

INTRODUCTION

Development of metathesis chemistry has comprised some of the largest contributions to synthetic methodology in the late 20th century. Metathesis can take place within three reaction manifolds: alkene, alkyne, and enyne metathesis. In all three of these reactions there is a redistribution of covalent bonds between the reacting partners. Enyne metathesis unifies an alkene and an alkyne to form a conjugated diene system in an atom economical fashion. This reaction can be conducted both intramolecularly and intermolecularly (Scheme 1). Although enyne metathesis is the least studied of the three-metathesis reactions it contains the potential of being the most powerful. Diene products can be utilized for sequential complexity-generating transformations and enyne metathesis intermediates can be harnessed in cascades that generate polycycles in a single step.

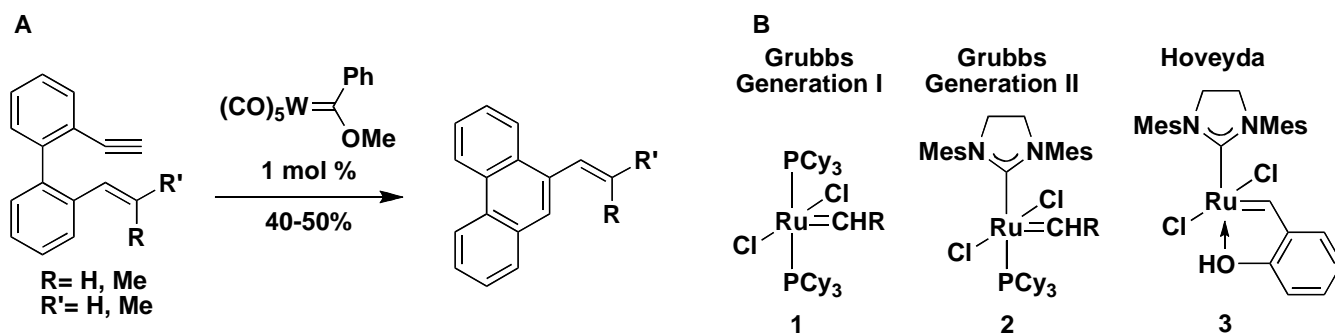
Scheme 1. Enyne Metathesis Variants



HISTORY AND EARLY DEVELOPMENTS

Katz and Sivavec reported the first enyne metathesis reaction in 1985.ⁱ In this seminal publication they reported a new rearrangement between an alkene and an alkyne promoted by a tungsten Fischer carbene providing a phenanthrene product (Scheme 2a). Subsequent publications demonstrated expansion of substrate scope and the use of different metal carbenes including molybdenumⁱⁱ and chromium.ⁱⁱⁱ The use of Fischer carbenes however had several limitations including suffering from low yields, undesired byproducts, and the use of a stoichiometric amount of carbene.

Scheme 2. a) Initial Demonstration of Enyne Metathesis. b) Ruthenium Carbene Catalysts



Enyne metathesis was fortunate to benefit from developments in olefin metathesis, especially in the area of catalyst development. The invention of the more active carbene catalysts shown in figure 2b greatly improved the catalyst loading, reaction yield, substrate scope, and functional group tolerance of enyne metathesis.^{iv} Grubbs generation I catalyst **1** initially revolutionized the field of enyne metathesis. Replacement of one of the tricyclohexyl phosphine ligands with a N-heterocyclic carbene led to the more active Grubbs Generation II catalyst **2**. The phosphine free complex **3** developed by Hoveyda and coworkers also is an excellent catalyst for enyne metathesis. Since these initial discoveries and developments, much effort has been spent expanding the scope of enyne metathesis as well as using this reaction in complex molecule synthesis.

