

RUTHENIUM CATALYZED ENYNE METATHESIS

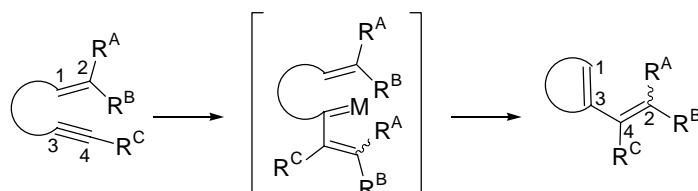
Reported by Justin I. Montgomery

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INTRODUCTION

With the discovery of new, well-defined and mild catalysts, olefin metathesis has transcended its original application to polymer chemistry and has become a powerful synthetic tool used in the preparation of many complex target molecules.¹ However, the related enyne metathesis, involving reaction between an alkene and an alkyne, has received much less attention. Intramolecular enyne metathesis involves the transition metal catalyzed carbon-carbon bond formation between an alkyne and an alkene (C-1 to C-3, Scheme 1). Subsequent alkylidene migration from the alkene to the other alkyne carbon (C-4) yields the 1,3-diene product.² Overall, two new C=C bonds are formed and the starting alkyne is reduced to a single bond. Unlike olefin metathesis, all carbons from the starting material are retained in the product, and this product contains a synthetically useful 1,3-diene moiety that can be elaborated through a Diels-Alder reaction or other transformations.

Scheme 1. Enyne Metathesis.

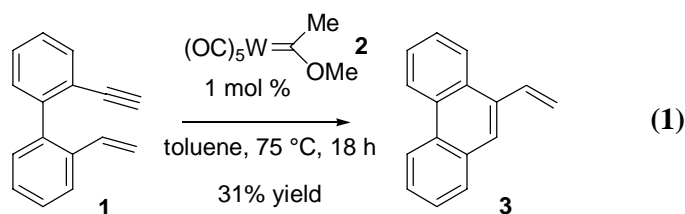


In the short time since its discovery in 1985,³ the scope and limitations of enyne metathesis have been studied extensively. Today, the importance of enyne metathesis in synthetic organic chemistry is evident by its application towards several complex molecule targets.

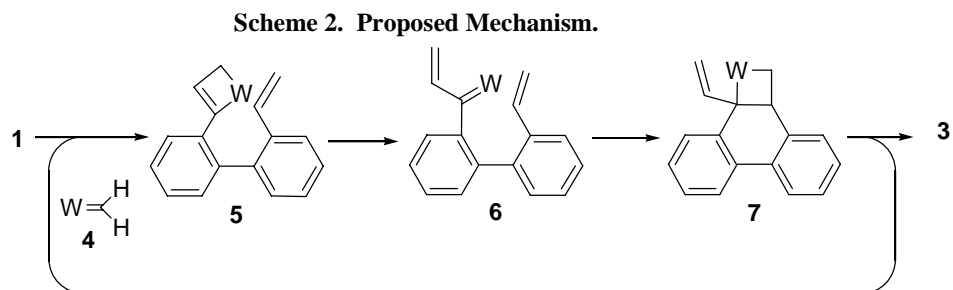
DISCOVERY AND EARLY WORK

Intramolecular Enyne Metathesis Catalyzed by Tungsten Carbene Complexes

Enyne metathesis was first described by Katz³ in 1985 (Equation 1). Treatment of enyne **1** with a catalytic amount of tungsten carbene complex **2** gives rearranged diene **3** in 31% yield.



