

**Beyond olefins: New metathesis directions for synthesis**

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## Beyond olefins: New metathesis directions for synthesis

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The olefin–olefin metathesis reaction has emerged to one of the most important carbon–carbon bond-forming reactions, as illustrated by its wide use in the synthesis of complex molecules, natural products and pharmaceuticals. The corresponding metathesis reaction between carbonyls and olefins or alkynes similarly allows for the formation of carbon–carbon bonds. Although these variants are far less developed and utilized in organic synthesis, they possess attractive qualities that have prompted chemists to incorporate and explore these modes of reactivity in complex molecule synthesis. This review highlights selected examples of carbonyl–olefin and carbonyl–alkyne metathesis reactions in organic synthesis, in particular in the total synthesis of natural products and complex molecules, and provides an overview of current advantages and limitations.

### Key Learning Points:

1. The metathesis reaction is a widely used strategy for the construction of carbon–carbon bonds.
2. Carbonyl–olefin and carbonyl–alkyne metathesis reactions have been used in the synthesis of natural products and complex molecules.
3. Understanding of the operative mechanisms for the different types of metathesis reactions.
4. The advantages and limitations of carbonyl–olefin and carbonyl–alkyne metathesis.

### 1. Introduction

Among the many bond-forming reactions in organic synthesis, reactions that enable the formation of carbon–carbon bonds are particularly important as they dictate the framework of an organic molecule in numerous ways.<sup>1</sup> The discovery of new carbon–carbon bond-forming reactions enables chemists to construct organic molecules more efficiently and to access

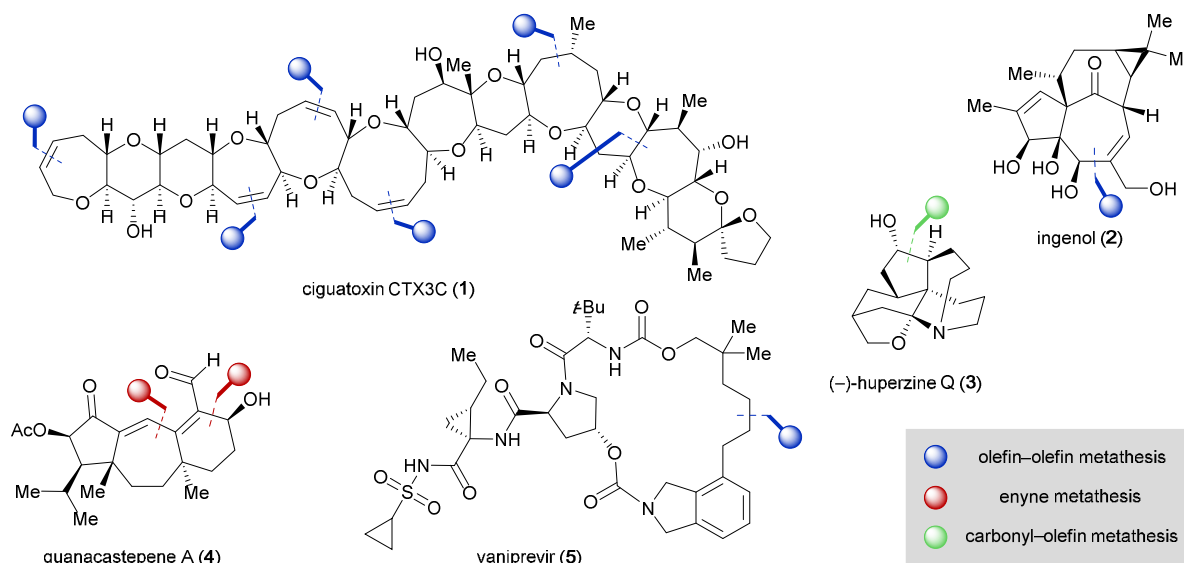


Figure 1 Natural products and pharmaceuticals synthesized employing metathesis strategies.

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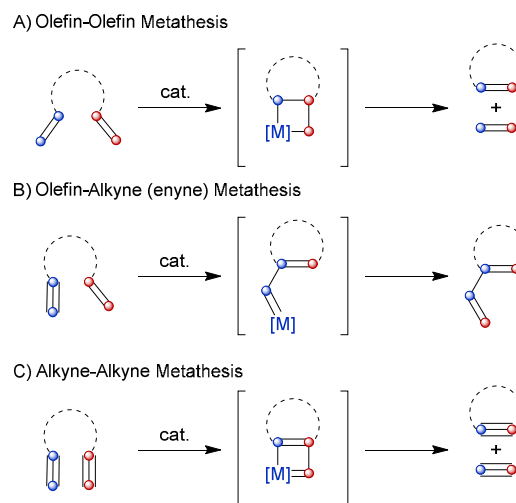
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

previously inaccessible structures of high impact in chemical industry, medicine, and materials science. Out of the vast number of carbon–carbon bond-forming processes that have been developed and employed in the last two decades, two reactions in particular have enabled important advances in the

field of organic synthesis: the olefin metathesis reaction and the palladium-catalyzed cross-coupling reaction, both awarded with the Nobel Prize in chemistry in 2005 and 2010, respectively.<sup>2</sup> Olefin metathesis is characterized by the exchange of double-bonded atoms within a pair of olefins to form a new pair of olefins. Olefin metathesis reactions have emerged as one of the most powerful ways to construct carbon–carbon bonds, highlighted by their extraordinary use in the synthesis of natural products and pharmaceuticals (Figure 1).<sup>3,4</sup> The total synthesis of ciguatoxin CTX3C (**1**) constitutes a benchmark example, in which a total of six olefin–olefin metathesis reactions were performed to construct the carbon framework of the large, complex neurotoxin.<sup>5</sup>

Facilitated by a metal alkylidene catalyst, the olefin–olefin metathesis reaction proceeds through a series of [2+2] cycloadditions and subsequent [2+2] cycloreversions between the two reactive partners. The key intermediate in this process is a metallacyclobutane, where the catalyst is integrated into the four-membered species, and [2+2] cycloreversion ultimately results in product formation and catalyst turnover (Scheme 1, A). Each step of this mechanism is in principle reversible, thus, the reactants eventually funnel to the thermodynamically most stable product(s). In addition, the driving force of the reaction highly depends on the mode in which the olefin metathesis reaction is carried out: in ring-opening metathesis ring-strain provides the driving force for the transformation; in cross-metathesis, where two olefin partners are reacted intermolecularly, typically an excess of one reactant promotes the formation of the desired product; and in ring-closing metathesis, two olefins are coupled intramolecularly to afford ring-closure by releasing a typically volatile byproduct, thus providing an entropic driving force. It is important to highlight that the ring-closing metathesis reaction is the most widely applied metathesis reaction in natural product synthesis. While the olefin–olefin metathesis reaction is the most commonly used metathesis reaction, two related transformations have been developed. One is the metathesis reaction between an olefin and an alkyne, typically referred to as enyne metathesis, that results in a 1,3-diene product (Scheme 1, B). It is important to note, that no olefin byproduct is produced in this process, therefore, the stability of the formed conjugated system serves as the driving force for the transformation. Additionally, the metathesis between two alkynes has been reported, a direct analogue of the olefin–olefin metathesis reaction, where the skeletal rearrangement of the four-membered intermediate produces a new pair of alkynes (Scheme 1, C).<sup>6</sup>

A detailed mechanistic understanding of the olefin metathesis reaction has been gained in the last 50 years, and has fostered the development of well-defined, stable and/or reactive catalysts. This strategic catalyst design has been significant to the success of the olefin metathesis reaction and allows chemists to carry out this transformation readily today (Figure 2). Although remarkable progress has been made, the field of olefin metathesis still features certain challenges. For example, typically employed catalyst loadings are still



Scheme 1 Different types of metathesis reactions between olefins and/or alkynes.

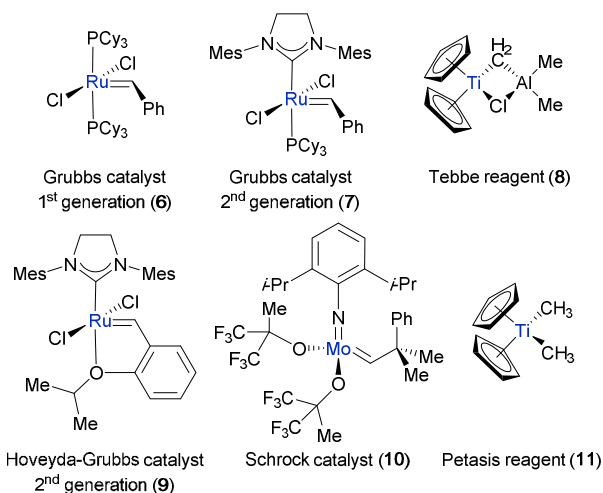
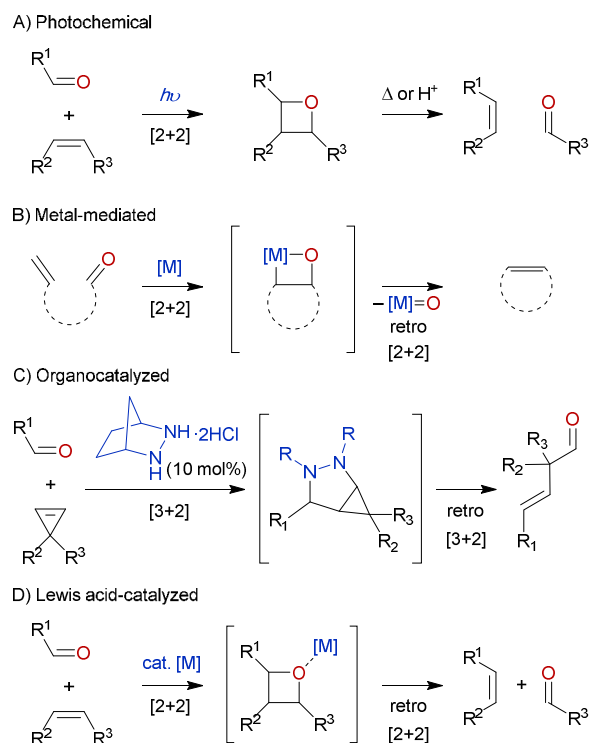


Figure 2 Selection of metathesis catalysts and olefination reagents commonly employed in organic synthesis.

considered too high to render the reaction cost-effective for an industrial process.<sup>1</sup> Furthermore, the limited control over homodimerization in cross-metathesis processes and the selective formation of *E*- or *Z*- olefins have only very recently been addressed through the development of new catalyst systems.<sup>7</sup> Alternative approaches have been reported that enable metathesis reactions with new functionalities, in particular with carbonyls. This review provides an overview of the most successful strategies to perform metathesis reactions with carbonyls and their application in complex molecule and natural product synthesis.