INTRAMOLECULAR ENYNE METATHESIS

Mechanism

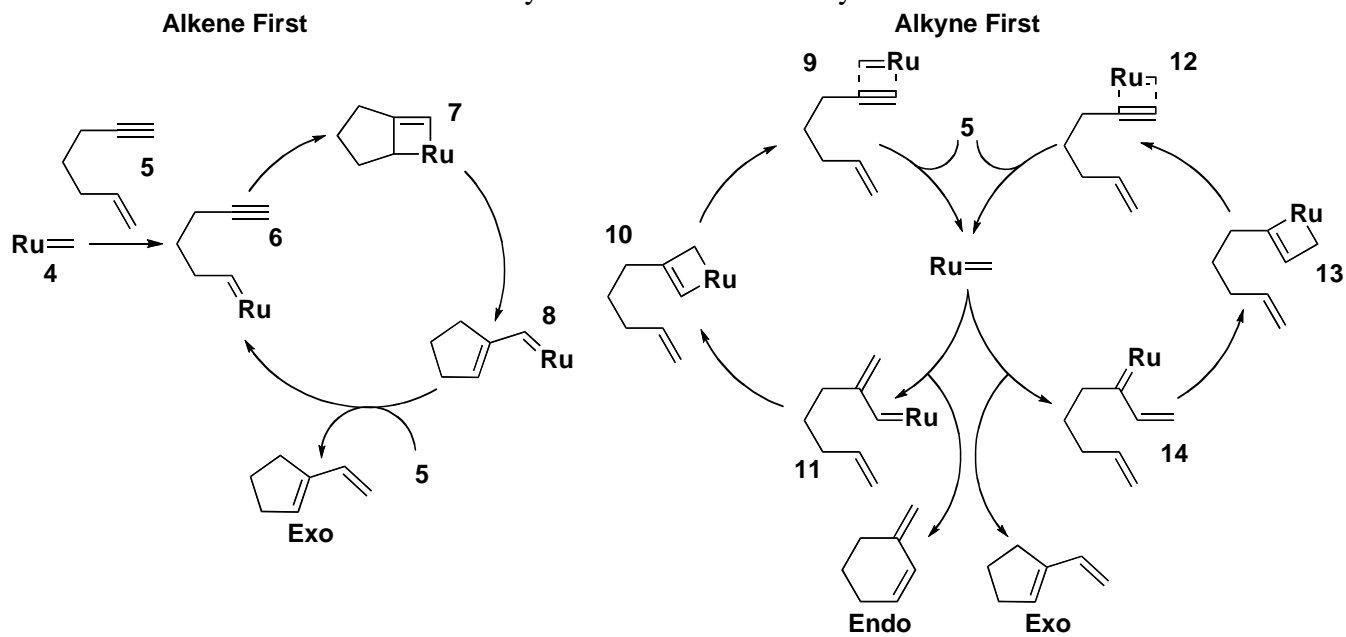
The possible mechanistic pathways for intramolecular enyne metathesis are shown in scheme 3.^v Upon association of active ruthenium methylidene catalyst **4** with 1,6 enyne **5** two distinct pathways are possible, either association with the alkene or association with the alkyne. If **5** inserts into the alkene via a [2+2], retro [2+2] mechanism new alkylidene **6** is produced. This species can then undergo intramolecular [2+2] with the alkyne generating ruthenacyclobutene **7**. Cycloreversion releases alkylidene **8** which upon next iteration of the catalytic cycle produces the “exo” product. The name “exo” refers to the exocyclic double bond generated during the course of the reaction. Alternatively, **4** could associate with the alkyne. Union with the terminus of the alkyne leads to metallacyclobutene **10**, which yields alkylidene **11** upon cycloreversion. Ring closing metathesis of **11** forms the “endo” product as both olefins are contained in the ring structure of the product. If the catalyst initially associates with the alkyne’s internal carbon, metallacyclobutene **13** is formed. Upon cycloreversion, vinyl alkylidene **14** is formed which is capable of ring closure to produce the “exo” product cyclopentene.