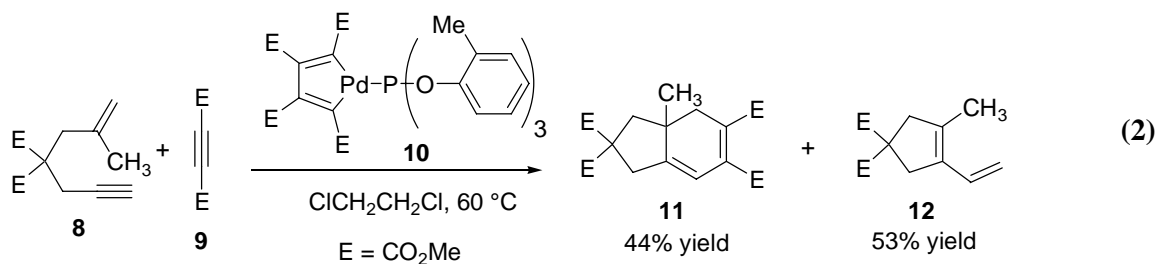
The proposed mechanism for this transformation (Scheme 2) involves [2+2] cycloaddition of the active catalyst **4** and the alkyne functionality of enyne **1** to give metallocyclobutene **5**, which undergoes electrocyclic ring opening to provide the vinyl substituted carbenoid complex **6**. Intramolecular [2+2] cycloaddition of carbene **6** forms metallocyclobutane **7**, which collapses to give diene **3**, regenerating the active catalyst.



Katz⁴ and Hoye⁵ published further studies that extended the scope of tungsten and chromium catalyzed enyne metathesis, but low yields and multiple reaction pathways prevented this reaction from becoming synthetically useful.

Intramolecular Enyne Metathesis Catalyzed by Palladium and Platinum

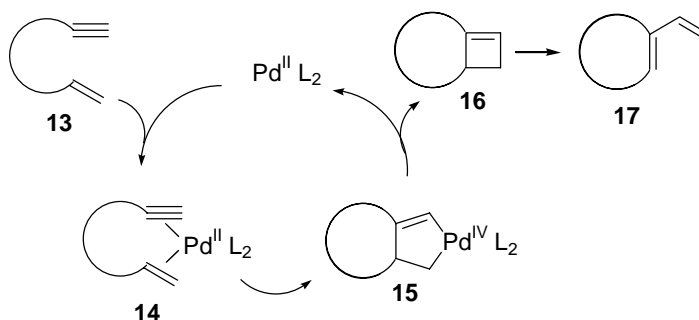
In 1988, while investigating palladium-catalyzed enyne cyclizations, Trost isolated an unexpected rearrangement product (Equation 2).⁶ Enyne **8**, when treated with dimethyl acetylenedicarboxylate (DMAD, **9**), tri-*o*-tolylphosphite, and tetracarbomethoxypalladacyclopentadiene (TCPC, **10**), gives a 1:1.2 ratio of the expected [2+2+2] cycloadduct **11** and unexpected vinylcyclopentene **12** in an overall yield of 97%.



Diene **12** is clearly the product of enyne metathesis. However, the proposed mechanism is quite different from that proposed for the tungsten carbene metathesis. Instead, a Pd^{II} - Pd^{IV} catalytic cycle, related to the competing enyne cycloisomerization mechanism, was advanced (Scheme 3).⁷ Enyne **13** coordinates to TCPC, forming complex **14**, which undergoes oxidative cyclization to afford metallocyclopentene **15**. Reductive elimination of the Pd catalyst from **15** generates cyclobutene **16**. Subsequent electrocyclic ring opening of **16** provides the enyne metathesis product **17**. Unfortunately,

this transformation lacks generality, because the balance between the two competing pathways is very sensitive to minor changes in the structure of enyne substrates.

Scheme 3. Catalytic Cycle of Palladium Catalyzed Enyne Metathesis.

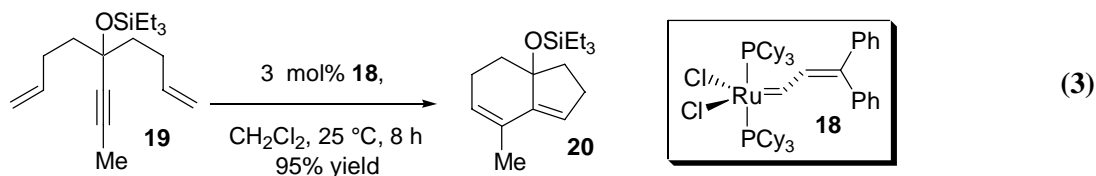


Murai has published a PtCl_2 catalyzed enyne metathesis involving intermediates similar to those shown in Scheme 3.⁸ These results led Fürstner to a PtCl_2 - or acid-catalyzed enyne metathesis believed to proceed via a novel pathway involving “nonclassical” cations as intermediates.⁹ At this point, the scope and utility of the Pd- and Pt-catalyzed enyne metatheses have not been investigated as thoroughly as ruthenium catalyzed enyne metatheses.

