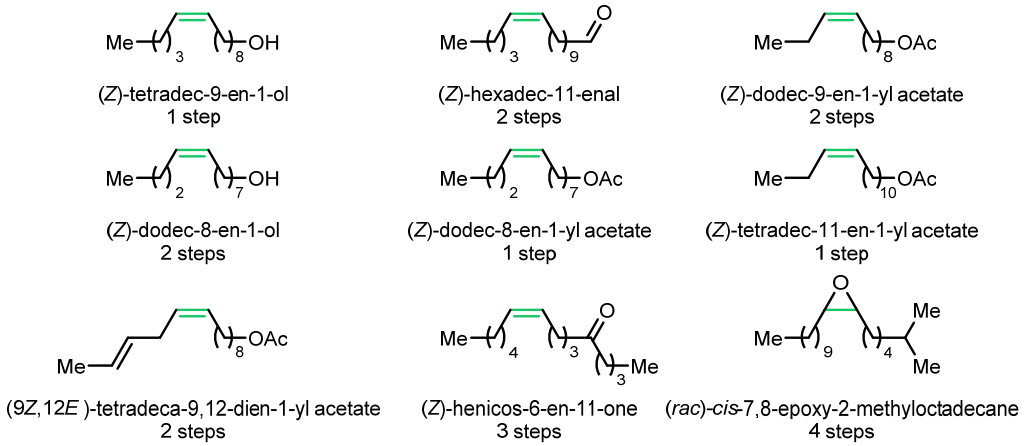
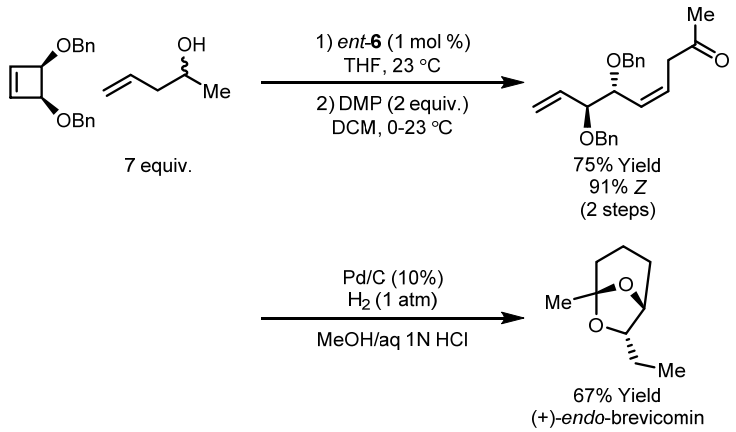



**Figure 16.** Lepidopteran insect pheromones synthesized by Grubbs and coworkers. Bonds formed by OM are highlighted.

As previously mentioned, the Grubbs group utilized *ent*-**6** in the AROCM of *meso*-cyclobutenes to generate 1,2-*anti*-diols [91]. They further elaborated the benzyl substituted diol to (+)-*endo*-brevicomin [103–125], a component of the male attractive pheromone system of *Dendoctonus frontalis* (southern pine beetle) [126]. This was done by oxidizing the AROCM product to the ketone followed by cleavage of the benzyl protecting group to generate the cyclic ketal product (Scheme 6).



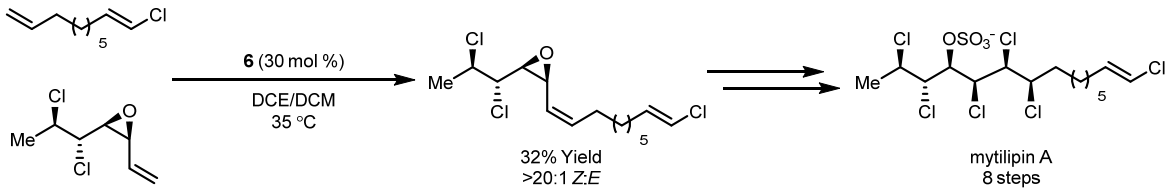

**Scheme 6.** Total synthesis of (+)-*endo*-brevicomin using *Z*-selective asymmetric ring-opening/cross metathesis (AROCM).

Employment of **9** in the synthesis of insect pheromones builds on the methodology that allows *Z*-selective metathesis on 3*E*-1,3-dienes [59]. Using this methodology, access to (*E*,*Z*)-5,7-dodecadienyl acetate [127], a *Malacosoma neustria* and *Dendrolimus punctatus* pheromone, and (*Z*,*E*)-9,11-tetradecadienyl acetate [128], a *Spodoptera littoralis* and *Spodoptera litura* pheromone, was granted.