Endo: Exo Selectivity

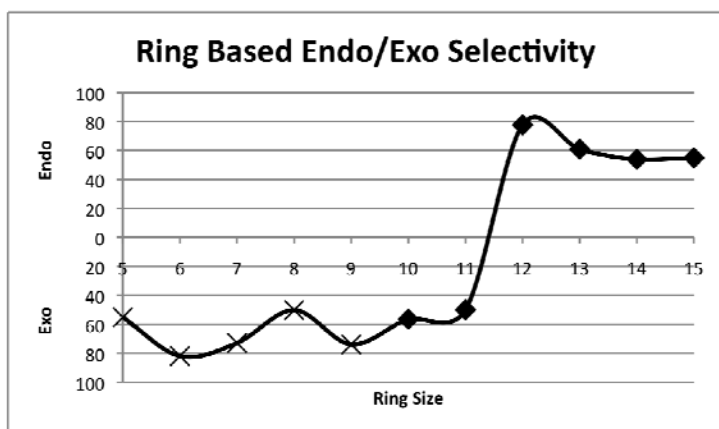
Since two ring products are mechanistically accessible the Lee group undertook a systematic study to determine the native endo: exo selectivity based on ring size.^{vi} Previous literature reports had studied the formation of medium sized rings up to 9 members in size (shown as X’s on the graph).^{vii} Ring sizes between 5 and 9 members displayed distinct exo selectivity. The Lee group demonstrated that further expansion of the ring to 11 members still displayed exo selectivity, but the trend transitioning between eleven and twelve membered rings. Rings larger than 11 atoms show distinctive endo selectivity. The selectivity arises from the ring strain associated with formation of either of the metallocyclobutenes shown in Scheme 5. For formation of medium sized rings up to 11 members,

ruthenacyclobutene **15** is the lowest energy conformation where as 12 membered rings and larger prefer conformation **16**.

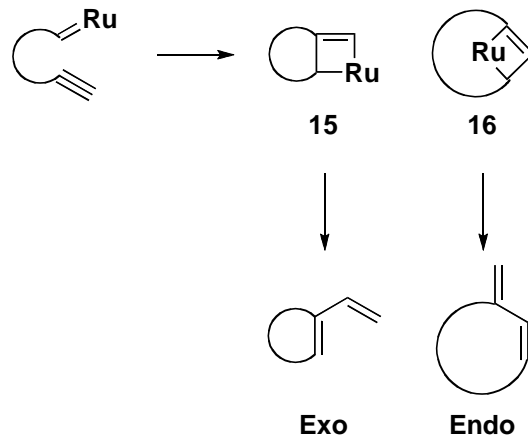
Scheme 3. Possible Mechanistic Pathways for Intramolecular Enyne Metathesis