RUTHENIUM CATALYZED ENYNE METATHESIS

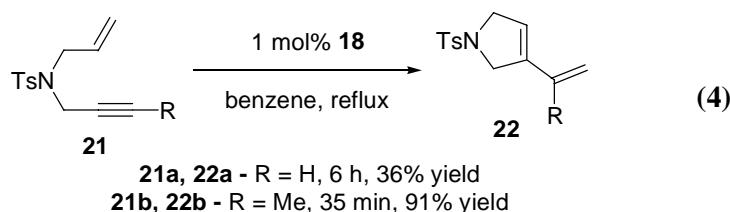
Intramolecular Diene Enyne Metathesis

The discovery of the well-defined ruthenium carbene complex **18** (Equation 3) by Grubbs¹⁰ revolutionized enyne metathesis chemistry. Even though it was developed for alkene metathesis, complex **18** can be used to catalyze tandem enyne metathesis/ring-closing metathesis, yielding a fused bicyclic ring system such as **20**.¹¹ Furthermore, unsymmetrical dienynes with varying tether lengths and sterically differentiated olefins allow access to other [4.3.0], [5.4.0], [4.4.0], and [5.3.0] bicyclic ring systems.



Ruthenium Catalyzed Intramolecular Enyne Metathesis

Mori first reported the use of the Grubbs catalyst for intramolecular enyne metathesis in 1994 (Equation 4).¹² Treatment of enyne **21** with 1 mol% of catalyst **18** gives cyclized diene **22**. Electron donating functionality on the alkyne is crucial to attaining high yields (**22b** vs. **22a**). Five-, six-, and seven-membered heterocycles can be accessed through reactions of 1,6-, 1,7-, and 1,8-enynes, respectively.



Two mechanistic pathways for this transformation have been proposed (Scheme 4).¹³ First, in pathway A, which is similar to that proposed by Katz,³ enyne **23** reacts with active catalyst **24** at the alkyne to form a metallocyclobutene **25**. Electrocyclic ring opening provides the diene **26**. [2+2] cycloaddition yields metallocyclobutane **27**, which opens to give diene **28** and regenerate the active catalyst. Alternatively, route B begins with reaction of the alkene. Carbenoid **29** undergoes intramolecular cycloaddition providing bicyclic metallocyclobutene **30**, which collapses to carbenoid **31**. Subsequent reaction with another molecule of **23** generates product **28** and continues the catalytic cycle.

Evidence supporting pathway A has been provided by Mori¹² through two competition experiments (one intramolecular and one intermolecular), leading to the conclusion that reaction of the alkyne part of an enyne is faster than that of the alkene moiety. However, an NMR experiment by Hoye¹³ suggests that pathway B is active. Two carbene proton resonances that were attributed to the intermediates type **29** and **31** were immediately observed. While these findings provide evidence that path B is viable, they do not rule out the possibility that both pathways are active. Currently, more evidence is needed before a solid conclusion can be attained.

Recently, Mori and coworkers have extended the scope of intramolecular enyne metathesis to include the construction of eight-membered rings (Table 1).¹⁴ Various eight-membered heterocycles are formed through metathesis of the general type enynes **33**. However, yields are substrate dependent, as illustrated in the reactions of **33b** and **33c**. This methodology has not been successful in the synthesis of larger rings.

Scheme 4. Mechanistic Possibilities.