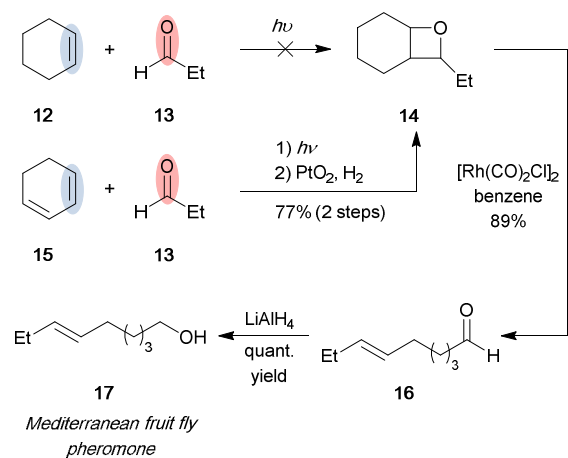
## 2. Carbonyl–Olefin Metathesis

The development of the carbonyl–olefin metathesis reaction has been motivated by its inherent ability to take simple carbonyls and olefins and to convert them into less accessible products with higher synthetic value. Net carbonyl–olefin metathesis reaction can proceed stepwise under



Scheme 2 Overview of metathesis reactions between olefins and carbonyls.

photochemical conditions, where in the first step irradiation by a light source induces a [2+2] cycloaddition between a carbonyl and olefin, known as the Paternó-Büchi reaction.<sup>8-10</sup> The isolated oxetane intermediate can subsequently be fragmented into a new carbonyl and olefin product under thermal or acidic conditions (Scheme 2, A). In contrast to this traditional approach, the most commonly employed way to perform carbonyl–olefin metathesis reactions involves the use of transition-metal reagents (Scheme 2, B).<sup>11-12</sup> Typically, these one-pot metal-mediated processes include a carbonyl–olefination and an olefin–olefin metathesis event, however, the order of these transformations can differ based on the selected metal reagent. In both cases an oxametallacyclobutane is generated, which upon fragmentation results in the formation of an olefin and a metal-oxo byproduct. Unfortunately, the latter has proven catalytically inert, which prevents catalyst turnover and thus stoichiometric or super-stoichiometric amounts of metal reagent are required. However, it is important to note that while no catalytic carbonyl–olefin metathesis reactions proceeding through an oxametallacyclobutane intermediate are known, catalytic techniques to solely methylenate a carbonyl group have been reported.<sup>13</sup> Recently, the Lambert group made an elegant contribution to the field when they reported a unique organocatalyzed approach relying on a hydrazine catalyst (Scheme 2, C).<sup>14</sup> In the described transformation, a [3+2] cycloaddition between an *in situ* generated hydrazone and a cyclopropene results in the formation of a strained bicyclic intermediate. Strain-induced [3+2] cycloreversion followed by hydrolysis provides the

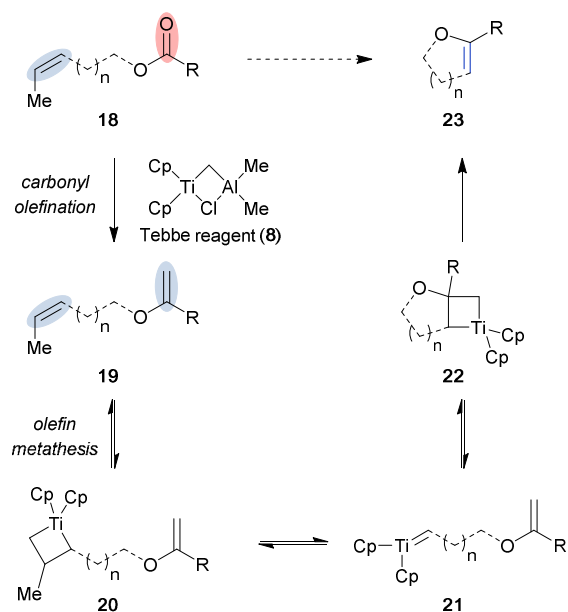


Scheme 3 Total synthesis of pheromone **17** (Jones and co-workers, 1975).<sup>8</sup>

desired carbonyl–olefin metathesis product. Furthermore, recent work has focused on promoting carbonyl–olefin metathesis through the use of Lewis acid catalysts (Scheme 2, D).<sup>15-17</sup> Coordination of the Lewis acid to the carbonyl moiety mediates a cycloaddition and cycloreversion sequence via an intermediate oxetane. As the Lewis acid only transiently coordinates to the carbonyl oxygen, no inert metal-oxo byproduct is formed allowing for turnover of the catalyst.

#### Early Examples of Carbonyl Olefin Metathesis in Total Synthesis

In an early example of natural product synthesis utilizing carbonyl–olefin metathesis, a photochemical [2+2] cycloaddition/fragmentation sequence was used during the synthesis of pheromone **17**, a sex attractant from the Mediterranean fruit fly (Scheme 3).<sup>8</sup> While irradiation of propionaldehyde (**13**) and cyclohexene (**12**) did not lead to formation of oxetane **14**, the desired product could be



Scheme 4 Mechanism for the carbonyl olefination/metathesis sequence with the Tebbe reagent (**8**).

obtained through a Paternó-Büchi reaction of **13** and 1,3-cyclohexadiene (**15**), followed by platinum-promoted hydrogenation in 77% yield. Oxetane ring-opening via pyrolysis was explored, but resulted in diminished yields; however, utilizing a dimeric Rhodium complex provided aldehyde **16** in 89% yield. Efficient aldehyde reduction was achieved with  $\text{LiAlH}_4$ , and the desired pheromone **17** was obtained in 4 steps and 40-50% yield. This synthesis proved to be an advantageous alternative to the previously reported 8-step sequence.

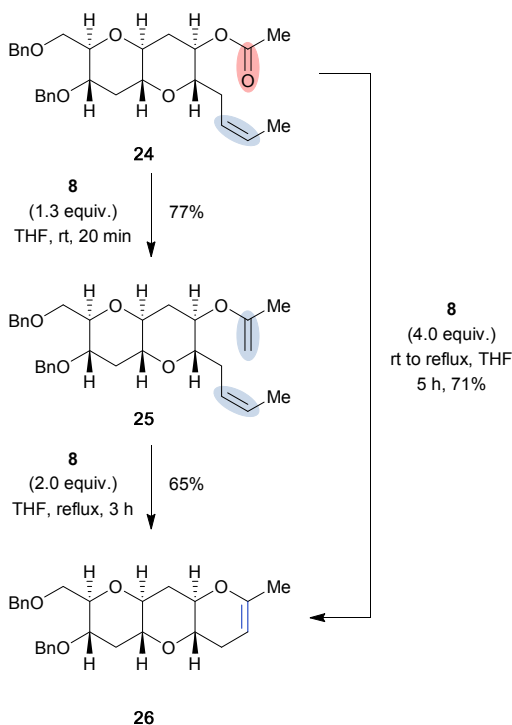
### Tebbe Reagent-Mediated Carbonyl–Olefin Metathesis in Total Synthesis

An alternative strategy to the stepwise process, involving the olefination of a carbonyl followed by an olefin-olefin metathesis reaction, methods have been developed to yield metathesis products directly from a carbonyl and an olefin. These methods often rely on specific reagent systems to perform both olefination of the starting carbonyl, and subsequent desired metathesis. As a result, cyclic enol ethers can be directly accessed from olefin and esters functionalities using the Tebbe (**8**) or Petasis (**11**) reagent.<sup>12</sup> In the Tebbe reagent-mediated carbonyl–olefin metathesis reaction, a first equivalent of **8** performs olefination of the ester functionality via a [2+2] cycloaddition/cycloreversion sequence to generate bis-olefin **19** and a titanium-oxo byproduct (Scheme 4). Subsequently, a second molecule of **8** promotes the formation of titanocyclobutane intermediate **20**, which upon