Scheme 4. Ring Size Based Endo/Exo Selectivity



Scheme 5. Possible Intermediates

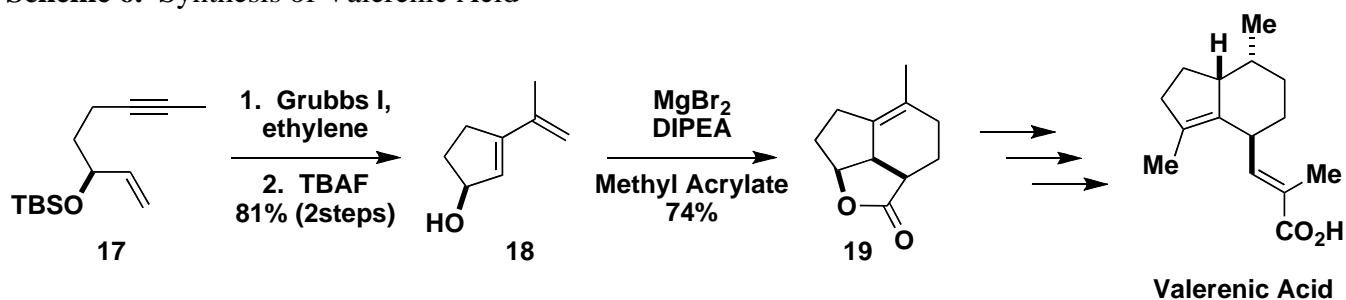


Applications in Synthesis

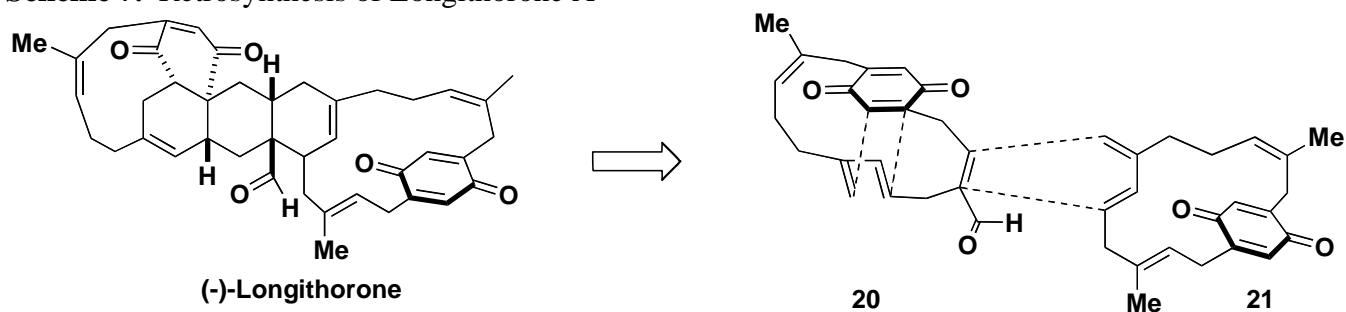
The inherent selectivity for small-to-medium-sized rings to form “exo” rings is utilized in the total synthesis of Valerenic Acid.^{viii} The synthesis begins with enyne **17** which undergoes ring closing enyne metathesis with Grubbs first generation catalyst to provide vinyl cyclopentene **18** upon desilylation. Metal-templated intermolecular Diels-Alder then provided tricyclic lactone **19**. This intermediate was further elaborated through multiple steps to Valerenic Acid. The Shair group highlights macrocyclization producing “endo” rings in the biomimetic synthesis of Longithorone A (scheme 5).^{ix}

The retrosynthesis is based on a possible biosynthesis proposed by the Schmitz group.^x A sequence of an intermolecular Diels-Alder reaction, followed by an intramolecular Diels-Alder reaction, forms the complete carbon skeleton of this natural product. The intermolecular Diels-Alder partners are both created through macrocyclic enyne ring closing metathesis. Both of the syntheses presented not only demonstrates endo:exo selectivity based on ring size, but that enyne metathesis products used in conjunction with Diels-Alder reactions generate complex architectures quickly.

Scheme 6. Synthesis of Valerenic Acid



Scheme 7. Retrosynthesis of Longithorone A

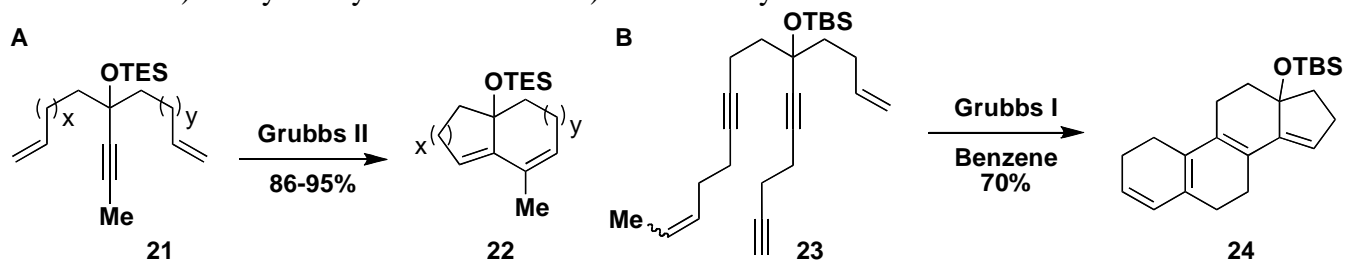


Cascade Reactions

Another approach to generating polycyclic structures is through a cascade involving multiple iterations of various metathesis reactions. The simplest demonstration is the formation of [x.y.0] bicyclic compounds by the Grubbs group (scheme 7a).^{xi} Dienynes **21** of various x and y tether lengths undergo ring closing enyne metathesis followed by ring closing diene metathesis to afford bicyclic compounds **22**.

Bicyclic structures, however, are the simplest polycycles that can be formed. Undergoing a cascade reaction in which a combination of several ring-opening metathesis (ROM) and/or ring closing metathesis (RCM) reactions takes place allows for the formation of a variety of complex polycycles. One of the earliest and most impressive transformations is the creation of the steroid skeleton **24** by Grubbs and co-workers in 1998(scheme 7b).^{xii} In this reaction, acyclic precursor **24** undergoes a cascade enyne metathesis promoted by Grubbs' first generation catalyst to create four new rings and four new carbon-carbon sigma bonds.