As previously mentioned, macrocycles play an important role in both the pharmaceutical and fragrance industries. Grubbs and coworkers employed **6** in mRCM to generate an intermediate (*Z*-**19**) in the synthesis of motuporamin C, a cytotoxic marine alkaloid [129,130]. Additionally, **6** was also used to synthesize compounds currently in demand by the fragrance industry (Table 4). As modifications were made to **6** to improve its catalytic activity and selectivity, **9** was also evaluated in these mRCM's [38].

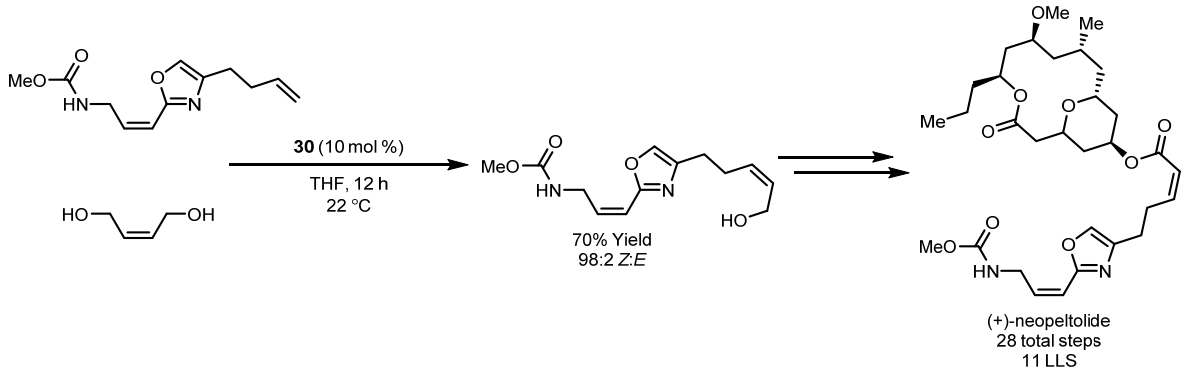
Mytilipin A is a member of the chlorosulpholipid family isolated from Adriatic mussels [131–133]. Its interesting structure has garnered much attention from the synthetic organic community [134–140]. Recently, the Vanderwal group synthesized this molecule using **6** in a key step to bring two pieces

of the molecule together, allowing mytilipin A to be synthesized in a longest linear sequence of only eight steps to the enantioenriched compound [141]. Complex **6** was able to perform OM on a vinyl epoxide, and although the vinyl epoxide product was obtained in poor yield, the selectivity remained exceptional (Scheme 7). Furthermore, this yield is competitive with other catalysts used in previous syntheses of mytilipin A.



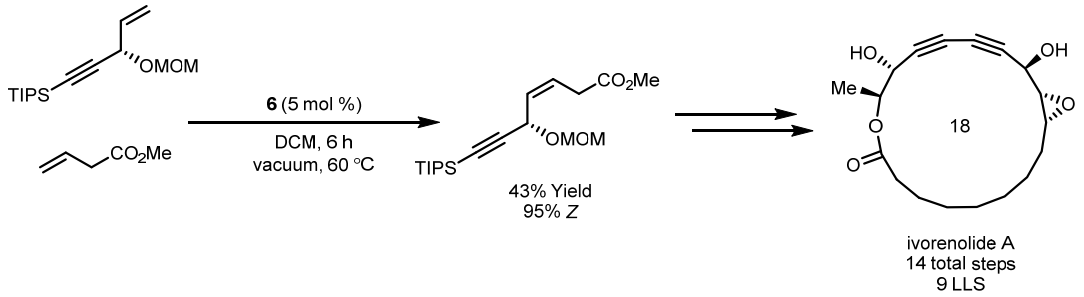

**Scheme 7.** Employment of *Z*-selective cross metathesis (CM) to join two fragments in the total synthesis of mytilipin A.

(+)-Neopeltolide [142] is a macrocyclic marine natural product that has shown antiproliferative activity against a variety of human cancer cell lines and has garnered much interest from the synthetic community [143–149]. Recently, Hoveyda, Schrock, and coworkers reported the shortest synthesis to date with a longest linear sequence of 11 steps while only requiring 28 total steps [150]. They employed four different *Z*-selective OM steps to construct the molecule, one of them employing ruthenium catalyst **30**. This step provided the desired *Z*-alcohol in moderate yield and high *Z*-selectivity (Scheme 8). Further elaboration revealed (+)-neopeltolide.