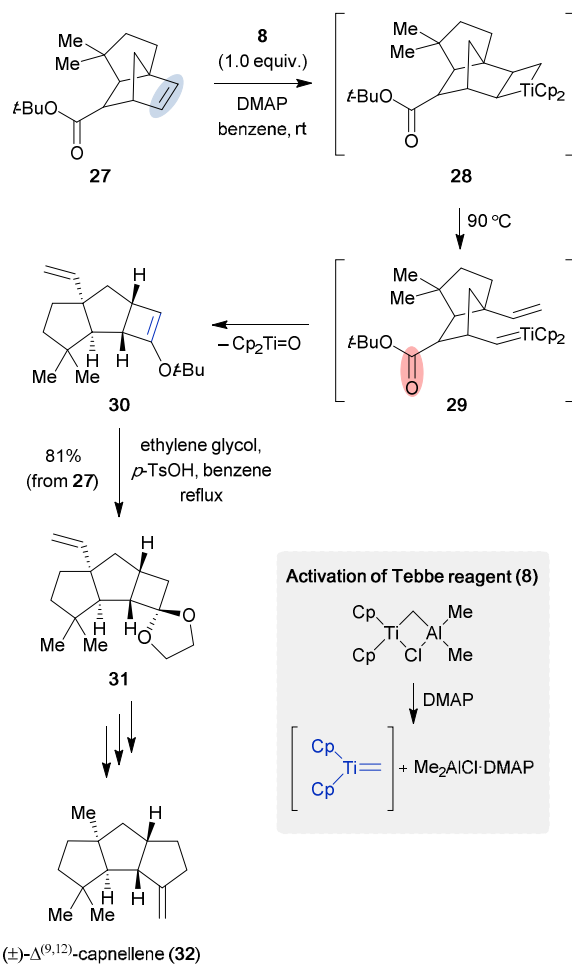
fragmentation generates titanium alkylidene **21**. Lastly, intramolecular metathesis between the titanium alkylidene and olefin generates the desired cyclic enol ether **23**.

Nicolaou showcased the utility of the Tebbe reagent to perform carbonyl–olefin metathesis in highly functionalized environments.<sup>12</sup> The Tebbe reagent was utilized to provide ring-closure in a tricyclic polyether, structurally reminiscent of marine neurotoxins brevetoxin B, ciguatoxin and maitotoxin, among others. The Tebbe reagent was used to perform the olefination of ester **24** in 77% yield, which could be further transformed in a second step into the desired cyclic enol ether **26** using an excessive amount of **8** in 65% yield (Scheme 5). However, it was found to be advantageous to perform the carbonyl–olefin metathesis reaction directly by utilizing excess Tebbe reagent (**8**), providing cyclic enol ether **26** in 71% yield. The authors suggest that the described experiment confirms their proposed mechanism starting with carbonyl-olefination, followed by olefin–olefin metathesis.

The Tebbe reagent-mediated carbonyl–olefin metathesis reaction has been used in the synthesis of  $(\pm)\text{-}\Delta^{(9,12)}$ -capnellene (**32**). In 1986, Grubbs and Stille reported the synthesis of **32** by using 4-dimethylaminopyridine (DMAP) activated Tebbe reagent (Scheme 6).<sup>18-19</sup> The activated metathesis reagent underwent [2+2] cycloaddition reaction with olefin **27** to form titanium metallacycle **28**, which upon fragmentation at elevated temperatures provided titanium alkylidene **29**. Subsequently, a second [2+2] cycloaddition/cycloreversion sequence between the newly generated titanium alkylidene and the carbonyl moiety provided the highly strained cyclic enol ether **30**, which was converted to acetal **31** in 81% yield with respect to olefin **27**. Finally, the authors were able to access  $(\pm)\text{-}\Delta^{(9,12)}$ -capnellene (**32**) with a final olefination of a ketone utilizing the Tebbe reagent (**8**).



**Scheme 5** Two-step carbonyl olefination/metathesis reaction with the Tebbe reagent (**8**) to access cyclic polyethers (Nicolaou and co-workers, 1996).<sup>12</sup>



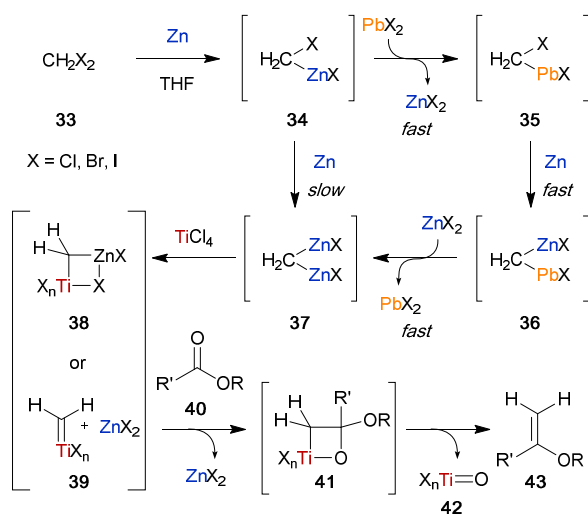
**Scheme 6** Total synthesis of (±)- $\Delta^{(9,12)}$ -capnellene (**32**) (Grubbs and Stille, 1986).<sup>18</sup>

### Rainier Metathesis Reaction in Total Synthesis

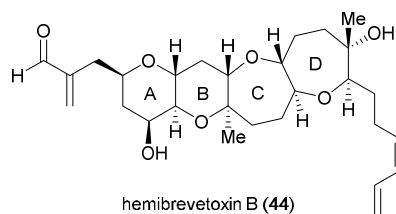
In addition to the Tebbe (**8**) and Petasis (**11**) reagents, other titanium-based protocols have been reported for the metathesis reaction between carbonyl and olefin moieties. Of particular note, Rainier has developed a protocol derived from the Takai-Utimoto olefination reaction to perform olefinic ester cyclizations.<sup>20</sup> The transformation today is referred to as the Rainier metathesis reaction, and the titanium-based reagent employed is advantageous due to its *in situ* generation, decreased Lewis acidity compared to the Tebbe reagent (**8**), and increased reactivity compared to the Petasis reagent (**11**).

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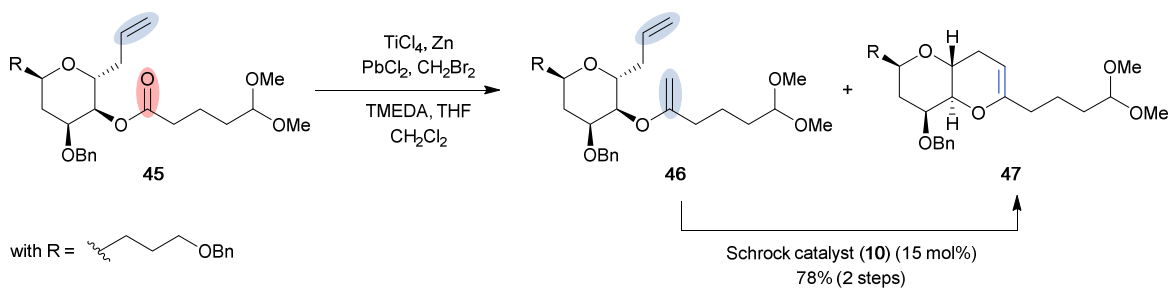
As described by Takai and Utimoto<sup>21</sup>, the active



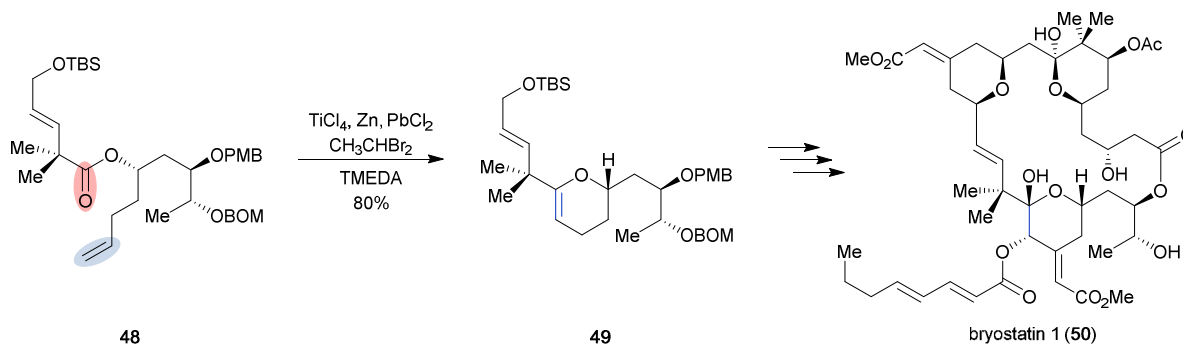
**Scheme 7** Proposed mechanism for the formation of the titanium reagent and subsequent carbonyl olefination.