Scheme 8. A) Dienyne Enyne Metathesis. B) Cascade Enyne Metathesis

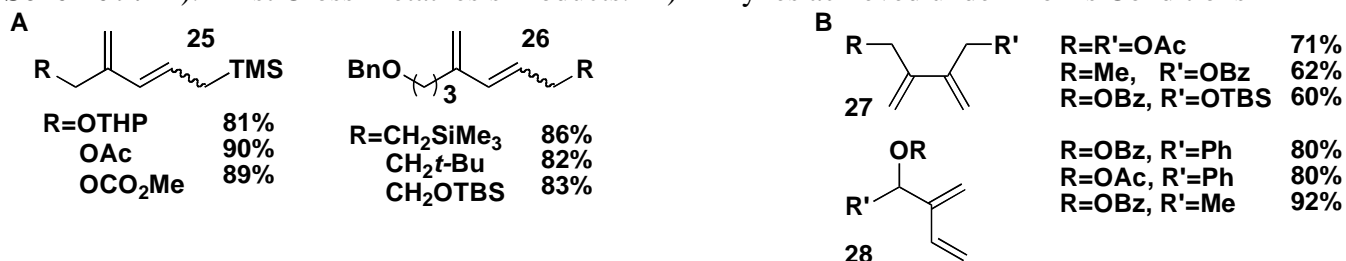


Both bicycle formation and more complex structures have been synthesized via iterative metathesis reactions. Movassaghi and coworkers completed a synthesis of the antitumor agent (-)-irofulven featuring a dienyne ring closing enyne metathesis.^{xiii} More complex cascades similar to the Grubbs steroid cascade have been used sparingly in the context of natural product synthesis. The Spring group accessed an interesting pentacyclic structure via a RCM, ROM, RCEYM, Diels-Alder cascade.^{xiv}

INTERMOLECULAR ENYNE METATHESIS

The first cross enyne metathesis was reported in 1997 by Blechert and coworkers.¹⁰ By combining terminal alkynes and terminal olefins with Grubbs' first generation catalyst, several substituted 1,3 dienes were prepared. They discovered that reaction of propargylic ethers, acetates and carbonates allyl silane products products of the type **25**. They also observed that allylic silanes, silyl ethers, and *tert* butyls products (**26**) could be formed. Several shortcomings were observed with this process. Although a variety of substituted alkenes were compatible partners, the ratio of E: Z isomers obtained ranged from 1:1 to 2:1. Also, competition arises between enyne metathesis and cross diene metathesis and/or cross diyne metathesis. This is suppressed in intramolecular metathesis due to increased effective molarity between the reaction alkene and alkyne. Despite these drawbacks, several unique solutions and applications of cross enyne metathesis have been reported.

Scheme 9. A). First Cross Metathesis Products. B) Alkynes achieved under Mori's Conditions



Mori's Conditions

To address both E:Z selectivity as well as alkene and alkyne dimerization, the Mori group used ethylene as the alkene partner.^{xv} Since ethylene is an unsubstituted alkene, E: Z isomers are not possible upon cross metathesis with an alkyne. The use of ethylene also limits the possible reaction pathways that can occur. Alkene cross metathesis is eliminated because such a reaction with ethylene is degenerate. In addition, by running the reactions at low concentrations of alkyne and high concentrations of ethylene,

the probability of diyne metathesis is greatly reduced. Therefore use of Grubbs first generation catalyst under an atmosphere of ethylene, a variety of internal and terminal alkynes such as **27** and **28** could be formed. These products included propargylic tosyl amides and acyl or benzyl alcohols as well as pendant silyl ethers, esters, and ketones.