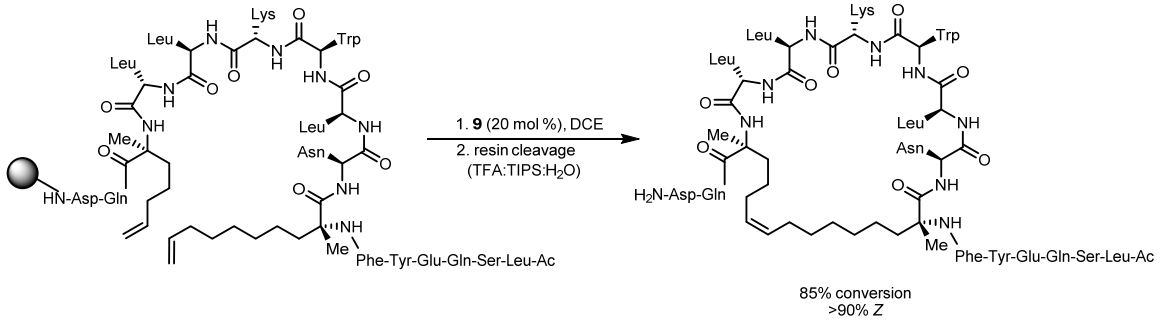

**Scheme 8.** Employment of ruthenium-catalyzed *Z*-selective CM (one of four *Z*-selective CM used) to join two fragments in the total synthesis of (+)-neopeltolide.

*Z*-Selective OM was also used in the formal synthesis of the macrolide ivorenolide A [151]. Ivorenolide A is an immunosuppressant isolated from the bark of *Khaya ivorensis* [152]. Collins and coworkers used **6** in a key step to synthesize one precursor for the Glaser-Hay coupling [153,154] (Scheme 9). They found that reproducibility was improved on larger scale when performing the reaction under vacuum to remove ethylene. It is thought that with increased ethylene availability, the ruthenium-methylidene is more likely to form, thus furnishing a path to secondary metathesis, which could lead to reduced selectivity or homocoupling.



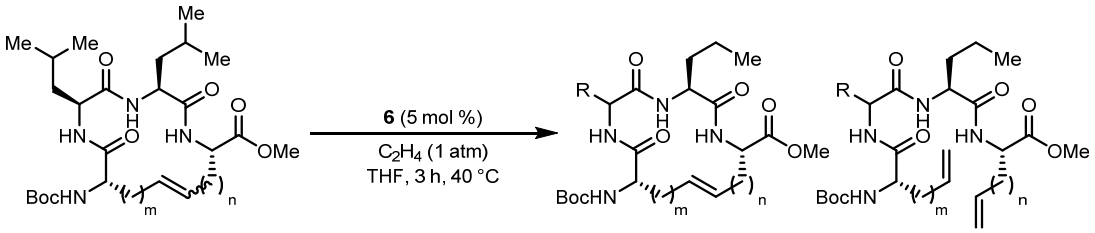

**Scheme 9.** Formal synthesis of ivorenalide A utilizing *Z*-selective CM.

Biological applications are a developing area for OM because of the ability to incorporate amino acids with pendant olefins into peptides and proteins [155–159]. Unfortunately, controlling olefin geometry in amino acid containing products has been difficult. Grubbs and coworkers evaluated *Z*-selective catalysts **6** and **9** in a variety of olefin metatheses of peptides [160]. The homodimerization of canonical amino acids proceeded with good yields and high *Z*-selectivity. Amino acids that performed poorly in this transformation were ones that contain a heteroatom, which could chelate the ruthenium. CM is also operable, delivering the products in modest yield but maintaining high *Z*-selectivity. Representative sequences found in parallel β-sheets also participate in CM. RCM to form "stapled" peptides was also probed (Scheme 10). High conversion and excellent *Z*-selectivity was observed with one of the most complicated structures assayed using **9**. Additional studies to generate macrocyclic peptides *via* RCM have been completed [161]. *Z*-selective ethenolysis can also be employed to form macrocyclic peptides with high *E*-content (Table 21) [161].




**Scheme 10.** Employment of 9 in ring-closing metathesis (RCM) to generate "stapled" peptides.

**Table 21.** *Z*-selective ethenolysis to furnish high *E* macrocyclic peptides.

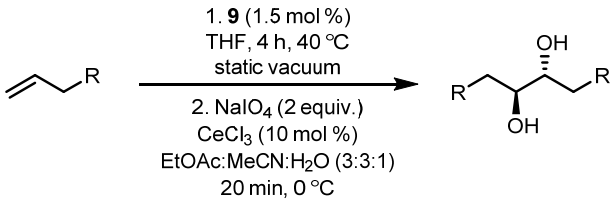



| Entry | *m* | *n* | Initial *E*:*Z* | Yield (%) | Final *E*:*Z* |
|---|---|---|---|---|---|
| 1 | $CH_2$ | $CH_2$ | 90:10 | 77 | >99:1 |
| 2 | $CH_2OCH_2$ | $CH_2OCH_2$ | 81:19 | 64 | 98:2 |
| 3 | $CH_2SCH_2$ | $CH_2SCH_2$ | 90:10 | 77 | 99:1 |