Synthesis of A, B- ring system:

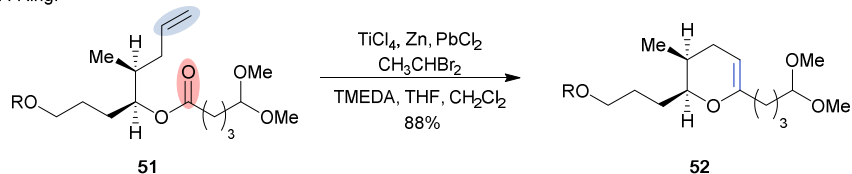


**Scheme 8** Total synthesis of hemibrevetoxin B (**44**) (Rainier and co-workers, 2001).<sup>22</sup>

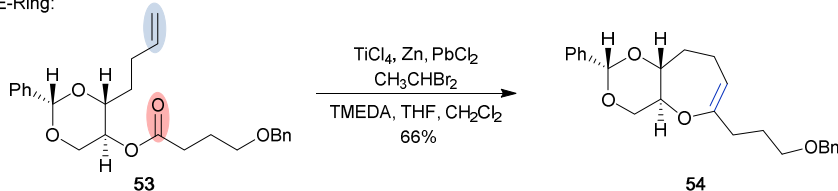


**Scheme 9** Total synthesis of broyostatin 1 (**50**) (Keck and co-workers, 2011).<sup>24</sup>

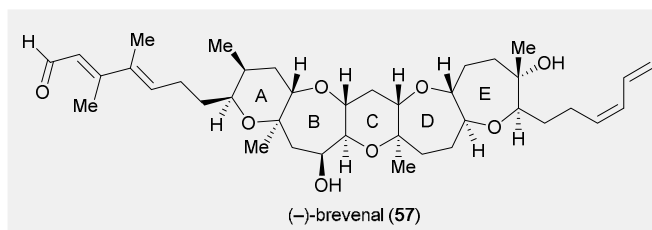
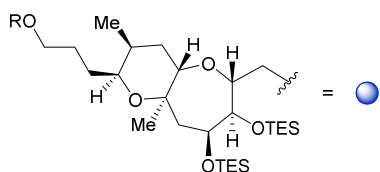
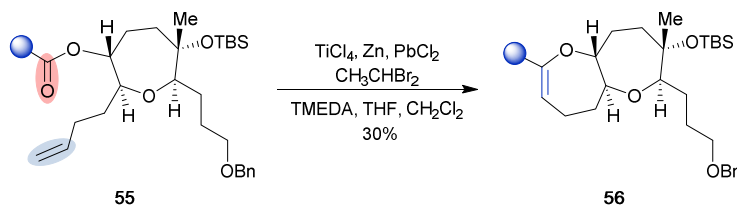
Synthesis of A-Ring:



Synthesis of E-Ring:



Synthesis of D-Ring:

Scheme 10 Total synthesis of brevenal (57) (Rainier and co-workers, 2011).<sup>27</sup>

methylenation reagent is generated from bishalide **33** through initial oxidative addition of zinc metal to form zinc carbenoid **34** (Scheme 7). A second zinc addition is slow, but can be greatly accelerated with catalytic amounts of  $\text{PbCl}_2$ . The catalyst undergoes transmetalation to provide lead carbenoid **35**, which can subsequently be reduced by a second molecule of zinc to form dimetallic species **36**. A second fast transmetalation event provides dizinc species **37** that is assumed to react with titanium to form the active reagent, which is proposed to be either a dimetallic species such as **38** or a titanium alkylidene (**39**). The reagent can perform a [2+2] cycloaddition/cycloreversion sequence with a carbonyl group (**40**) to provide the desired methylenation product **43** and titanium-oxo byproduct **42**. Rainier applied this method in the formal total synthesis of the marine ladder toxin hemibrevetoxin B (**44**) (Scheme 8).<sup>22</sup> In this example, cyclic ether **45** was converted to a mixture of olefinated product **46** and desired metathesis product **47** utilizing the *in situ* generated titanium reagent. Efficient conversion of the mixture was achieved using Schrock catalyst **10** (15 mol%) in 78% yield over the two steps to provide the A,B-ring system **47** of the desired tetracycle. It was later found that poor conversion to the desired product was more often observed

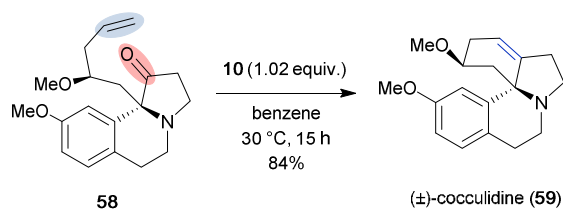
when dibromomethane was employed to generate the titanium reagent, and that the use of dibromoethane could provide significant improvement.<sup>23</sup> These modified reaction conditions were implemented in the first total synthesis of bryostatin 1 (**50**) by Keck and co-workers (Scheme 9).<sup>24</sup> They were able to obtain cyclic enol ether **49** in 80% yield, which they were able to elaborate to the final target in 30 steps overall from (*R*)-isobutyl lactate. The high conversion to desired product can most likely be attributed to the use of dibromoethane.

The Rainier metathesis reaction utilizing titanium ethylidenes generated from dibromoethane can also be used to cyclize both olefinic amides and lactams.<sup>25</sup> Furthermore, the potential of this cyclization technique was explored in the total synthesis of ( $\pm$ )-myrioneurinol by Reinweb and co-workers in 2015.<sup>26</sup> While the Rainier metathesis reaction was successful for obtaining the desired cyclic enamide intermediate, subsequent steps were unsuccessful and a different strategy was utilized for the final sequence.

The utility of the Rainier metathesis reaction was showcased in the total synthesis of (-)-brevenal (**57**) by Rainier and co-workers in 2011 (Scheme 10).<sup>27</sup> They were able to synthesize the A, D, and E-rings of this complex pentacycle



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Scheme 11 Total synthesis of cocculidine (59) (Sarpong and co-workers, 2013).<sup>28</sup>

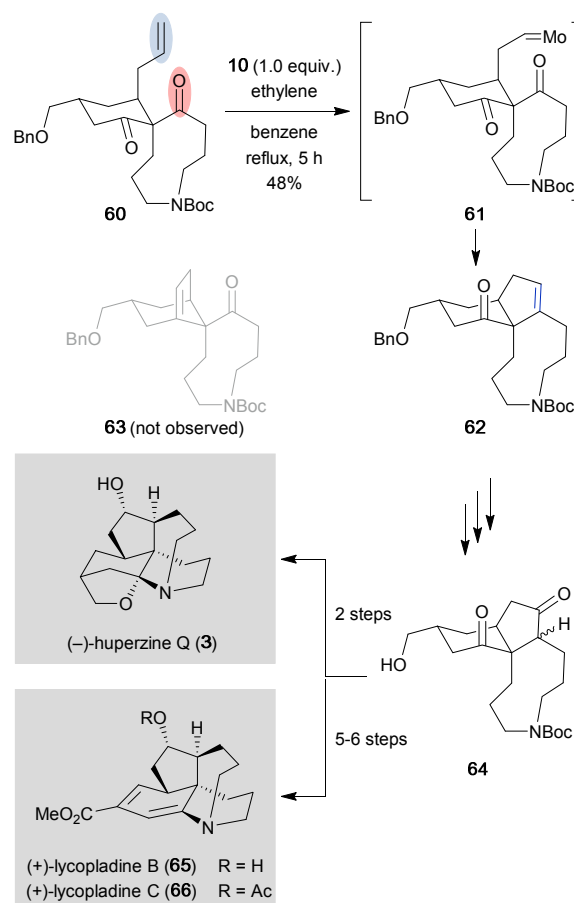
using their developed method. Non-cyclic ester **51** was efficiently converted to cyclic enol ether **52** in 88% yield on multi-gram scale to access the A-ring of (–)-brevenal. The authors also evaluated other metathesis reaction conditions for this early step in their total synthesis. When dibromomethane was used instead of dibromoethane, a 1:1 mixture of cyclic enol ether **52** and the corresponding acyclic enol ether were isolated in 70% yield. The mixture could be subjected to Grubbs second-generation catalyst (**7**) to obtain the desired cyclic enol ether **52** in 75% yield over the two steps. Furthermore, the Tebbe reagent (**8**) was evaluated, and resulted in decomposition and none of the desired product (**52**). Ultimately, the original conditions employed involving dibromoethane were used in the final sequence. The E-ring of (–)-brevenal was also obtained using the Rainier metathesis reaction. Ester **53**, which was obtained from L-glyceraldehyde acetonide in 4 steps, provided cyclic enol ether **54** and the corresponding acyclic enol ether in 66% and 22% yield, respectively. The use of dibromoethane did not prevent the formation of acyclic enol ether in this case. Conversion of the acyclic enol ether to the cyclic variant (**53**) could be achieved using second-generation Grubbs catalyst **7**, albeit in low conversion (35%) and also resulted in the formation of undesired byproducts. Additionally, the D-ring of (–)-brevenal was generated in 30% yield from ester **54**. Once again, the corresponding acyclic enol ether was generated, this time as the major product. Fortunately, the described acyclic enol ether could be recycled upon exposure to second-generation Grubbs catalyst **7** and ethylene gas in 35% yield.

**Carbonyl–Olefin Metathesis in Total Synthesis with Olefin Metathesis Catalysts**

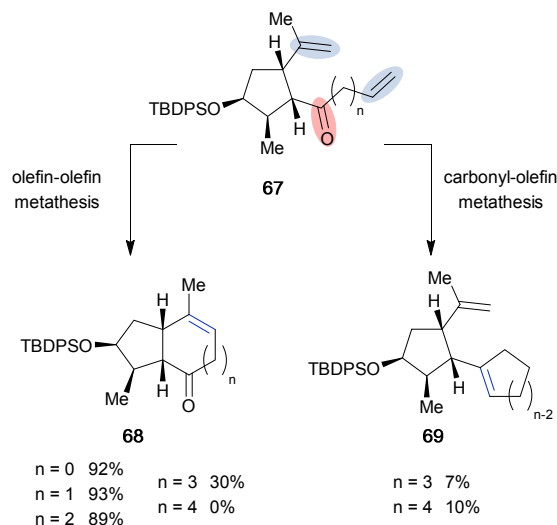
Classical olefin–olefin metathesis reagents, in particular the Schrock catalyst (**10**), have been used in the synthesis of natural products and complex molecules to perform carbonyl–olefin metathesis. However, the formation of a metal-oxo byproduct renders the system non-catalytic and the high cost of these reagents has hampered their use as carbonyl–olefin metathesis reagents in organic synthesis.