The Mori group noted additional benefits to the use of an atmosphere of ethylene in both inter and intramolecular metathesis reactions even when ethylene is not used as the partner alkene. Faster reaction rates were observed, presumably from decreased time spent in the resting state of inactive catalyst species. Also cross metathesis reactions have been reported to proceed with greater E selectivity under these conditions.^{xvi} Performing an enyne metathesis under an atmosphere of ethylene is now known as “Mori’s conditions”. Mori’s conditions have found some utility in natural product synthesis notably as the final step in the synthesis of Amphidinolide V.^{xvii}

Alternative Methods

Achieving a high degree of stereocontrol and regiocontrol using substituted alkenes remains a challenge in enyne cross metathesis. The use of ethylene is one approach however the Lee group has developed several alternative methods using substrate control to access acyclic 1,3-Dienes in a regio- and stereoselective manner.^{xviii} Using pinacol boronic ester substituted alkynes high degrees of E or Z selectivity can be achieved. Several of the products obtained from this method are portrayed in Scheme 10. The rationale for the observed stereoselectivity has not been fully elucidated yet. This method has however found utility in the realm of total synthesis as the natural product (-)-amphidinolide K was recently accomplished using an intermolecular enyne cross metathesis using a pinacol boronic ester substituted alkyne.^{xix} This synthesis is also notable as it is the first cross metathesis used in the context of total synthesis that does not use ethylene as the reacting alkene.

Scheme 10. Stereoselective Cross Metathesis

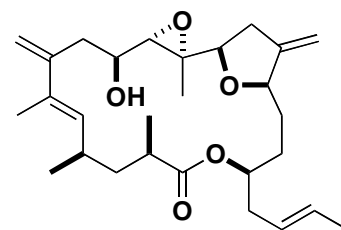
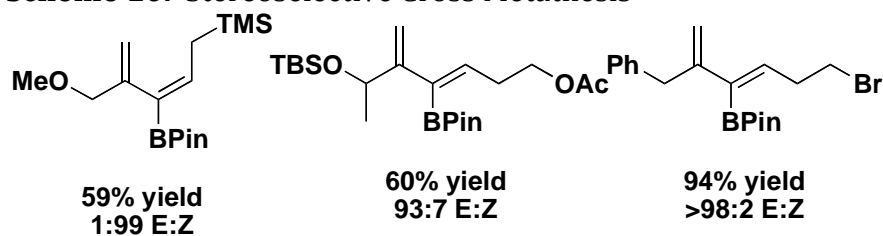


Figure 1. (-)-Amphidinolide K

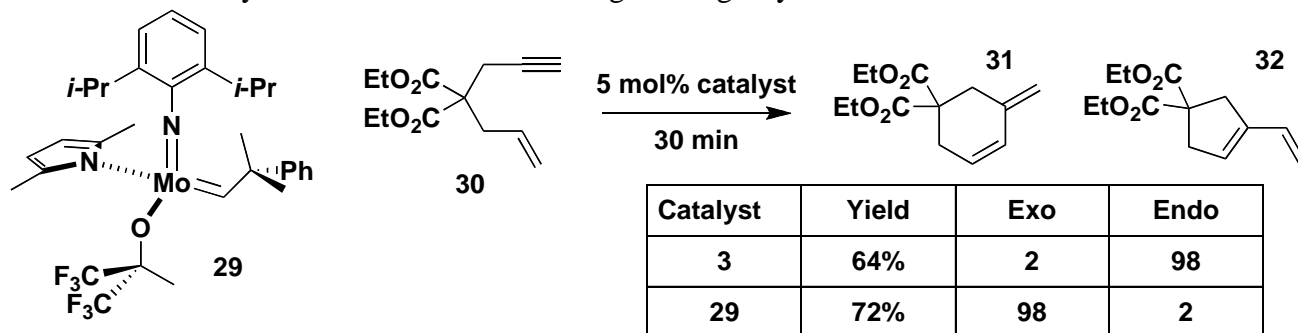
RECENT DEVELOPMENTS

Endo Selective Ring Closing Metathesis

As discussed previously, typical conditions will form medium sized rings in an exo selective manner. Endo products could also be useful synthetic intermediates. Schrock and Hoveyda demonstrated that utilizing stereogenic-at-molybdenum catalysts leads to selective formation of endo selective

medium rings (scheme 11).^{xx} Theoretical studies of enyne metathesis predicted that high oxidation state metals would favor initial association with the alkyne.^{xxi} Placement of substantial bulk at the catalyst center would direct the metal to the terminus of the alkyne therefore favoring the formation of endo products. A series of experiments led them to molybdenum catalyst **29**. It was demonstrated that enyne **30** could be converted to either endo product **31** or exo product **32** solely by proper catalyst choice.