Assisted tandem catalysis is a method that employs a single catalyst to perform multiple transformations. Ruthenium metathesis catalysts have been utilized in transformations as C–C

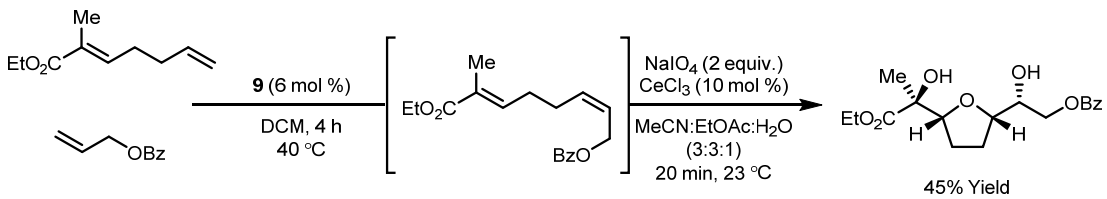
bond forming agents that can promote additional structural elaborations [162–168]. CM promoted by **1** followed by dihydroxylation using $NaIO_4$ as an oxidant delivered diol products through ruthenium-catalyzed dihydroxylation. The ruthenium alkylidene functioned as the oxidation catalyst in the presence of $NaIO_4$ [167–172]. Dihydroxylation is a stereospecific process, and because the metathesis was under thermodynamic control, the *E*-olefin was formed in excess leading to *syn*-diols. *Anti*-diols, which are important moieties in natural products, were inaccessible with this method since *Z*-olefins are required. Grubbs and coworkers utilized **9** in this transformation, as **9** is highly *Z*-selective and promotes the formation of *anti*-diols [173]. Many stereodefined *anti*-diols containing various functionalities could be prepared using this method (Table 22). Additionally, this transformation displayed scalability, as the reaction using the benzoate (Table 22, entry 3) could be performed on gram-scale furnishing the product in 66% yield.

**Table 22.** *Anti*-diols synthesized through tandem catalysis.




| Entry | *R* | Yield (%) |
|---|---|---|
| 1 | $OCO^nPr$ | 72 |
| 2 | OAc | 59 |
| 3 | OBz | 71 |
| 4 | $OCO_2Ph$ | 61 |
| 5 | NHTs | 70 |
| 6 | NHCBz | 53 |

Tetrahydrofuran (THF) diols are found in a wide variety of natural products [174–177]. A convenient method for the formation of THF diols is through the oxidative cyclization of 1,5-dienes to form 2,5-disubstituted THF diols. Early work found that permanganate could mediate this process [178], but subsequent work discovered $RuO_4$ [179] and $OsO_4$ [180] could also perform this cyclization in the presence of an oxidant such as $NaIO_4$. It is accepted that this transformation proceeds through sequential [3+2] cycloadditions followed by hydrolysis of the metallo ester to deliver the THF diol [181]. As seen in the dihydroxylation example, olefin geometry controls the stereochemistry of each dioxygenation step, and the cyclization step is stereoselective, typically favoring the *cis*-2,5-disubstituted THF. Grubbs and coworkers took advantage of this process and combined it with OM to perform an assisted tandem metathesis/oxidative cyclization to generate 2,5-disubstituted THF diols [182]. Although the majority of the work reports utilizing **1**, which provides the *syn*-1,2-dioxygen product, they demonstrate that **9** also participates in this tandem process, furnishing the *anti*-1,2-dioxygen species (Scheme 11).




**Scheme 11.** Formation of tetrahydrofuran (THF) diols through ruthenium-catalyzed tandem *Z*-selective CM/oxidative cyclization.

## 6. Conclusions

The discovery of well-defined ruthenium OM catalysts has opened the door for investigations into the structure-activity relationships of the ligand framework. Further pursuits into the design of stereoselective ruthenium metathesis catalysts have led to interesting discoveries and a much enhanced understanding of the role olefin complexation and the ruthenacyclobutane play in the setereoselectivity of OM. These ideas have led to incredible advancements in the synthesis of *Z*-olefins. Three major catalyst designs rose to meet this challenge: cyclometalated catalysts, monothiolate catalysts, and dithiolate catalysts. These systems have proven extremely powerful in homodimerization, CM, ROCM, and mRCM. Consequently, synthetic and industrial applications of these catalysts have been implemented. Progress has also been achieved in the area of asymmetric OM. Chiral catalysts have been employed to furnish useful synthetic products by way of ARCM, AROCM, and ACM. These transformations have led to the development of new and interesting catalytic designs that complement the understanding gained in other areas of metathesis. Stereoretentive OM represents the first example of a kinetically *E*-selective OM process. Continued research on these catalysts will assist the development of new and exciting OM catalysts for implementation in the synthetic chemist's toolbox to aid in the synthesis of valuable chemical products.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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