In the 2013 synthesis of cocculidine (**59**), Sarpong and co-workers pursued a carbonyl–olefin metathesis strategy to complete their target.<sup>28</sup> The authors used a stoichiometric amount of **10** to convert cyclic amine **58** into the desired metathesis product as their last step in the synthesis (Scheme 11). They also evaluated other direct and indirect ring-closing metathesis strategies, such as olefin–olefin and relay ring-closing metathesis, among others, however, the

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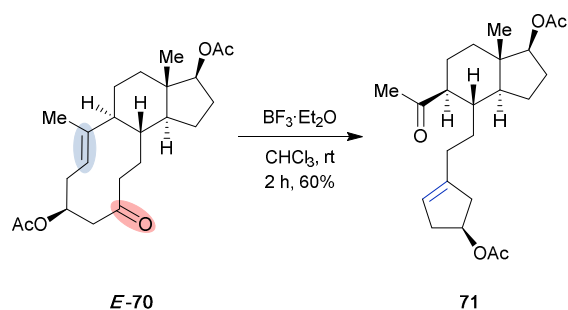


Scheme 12 Total synthesis of huperzine Q (**3**) and lycopladine B (**65**) and C (**66**) (Lei and co-workers, 2015).<sup>29</sup>



Conditions: Grubbs-II (10 mol%), toluene.

Scheme 13 Competing olefin-olefin and carbonyl–olefin metathesis (Roy and co-workers, 2016).<sup>30</sup>



**Scheme 14** Unexpected transannular carbonyl–olefin metathesis (Khripach and co-workers, 2006).<sup>31</sup>

protocol relying on stoichiometric amounts of Schrock catalyst **10** proved superior, providing cocculidine (**59**) in 84% yield.

A similar approach was employed by the Lei group in their total synthesis of (–)-huperzine Q (**3**) and (+)-lycopoladines B (**65**) and C (**66**) (Scheme 12).<sup>29</sup> Spirocycle **60** was converted efficiently to cyclopentene **62** in 48% yield after exposure to Schrock catalyst **10** and ethylene gas. The authors hypothesized that the ethylene gas served two key functions in order to obtain the desired reactivity: a) activation of the molybdenum complex by converting the bulky complex into a more active and sterically less hindered form  $[\text{Mo}=\text{CH}_2]$ , and b) reacting with generated molybdenum alkylidene intermediate **61** to regenerate starting spirocycle **60**, and prevent undesired side reactions. Importantly, the generated molybdenum alkylidene intermediate **61** never reacted with the second ketone present in spirocycle **60** to generate the other potential metathesis product **63**, most likely due to the high torsional strain of the bridged system.

In addition, Roy and co-workers observed, that ruthenium based catalysts originally designed to promote olefin–olefin metathesis can perform carbonyl–olefin metathesis. In the 2016 report, competition between ring-closing olefin–olefin metathesis and ring-closing carbonyl–olefin metathesis was observed, when probing the reactivity of cyclopentane **67** using second-generation Grubbs catalyst **7** (Scheme 13).<sup>30</sup> Olefin–olefin metathesis was the only mode of reactivity observed when the resultant bicycles formed were 5-5, 5-6, and 5-7 fused rings systems (**68**). However, when the possibility to form a 5-8 fused bicycle emerged, the selectivity of the system diminished, and the carbonyl–olefin metathesis product was observed along with the olefin–olefin metathesis product (**68**, **69**). Furthermore, when the chain length of **67** was extended one carbon further ( $n=4$ ), only carbonyl–olefin metathesis was observed and **69** was isolated in 10% yield. For this transformation, the authors propose a ruthenium-oxo byproduct that eliminates the possibility for catalytic turnover. Thus, the 10% yield of carbonyl–olefin metathesis product (**70**) is consistent with the 10 mol% catalyst loading employed.

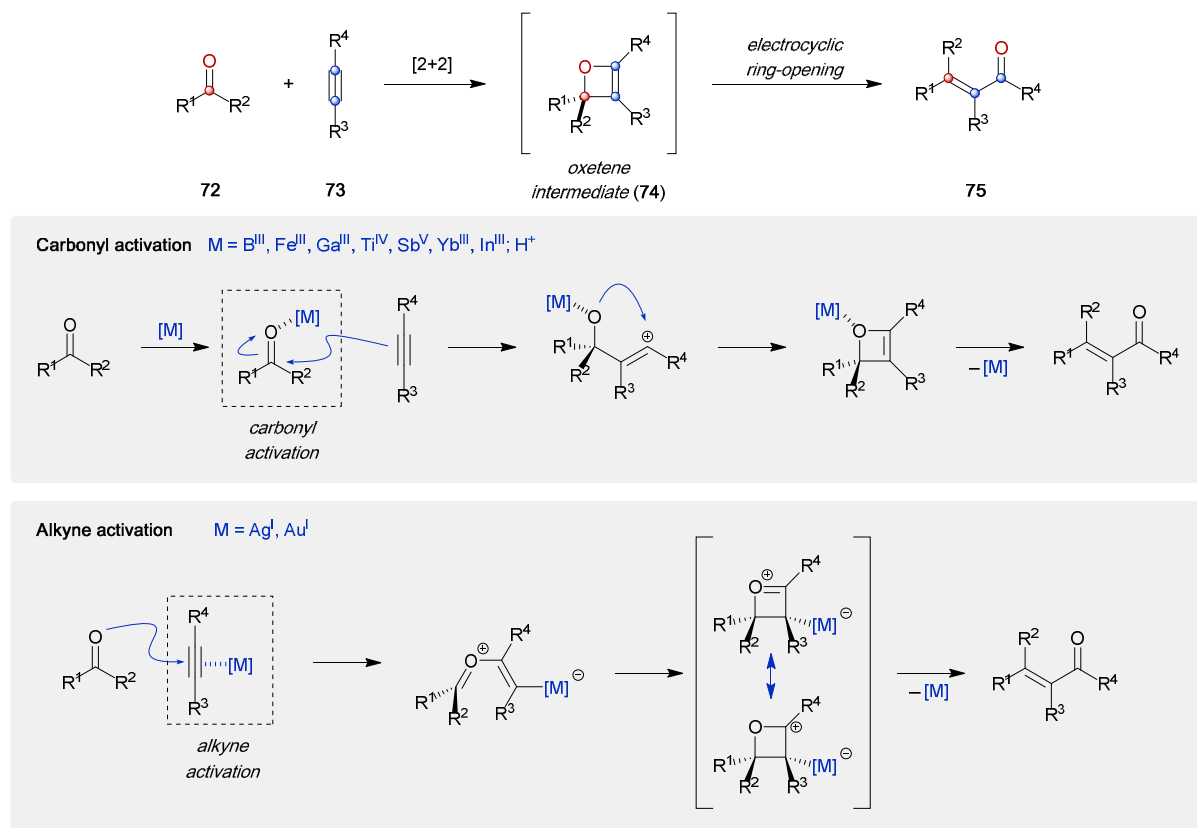
### Lewis Acid Mediated Carbonyl–Olefin Metathesis in Complex Molecule Synthesis

Recently, Lewis acid-catalyzed carbonyl–olefin metathesis has emerged as a useful tool for the synthesis of five- and six-membered ring systems.<sup>15–17</sup> Although the reaction has not been applied in natural product synthesis, it has been shown that carbonyl–olefin metathesis can be performed in complex settings. When Khripach and co-workers were attempting to protect the ketone functionality of **E-70** as a dithioketal, they were surprised that upon exposure of macrocycle **E-70** to the Lewis acid  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  (Scheme 14), they isolated cyclopentene **71** in 60%; a product they hypothesized resulted from an “unusual” intramolecular rearrangement.<sup>31</sup> After conformational analysis based on density functional theory calculations, they proposed a Lewis acid promoted [2+2] cycloaddition to form an oxetane intermediate, followed by a [2+2] cycloreversion reaction. The authors hypothesized that this mode of reactivity was a result of the steric arrangement of the (*E*)-alkene and carbonyl group, as the same reactivity was not observed with the (*Z*)-isomer of macrocycle **70**. While at the time, a Lewis-acid promoted [2+2] cycloaddition/cycloreversion sequence may have been unanticipated, this example highlights the fact that this mode of reactivity can be used in a complex setting.

Carbonyl–olefin metathesis has been used in the total synthesis of complex molecules and natural products for decades, with more examples emerging as the field advances. However, many of these examples involve the use of stoichiometric or super-stoichiometric amounts of metal catalyst, while the more recent examples that rely on organocatalysis and Lewis-acids require further development. Overall, the selected examples showcase the advancements in the field and inspire the development of new catalytic systems.