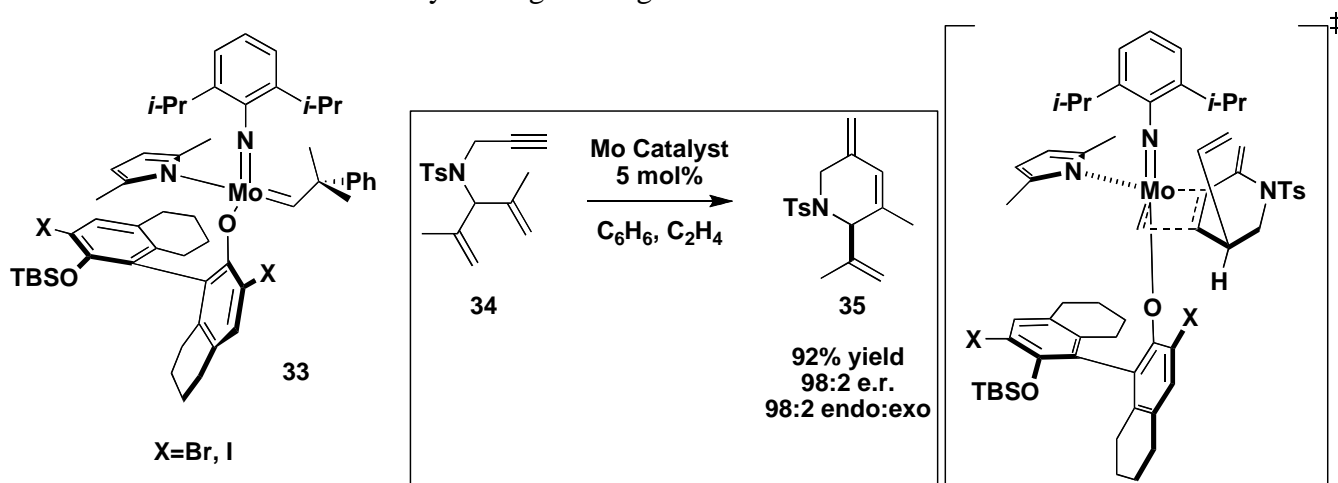
Scheme 11. Catalyst Control of Endo/Exo Ring Closing Enyne Metathesis



Scheme 5: Enantioselective Enyne Metathesis
Enantioselective Ring Closing Metathesis

The collaboration between Schrock and Hoveyda also produced the first example of an enantioselective enyne ring-closing metathesis (scheme 12). Replacing the alkoxide ligand of catalyst **29** with a chiral biphenyl alkoxide ligand produced chiral catalyst **33**. Exposure of propargyl tosyl amide **34** to this catalyst under Mori's conditions produced enantioenriched triene **35**. The transition state in scheme 12 provides a possible explanation for the observed enantioselectivity. The biphenyl ligand provides a floor that imparts steric hindrance. If the exocyclic olefin points down it feels steric hindrance from into chiral ligand. Alternatively placing the olefin up and hydrogen down creates a lower energy conformation favoring the formation of the observed enantiomer.

Scheme 12. Enantioselective Enyne Ring Closing Metathesis



CONCLUSIONS AND FUTURE OUTLOOK

Enyne metathesis has undergone significant improvements since its discovery in 1985. The growing number of applications in total synthesis and continued interest in methodological development demonstrate the utility of this transformation. Enyne metathesis has shown its ability to rapidly generate molecular complexity either through a cascade process of various metathesis reactions or sequential applications of enyne metathesis and Diels-Alder reactions. Of course there are still shortcomings to this reaction. Cross metathesis still proceeds with low E/Z selectivity and only a few substitution patterns are currently accessible in a predictable manner. Also, further development of the enantioselective ring closing metathesis is needed in order to access more general cyclic systems, such as an entirely carbocyclic ring.

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