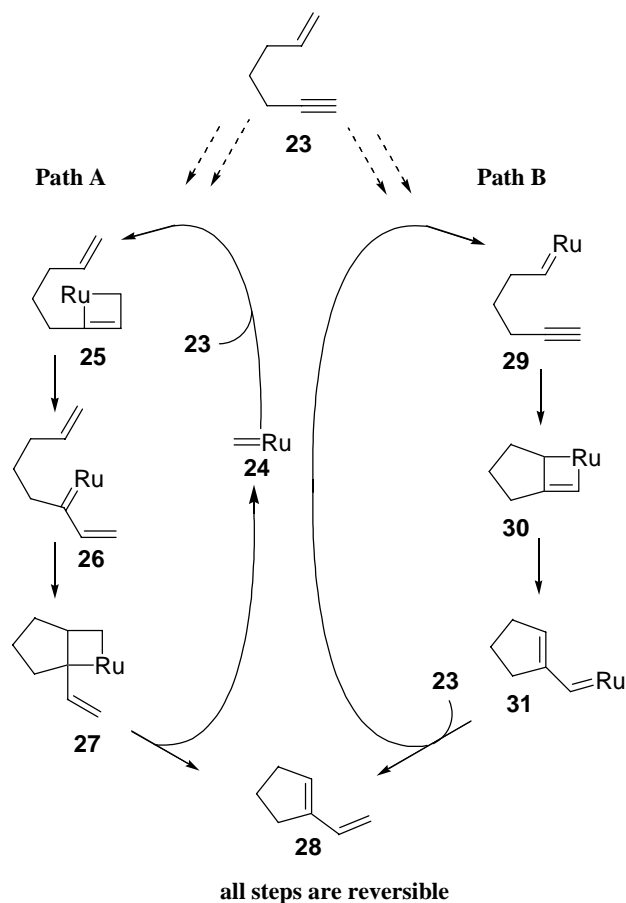
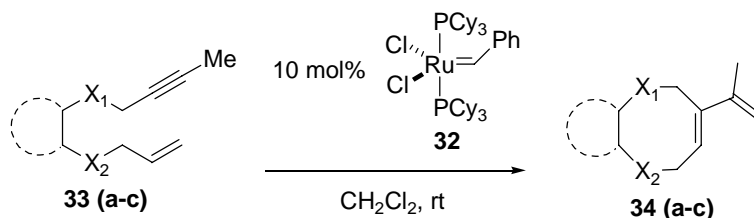
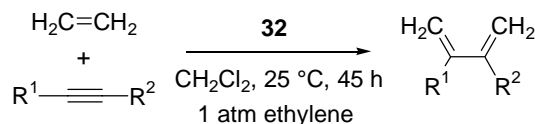


Table 1. Synthesis of Eight-Membered Rings.

| Substrate | X ₁ | X ₂ | Ring | Time | Product | Yield |
|------------|----------------|-----------------|------|--------|------------|-------|
| 33a | O | N-Ts | Ph | 24 h | 34a | 84% |
| 33b | N-Ts | N-Ts | None | 14.5 h | 34b | 95% |
| 33c | N-Ts | CH ₂ | None | 14.5 h | 34c | 11% |

Ruthenium Catalyzed Intermolecular Enyne Metathesis

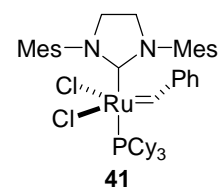
Due to multiple competing reaction pathways, intermolecular enyne metathesis of complex alkenes and alkynes can lead to a range of alkene, alkyne, and polymeric compounds.² However, researchers have been able to carry out this transformation on simple systems. The simplest of alkenes, ethylene, was used by Mori to convert alkynes to 2,3-substituted dienes (Table 2).¹⁵

Table 2. Intermolecular Enyne Metathesis Using Ethylene.

| Entry | Substrate | 32 (mol %) | Product | Yield (Conversion) |
|-------|-----------|------------|---------|--------------------|
| 1 | | 3 | | 62% (100%) |
| 2 | | 10 | | 60% (86%) |
| 3 | | 3 | | 74% (89%) |