### 3. Carbonyl–Alkyne Metathesis

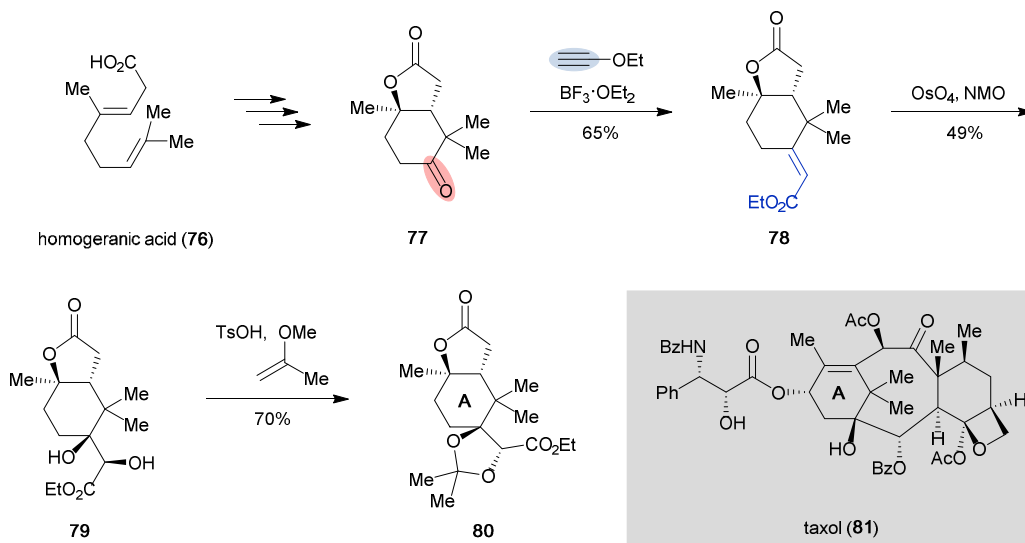
The metathesis reaction between a carbonyl and an alkyne, also referred to as yne-carbonyl metathesis, is a powerful method for the construction of  $\alpha,\beta$ -unsaturated carbonyls. The reaction was first discovered by Büchi in 1956 during studies based on the [2+2] cycloaddition of carbonyls and olefins. When attempting to prepare oxetenes through irradiation of carbonyls and alkynes, the formation of the corresponding carbonyl–alkyne metathesis product was observed.<sup>32</sup> Three years later an important contribution to the field was made by Vieregge, when he reported the first Lewis acid-catalyzed variant of the described transformation, resulting in higher yield, regio- and stereoselectivity in comparison to the photochemical method.<sup>33</sup>



Scheme 15 Mechanism of the carbonyl-alkyne metathesis reaction.

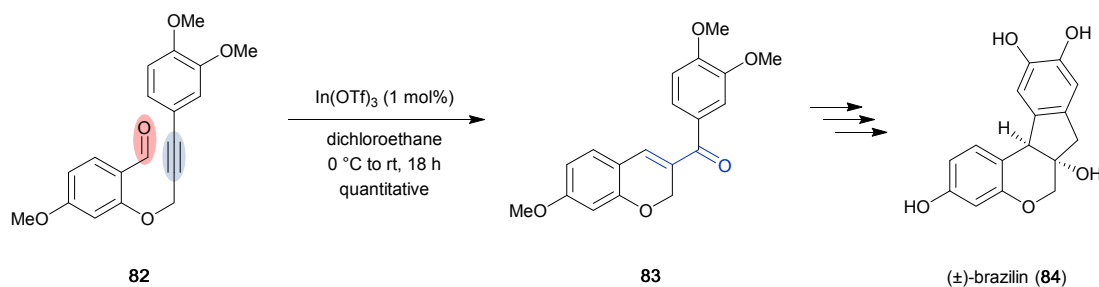
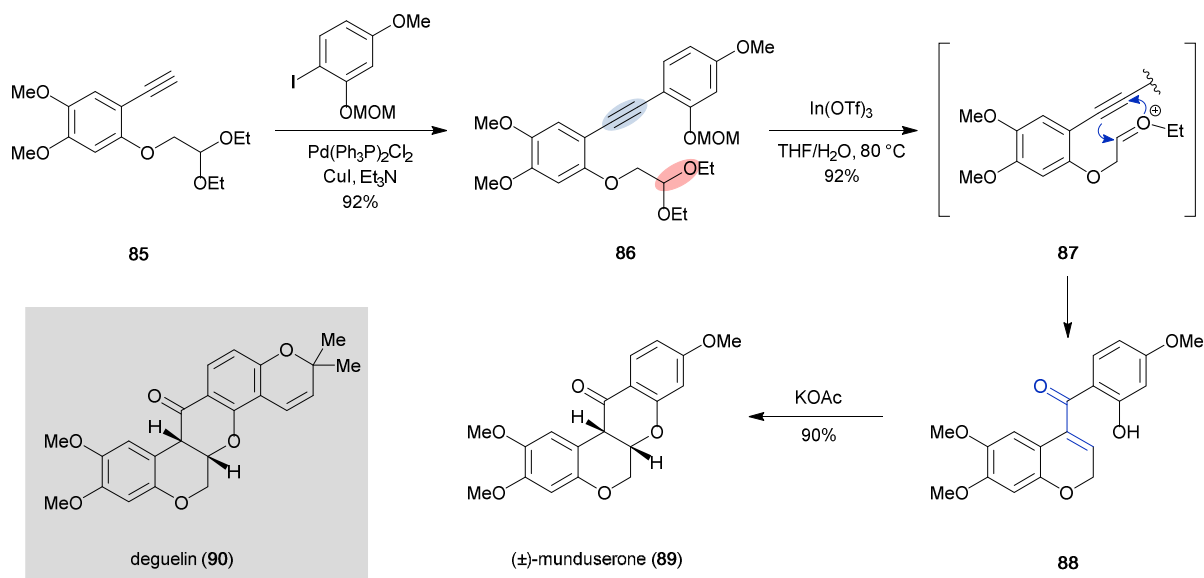
Unlike the carbonyl-olefin metathesis reaction, the carbonyl-alkyne metathesis reaction can be characterized as completely atom economical due to the fact that no byproduct is formed during the reaction. As a result, the reaction is driven by enthalpic factors rather than entropic, and thus relies on the thermodynamic stability of the product. The first step of

cycloaddition between a carbonyl and an alkyne, followed by an electrocyclic ring-opening of the resulting unstable oxetene intermediate to generate an  $\alpha,\beta$ -unsaturated carbonyl product (Scheme 15). Interestingly, the mechanism of this transformation is highly dependent on the choice of Lewis acid catalyst. Oxophilic Lewis acids, such as  $BF_3$ ,  $FeCl_3$  or  $InCl_3$ , as



Scheme 16 Synthesis of the taxol A-ring synthon **80** (Crich and Crich, 1994).<sup>38</sup>

the described metathesis reaction involves a stepwise [2+2] well as Brønsted acids activate the carbonyl (72) for

Scheme 17 Total synthesis of brazilin (**84**) (Kim and Jung, 2015).<sup>39</sup>Scheme 18 Total synthesis of munduserone (**89**) and deguelin (**90**) (Kim and Nayak, 2015).<sup>40</sup>

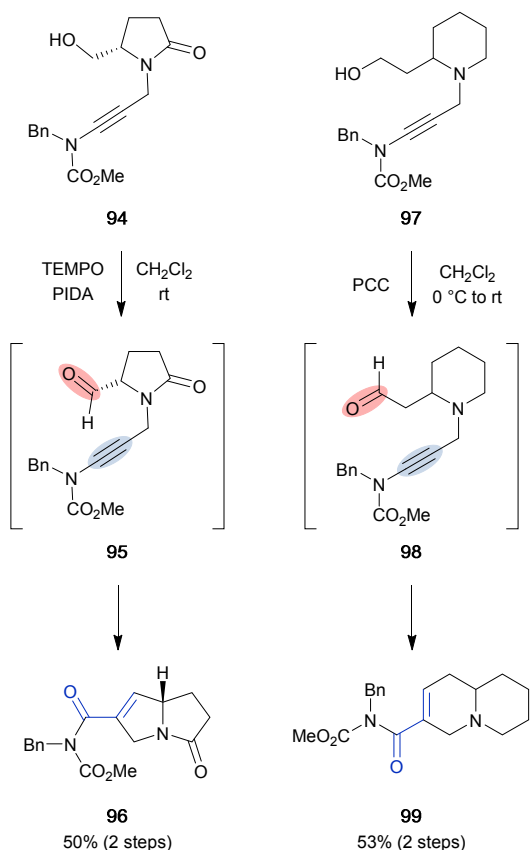
nucleophilic attack by the alkyne (**73**) resulting in a vinylic cation, which subsequently ring-closes to form the oxetene intermediate (**74**). In the last step, electrocyclic ring-opening provides the carbonyl–alkyne metathesis product (**75**) (Scheme 15). In contrast,  $\pi$ -electrophilic Lewis acids, such as Ag(I) and Au(I) salts, preferentially coordinate to the alkyne, allowing for nucleophilic attack by the carbonyl oxygen. Subsequent electrocyclizations, which are proposed to proceed through an oxetene intermediate, ultimately generate the carbonyl–alkyne metathesis product (**75**).<sup>34–35</sup>

In the last decade, carbonyl–alkyne metathesis has been utilized for the synthesis of a variety of carbocycles, heterocycles and polycyclic aromatic frameworks.<sup>36</sup> Additionally, the transformation represents an alternative to classical olefination techniques such as the Horner–Wadsworth–Emmons or Wittig reaction.<sup>37</sup> Although the carbonyl–alkyne metathesis reaction allows for the synthesis of  $\alpha,\beta$ -unsaturated ketones, esters and amides, common

structural motifs in natural products, the carbonyl–alkyne metathesis reaction has been used less frequently in natural product synthesis than the carbonyl–olefin metathesis reaction.