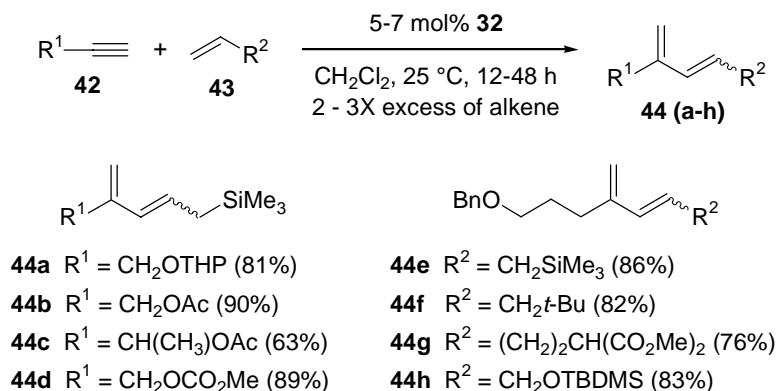
Yields are moderate and products of this transformation have been used in the type-two intramolecular Diels-Alder reaction to synthesize bridgehead olefins.¹⁵ The scope of the ethylene-alkyne cross-metathesis has recently been expanded, using the 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene ruthenium carbene complex **41** (Figure 1),¹⁶ to include compounds with unprotected heteroatoms at the propargylic position.

Blechert and coworkers have reported an intermolecular enyne metathesis

**Figure 1. New Catalyst.**

that transforms terminal alkynes and alkenes to 1,3 disubstituted dienes (Scheme 5).¹⁷ Yields of dienes **44a-h** are generally high when only 2-3 equivalents of alkene **43** are used. Unfortunately, the olefin geometry of products **44** cannot be controlled.

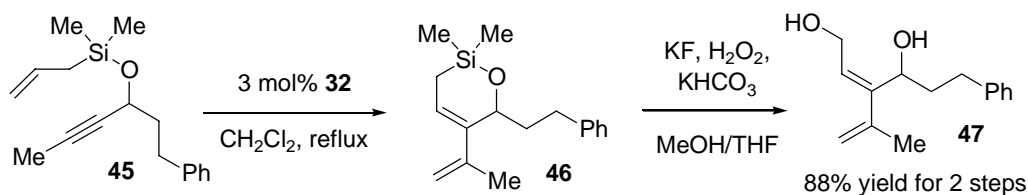
Scheme 5. Crossed Enyne Metathesis.



Ruthenium Catalyzed Tethered Enyne Metathesis

To access intermolecular enyne metathesis products while still retaining the stereo- and regiochemical control allowed by its intramolecular variant, tethered enyne metathesis has been developed (Scheme 6).¹⁸ Treatment of tethered enyne **45** with catalyst **32** gives silyl ether **46**. Oxidative cleavage of the tether in **46** affords the trisubstituted diene **47** in 88% overall yield. This new methodology can be used to generate seven-membered tethered dienes by simply changing the catalyst to the more active carbene complex **41**.

Scheme 6. Tethered Enyne Metathesis.



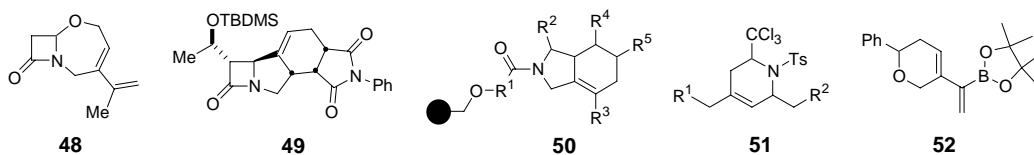
APPLICATION TO SYNTHESIS

Small Molecule Synthesis

In addition to the synthesis of the various dienes and cyclic compounds already mentioned, enyne metathesis has found utility in numerous small molecule syntheses. Highly functionalized bicyclic¹⁹ and tricyclic²⁰ β-lactams (Chart 1, **48–49**), as well as a solid-supported library of hexahydroisindoles²¹ **50**, have been synthesized using enyne metathesis. Blechert and coworkers have used enyne cross metathesis combined with the aza-Diels-Alder reaction to construct substituted

tetrahydropyridines **51**.²² Finally, a concise route to afford 1,3-dienylboronic esters **52** through enyne metathesis has been described.²³ These syntheses demonstrate the exceptional functional group tolerance of this transformation and provide compounds that have been used in pharmaceutical (**48–50**) and cross-coupling (**52**) applications.