#### Applications of Carbonyl–Alkyne Metathesis in Natural Product Synthesis

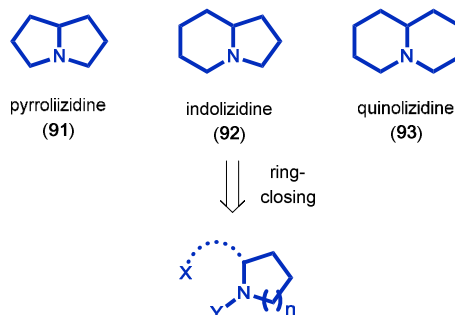
The synthetic utility of the carbonyl–alkyne metathesis reaction was first exploited by Crich in the synthesis of a taxol A-ring synthon (**80**) (Scheme 16).<sup>38</sup> In this example, classical olefination methods, including the Wittig, Horner–Wadsworth–Emmons or Julia reaction, failed to convert ketone **77** to the olefinated product **78**. However, when **77** was treated with ethoxyacetylene and  $\text{BF}_3$ , the desired  $\alpha,\beta$ -unsaturated ester **78** could be isolated in 65% yield as a single isomer. The product was further elaborated to the desired taxol A-ring synthon **80** in two steps including a dihydroxylation and diol protection.



**Scheme 19** Oxidation/carbonyl-alkyne metathesis sequence (Hsung and co-workers, 2006).<sup>41</sup>

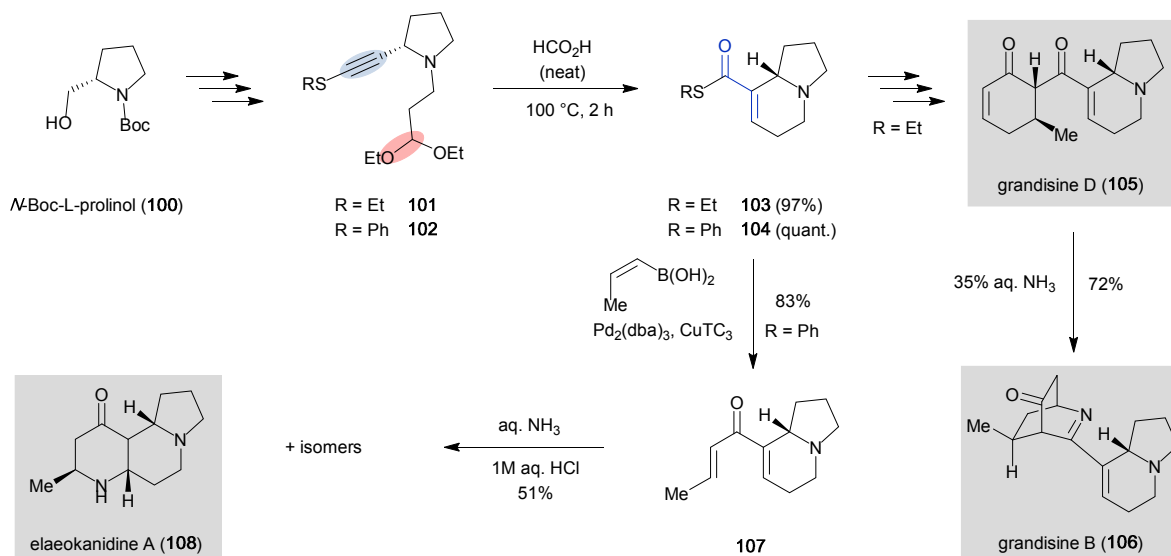
More recently, intramolecular carbonyl-alkyne metathesis has been shown to be a powerful tool for the construction of densely functionalized five- and six-membered rings. Kim's total synthesis of the tetracyclic homoisoflavonoid brazilin (**84**) highlights the molecular complexity that can be generated rapidly through ring-closing carbonyl-alkyne metathesis

(Scheme 17).<sup>39</sup> For the construction of the brazilin core, the authors performed the metathesis reaction on aldehyde **82** with catalytic amounts of  $\text{In}(\text{OTf})_3$ , which produced exocyclic enone **83** in quantitative yield. A series of subsequent steps resulted in the total synthesis of ( $\pm$ )-brazilin (**84**) in nine steps and 70% overall yield.

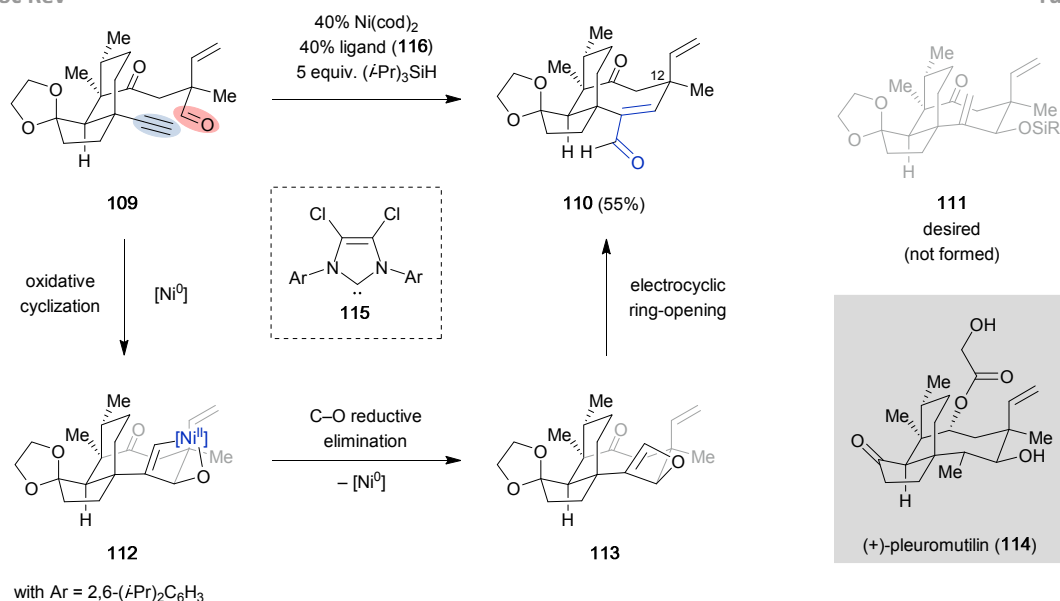


**Figure 3** Molecular structure of selected bicyclic alkaloid cores.

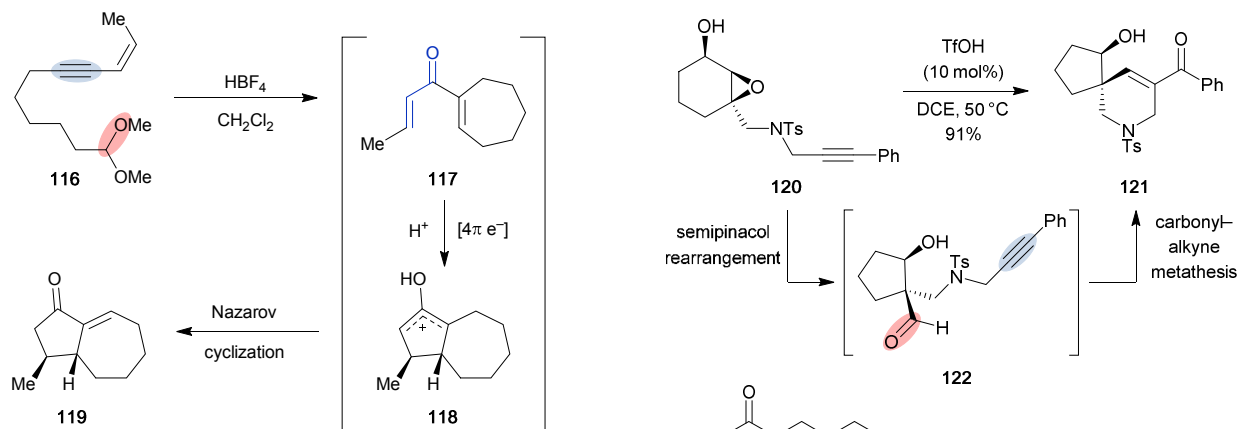
Carbonyl-alkyne metathesis also provided access to the rotenoid natural product munduserone (**89**) featuring a chromano[3,4-*b*]chromanone framework.<sup>40</sup> Enone **88** was identified as an advanced intermediate *en route* to the desired target that could be constructed through a ring-closing metathesis reaction from precursor **86** (Scheme 18). Treatment of **86** with catalytic amounts of  $\text{In}(\text{OTf})_3$  in aqueous media generated the corresponding oxonium intermediate **87**, which subsequently underwent ring-closing metathesis with the adjacent alkyne smoothly in 92% yield. Advantageously, the authors observed the loss of the methoxymethyl (MOM) group under the employed reaction conditions. One more synthetic transformation, a base-mediated conjugate addition reaction, provided ( $\pm$ )-munduserone (**89**) in 90% yield. In the same report the authors formally synthesized ( $\pm$ )-deguelin (**90**), a structurally similar natural product belonging to the same family as munduserone (**89**), by following a similar sequence of transformations.