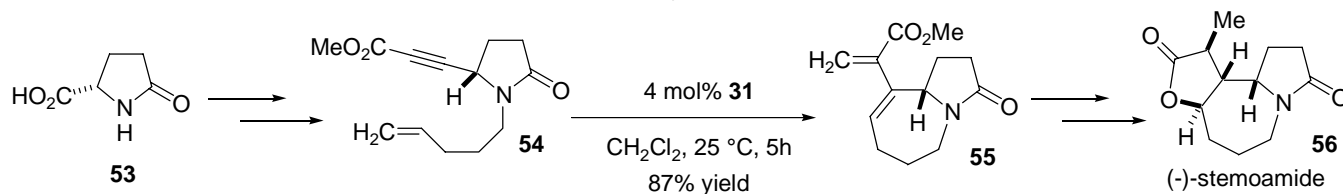
Chart 1. Small Molecules through Enyne Metathesis



Complex Molecule Synthesis

In 1996, (–)-stemoamide was successfully synthesized through an enyne metathesis approach (Scheme 7).²⁴ The key step involved metathesis of enyne **54** to diene **55** in 87% yield and in only 5 hours. (–)-Stemoamide **56** was completed in 14 steps in 9% overall yield from (–)-pyroglutamic acid **53**.

Scheme 7. Synthesis of (–)-Stemoamide.

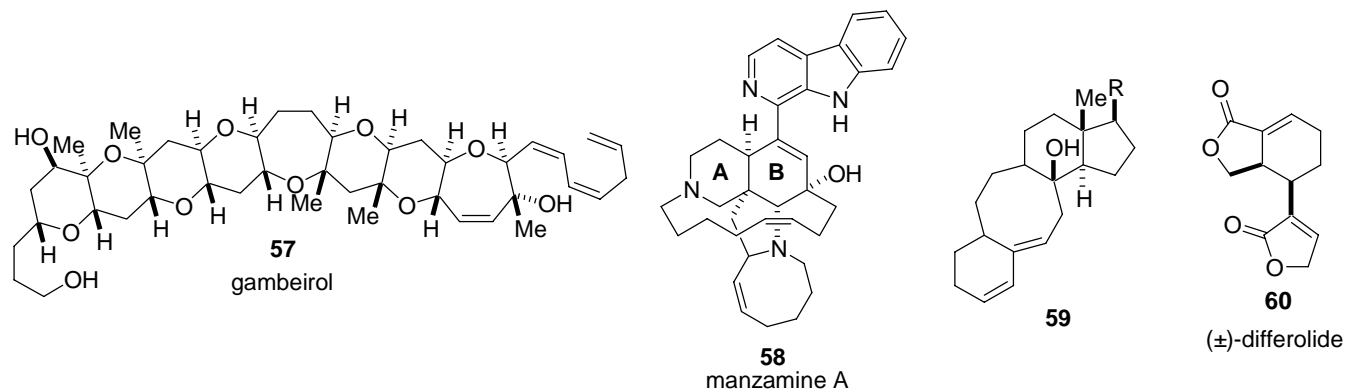


In addition, approaches to various complex molecules (Chart 2) including the cyclic enol ethers of gambeiroil **57**²⁵ and the AB ring system of the manzamine alkaloids **58**²⁶ using enyne metathesis have been described. The completed syntheses of a previtamin D₃ to vitamin D₃ transition state analog **59**²⁷ and the natural product (±)-differolide **60**¹³ through enyne metathesis have also been reported.

CONCLUSION

Enyne metathesis is an efficient carbon-carbon bond forming reaction that leads to a variety of useful organic molecules. 1,3-Dienes are available through simple transformations involving enyne or

Chart 2. Enyne Metathesis for the Construction of Complex Molecules



alkyne starting materials. In addition, unsaturated carbo- and heterocycles can be formed from acyclic precursors. The development of novel ruthenium catalysts by Grubbs has significantly impacted the scope of the transformation. Enyne metathesis has proven to be useful in the synthesis of small organic molecules and complex targets.

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