**Scheme 20** Total synthesis of grandisine B (**106**) and D (**105**) and elaeokanidine A (**108**) (Taylor and co-workers, 2011 and 2015).<sup>42,45</sup>



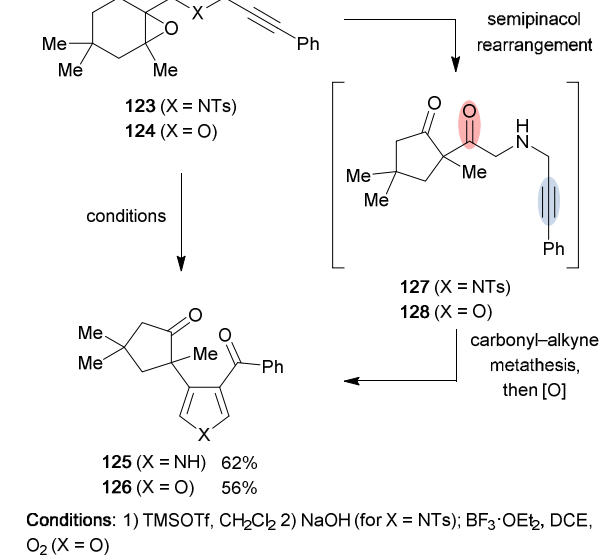
**Scheme 21** Unexpected nickel-catalyzed carbonyl-alkyne metathesis reaction observed *en route* to pleuromutilin (**114**) (Herzon and co-workers, 2017).<sup>46</sup>



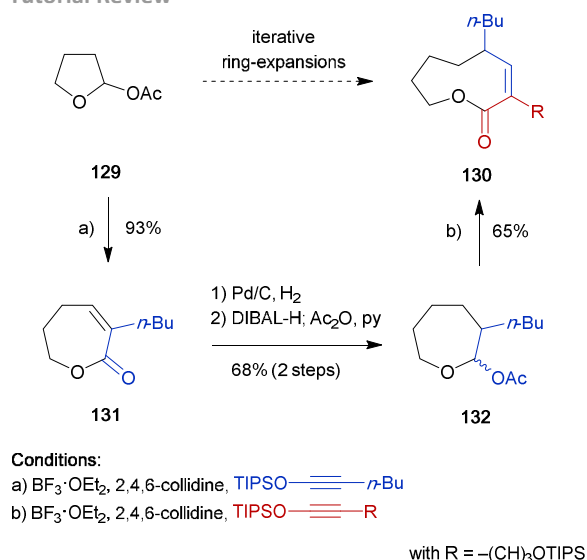
**Scheme 22** Carbonyl-alkyne metathesis/Nazarov cyclization cascade (Saá and co-workers, 2012).<sup>43</sup>

Due to their structural diversity and biological activity, bicyclic alkaloids such as the pyrrolizidine (**91**), indolizidine (**92**) and quinolizidine (**93**) alkaloids have attracted high levels of interest from the synthetic community for decades (Figure 3). Hsung showcased the potential of utilizing a ring-closing carbonyl-alkyne metathesis reaction to access the described pyrrolizidine and quinolizidine cores. In his report, ynamides were employed as the alkyne component and underwent BF<sub>3</sub>-mediated metathesis in overall good yields.<sup>41</sup> When attempting to oxidize chiral prolinol derivative **94** pyrrolizidine **96** was isolated as the sole product in 50% yield, resulting from a carbonyl-alkyne metathesis reaction under the reaction conditions. The authors were able to further elaborate this tandem oxidation-metathesis sequence to access quinolizidine **99** in 53% yield, providing a new synthetic entry to these types of alkaloid core structures (Scheme 19).

The first total synthesis of an indolizidine alkaloid utilizing a formal carbonyl-alkyne metathesis was reported by Taylor and



**Scheme 23** Semipinacol-rearrangement/carbonyl-alkyne metathesis cascade (Yeh and co-workers, 2011 and 2013).<sup>47-48</sup>



Scheme 24 Iterative ring-expansion strategy (Sun and co-workers, 2013).<sup>49</sup>

co-workers, who synthesized the two closely related natural products (–)-grandisine B (**106**) and (+)-grandisine D (**105**), both isolated from the Australian rainforest tree *elaeocarpus grandis* (Scheme 20).<sup>42</sup> In addition to the indolizidine core, grandisine B (**106**) features a unique isoquinuclidinone unit, which is proposed to originate from a double addition of ammonia to grandisine D (**105**). Key intermediate **101** was accessed from *N*-Boc-L-prolinol (**100**) in seven steps and contains a thioalkyne and an acetal, which were prompted to cyclize in refluxing formic acid to provide **103** in 97% yield. Although no mechanistic investigations were performed, similar reports suggest a metathesis pathway for this reaction.<sup>43–44</sup> Subsequent redox manipulations and an aldol reaction gave access to grandisine D (**105**). Treatment of **105** with aqueous ammonia resulted in the expected conjugate addition/imine formation sequence to construct the isoquinuclidinone core and provide grandisine B (**106**). However, the authors noted that the conditions employed for the conversion of grandisine D (**105**) to grandisine B (**106**) were extremely close to the conditions used during the isolation and therefore questioned if grandisine B (**106**) was an artefact generated during the isolation process rather than a natural product. Similar concerns were raised during the total synthesis of (+)-elaeokanidine A (**108**), a structurally related indolizidine natural product, originating from the same plant family as grandisine B and D.<sup>45</sup> In contrast to Taylor's previously developed approach, the synthetic route proceeded through phenylthioalkyne **102**, which allowed conversion of carbonyl–alkyne metathesis product **104** to enone **107** in 83% yield via a Liebeskind-Srogl coupling. Treatment of **107** with aqueous ammonia resulted in the expected double conjugate addition and provided a mixture of three isomers in 51% combined yield. However, due to the poor resolution of the spectroscopic data reported for the natural samples, out of the three isomers only elaeokanidine A (**108**) could be assigned with certainty.

Recently, Herzon reported the development of a modular synthetic route to (+)-pleuromutilin (**114**), a diterpene fungal

metabolite that inhibits the growth of Gram-positive pathogens.<sup>46</sup> The key disconnection to access the densely functionalized eight-membered carbocycle relied on a nickel-catalyzed reductive coupling (Scheme 21). The initial strategy aimed to convert **109** into carbocycle **111** via a process, in which nickel undergoes oxidative cyclization with **109**, followed by  $\sigma$ -bond metathesis with a silane, and reductive elimination. However, when (*i*-Pr)<sub>3</sub>SiH was used as the silane source, enone **110** was isolated as the sole product in 55% yield, thus, representing a formal carbonyl–alkyne metathesis reaction (Scheme 21). The product was proposed to result from the initial desired oxidative cyclization of nickel(0) to form metallacycle **112**. However, instead of reacting with the bulky (*i*-Pr)<sub>3</sub>SiH, the nickel(II) center (**112**) underwent reductive elimination to form oxetene **113**. Subsequently, an electrocyclic ring-opening provided **110** as the formal metathesis product. It is important to note that this is the only example of a nickel-catalyzed carbonyl–alkyne metathesis reaction to date.

#### Application of Carbonyl–Metathesis to Access Complex Structures

The carbonyl–alkyne metathesis reaction has also been used in cascade processes. For example, Saá and co-workers report utilizing a Brønsted acid-promoted carbonyl–alkyne metathesis/Nazarov cyclization to access hydroazulenones, a prevalent structure in natural products such as guanacastepene A (**4**) and pleocarpenone (Scheme 22).<sup>43</sup> In the authors report, the carbonyl–alkyne metathesis reaction was performed with enyne acetals (**116**) to yield intermediate enones (**117**) that rapidly underwent a Nazarov cyclization (**118**) to provide the corresponding enone as the product (**119**). Yeh reported a catalytic semipinacol rearrangement/carbonyl–alkyne metathesis cascade with cyclic epoxides bearing a pendant alkyne.<sup>47–48</sup> Depending on the substitution pattern of the epoxide, these compounds (**120**, **123**, **124**) would provide either functionalized spirocycles (**121**) or heterocycles such as furans and pyrroles (**125**, **126**) (Scheme 23).

An interesting strategy for the synthesis of large-ring lactones was reported by Sun and has enabled access to up to 18-membered lactones through a ring-expansion protocol.<sup>49</sup> By treating cyclic acetals with stoichiometric amounts of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ , an oxocarbenium species can be generated, which reacts with a siloxyalkyne. The resulting oxetanium intermediate undergoes electrocyclic ring-opening to provide the ring-expanded product. The synthetic potential of the developed method was highlighted when the authors converted five-membered acetal **129** into a nine-membered lactone **130** through two iterative ring-expansions (Scheme 24).

Carbonyl–alkyne metathesis has been employed in the synthesis of numerous natural products and related complex molecules. It has been used as an alternative to current olefination strategies, and has facilitated efficient ring-closure in the presence of highly functionalized environments. However, many examples still require the use of harsh

conditions or stoichiometric amounts of Brønsted or Lewis acids, thus demanding the development of milder protocols.

#### 4. Summary and Outlook

For decades, carbonyl–olefin and carbonyl–alkyne metathesis strategies have been used in the synthesis of natural products and complex molecules, with selected examples being highlighted in this review. Most of these strategies have been inventive and inspire the pursuit of new protocols; however, many reported examples require the use of stoichiometric amounts of reagents or harsh reaction conditions. While some examples presented herein were found superior to the classical olefin–olefin metathesis reaction, there is an unmet need for the further development of novel catalytic protocols to rapidly obtain these important metathesis products. Novel ways to perform metathesis reactions continue to be developed and their synthetic potential will be assessed when these strategies are applied in chemical synthesis.<sup>50</sup>

#### Conflicts of interest

There are no conflicts to declare.

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